CTD 第 2 部

2.7　臨床概要

2.7.3　臨床的有効性

MSD 株式会社

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation/Term	Definition
3TC	Lamivudine
AE	Adverse event or adverse experience
AIDS	Acquired Immune Deficiency Syndrome
CI	Confidence interval
CSR	Clinical study report
CYP	Cytochrome P450
DOR	Doravirine (MK-1439)
DRV	Darunavir
DRV+r	Darunavir boosted with ritonavir
EFV	Efavirenz
EPZICOM / KIVEXA	Alternative brand names for fixed dose combination of abacavir (ABC) plus lamivudine (3TC)
FAS	Full Analysis Set (analysis population)
FDA	Food and Drug Administration
FTC	Emtricitabine
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV-1	Human immunodeficiency virus type 1
IC_{50}	50% inhibitory concentration
MK-1439A	Fixed-dose combination of DOR, 3TC, and TDF
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleos(t)ide reverse transcriptase inhibitors
PDVF	Protocol-defined virologic failure
PI	Protease inhibitor
PK	Pharmacokinetic
PP	Per-Protocol (analysis population)
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 BACKGROUND AND OVERVIEW OF CLINICAL EFFICACY

1.1 Background and Rationale

Doravirine (DOR; also referred to as MK-1439) belongs to the non-nucleoside reverse transcriptase inhibitor (NNRTI) class of antiretroviral medications. As a class, NNRTIs are highly effective against human immunodeficiency virus type 1 (HIV-1) in treatment-naïve patients and have been in use since 1996, when nevirapine received marketing authorization in the United States (US) [Ref. 5.4: 04PB3J]. While nevirapine is no longer recommended for initial therapy regimens, the NNRTIs efavirenz (EFV) and rilpivirine (RPV) are among the most commonly prescribed anti-HIV-1 therapies. Both of these drugs, however, have limitations; treatment-limiting neuropsychiatric adverse events (AEs) are associated with EFV [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].

These limitations have resulted in the downgrading of NNRTI-based regimens from recommended to alternative therapies in the 2016 guidelines of the US Department of Health and Human Services [Ref. 5.4: 04LV4N], although the World Health Organization (WHO) [Ref. 5.4: 04MN5R] and the European AIDS Clinical Society [Ref. 5.4: 04MZSY] still include NNRTI-based regimens among recommended regimens. An unmet clinical need therefore exists for new NNRTI agents with improved tolerability and effectiveness compared with currently available drugs in this class.

Doravirine (DOR) is a novel NNRTI being developed by the Applicant as a once-daily (QD) oral treatment for 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).

1.2 Overview of the Clinical Development Program for Doravirine

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 [Table 2.7.3-trtmtnve48wk: 1]. Both Phase 3 trials are ongoing. In addition, 2 Phase 2 trials (P028, P030) and 1 additional Phase 3 trial (P024) are ongoing.

With respect to demonstrating efficacy, the clinical development program for DOR and DOR/3TC/TDF proceeded as follows:

1. Demonstration of in vivo HIV-1 antiretroviral activity in the Phase 1 trial, P005:

   Results from this Phase 1, placebo-controlled trial in HIV-1-infected, treatment-naïve men provided evidence of the short-term antiretroviral activity of DOR as monotherapy and supported continuation of the clinical program. A total of 18 subjects were randomized to receive either 25 or 200 mg DOR (n=6 each) or placebo (n=6) once daily (QD), as a single agent, for 7 days. Robust antiretroviral efficacy, measured as a decrease in HIV-1 RNA level from baseline to Day 7, was seen with both doses, thus supporting initiation of the Phase 2b dose-ranging trial (P007) using a dose range of 25 through 200 mg.

2. Selection of the clinical dose in the Phase 2b trial, P007:

   Results of this Phase 2b, multicenter, double-blind, randomized, dose-ranging trial in HIV-1-infected, treatment-naïve men and women provided evidence to support dose selection for subsequent Phase 2 and Phase 3 trials and demonstrated long-term (through 96 weeks) efficacy and safety data for the selected dose. Subjects in Part I of P007 were randomized to receive DOR for 24 weeks in doses of 25, 50, 100 or 200 mg QD or EFV 600 mg QD, each in combination with emtricitabine (FTC)/TDF (administered in this trial as TRUVADA). Subjects in Part II were randomized to the DOR dose that was selected based on efficacy and safety results from Part I (100 mg) or EFV 600 mg, each in combination with FTC/TDF. Subjects in both Part I and Part II continued treatment through Week 96. Antiretroviral efficacy of, and immunologic response to, each of the DOR doses was robust and comparable to that of EFV; no functional distinction among doses could be made based on these variables.

3. Demonstration of efficacy in the Phase 3 trials, P018 and P021:

   Results of these Phase 3 trials in HIV-1 infected treatment-naïve men and women, with global enrollment, demonstrate the non-inferior efficacy of DOR 100 mg as compared with the commonly prescribed protease inhibitor (PI) darunavir (DRV) boosted with ritonavir (DRV+r) in P018, and, with the commonly prescribed EFV-based regimen EFV/FTC/TDF (administered in this trial as ATRIPLA) in P021. In P018, DOR was evaluated as a single agent in combination with either FTC/TDF or abacavir (ABC) plus 3TC (ABC/3TC; administered in this trial as either EPZICOM or KIVEXA), as chosen by the investigator. In P021, DOR was evaluated as the fixed-dose combination DOR/3TC/TDF. The complete 48-week data from P018 and P021 are provided in this application. Subjects in each of these trials will continue blinded treatment through 96 weeks, with an optional open-label extension for an additional 96 weeks.

4. Additional characterization of the efficacy and safety profile of DOR in trials P024, P028, and P030:

   Three additional trials of DOR/3TC/TDF are ongoing at the time of this application (2 Phase 2 and 1 Phase 3); limited safety data (including any reported SAEs) are provided for these studies [2.7.4] and full safety data will be provided at a later time.

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

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

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

As of the data cutoff date for the integrated analysis, DOR (as a single agent or as DOR/3TC/TDF) has been administered to a total of 2307 subjects in the clinical development program: 678 subjects in the Phase 1 trials and 1629 subjects in the Phase 2 and 3 trials, as described below.

- Phase 1: 678 subjects in the trials received at least 1 dose of DOR or DOR/3TC/TDF: 650 healthy subjects, 12 HIV-1-infected subjects, 8 subjects with moderate hepatic impairment, and 8 subjects with severe renal impairment. DOR was administered as a single dose up to 1200 mg and as multiple doses up to 750 mg QD for 10 days in the Phase 1 trials.

- Phases 2 and 3 (completed and ongoing): 1629 HIV-1-infected subjects received DOR or DOR/3TC/TDF in 6 trials: 232 in the completed P007 trial, 747 in the pivotal Phase 3 trials (P018, P021), and 850 in the 3 other ongoing trials (P024, P028, P030). The characterization of the efficacy and safety of DOR and DOR/3TC/TDF in this application is primarily based on data from the 979 HIV-1-infected, treatment-naïve subjects who received DOR or the FDC DOR/3TC/TDF in trials P007, P018 or P021; a total of 855 of these subjects were randomized to and received the 100-mg dose of DOR throughout the trial (including P007).

The Phase 2b and 3 trials that provide the data for this application are summarized in [Table 2.7.3-trtmtnve48wk: 1]; efficacy findings from these trials are found in [Table 2.7.3-trtmtnve48wk: 3].

Table 2.7.3-trtmtnve48wk: 1

Brief Overview of Phase 2b and Phase 3 Clinical Trials Providing Efficacy Data for the Current Application

Phase	Protocol	Dose	Number of Subjects Treated	Population	Key Purpose
2b	P007 Subjects treated with **DOR**, each in combination with FTC/TDF Completed	25 mg QD	40 [Part I]	Treatment-naïve HIV-1-infected adults	Part I: Dose selection Part II: Efficacy and safety /tolerability
		50 mg QD	43 [Part I]		
		100 mg QD	108 [Part I: 42, Part II: 66]		
		200 mg QD	41 [Part I]		
3	018 Subjects treated with **DOR** in combination with FTC/TDF or ABC/3TC Ongoing (Week 48 data provided here)	100 mg QD	383	Treatment-naïve HIV-1-infected adults	Efficacy and safety /tolerability
	021 Subjects treated with **DOR/3TC/TDF** Ongoing (Week 48 data provided here)	100 mg QD (combined with 300 mg each 3TC and TDF)	364	Treatment-naïve HIV-1-infected adults	Efficacy and safety /tolerability

1.3 Overview of the Data Presented in This Summary of Clinical Efficacy

This integrated efficacy summary provides data from the first 48 weeks of treatment in the ongoing Phase 3 trials (P018 and P021) and from 96 weeks of treatment in the completed Phase 2b trial (P007), including the 24-week dose-selection phase, in support of the proposed indication and dose. Efficacy data from these trials demonstrate the potency and durable antiretroviral efficacy of both DOR, when used in combination with other antiretroviral drugs, and DOR/3TC/TDF. Presentations of efficacy are organized as follows:

- Efficacy results from the individual trials are presented in Section 2 [Sec. 2.7.3.2-trtmtnve48wk].

- Integrated efficacy results for pooled data from P018 and P021 are presented in Section 3 [Sec. 2.7.3.3-trtmtnve48wk], with the rationale for the pooling strategy in [Sec. 2.7.3.3.1-trtmtnve48wk].

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

1.4 Clinical Efficacy Analyses

1.4.1 Efficacy Endpoints Presented in This Summary of Clinical Efficacy

Consistent with guidelines for the clinical development of HIV drugs [Ref. 5.4: 04KB08, 04DT6Q], efficacy was assessed by measuring change in viral load (ie, level of HIV-1 RNA in plasma) and in level of $CD4^+$ T-cells after 48 weeks' treatment. Plasma HIV-1 RNA levels were measured by the Abbott 'RealTime HIV-1 Assay' (with a lower limit of quantification of 40 copies/mL) and $CD4^+$ T-cell counts were measured using flow cytometry.

The efficacy of DOR 100 mg, as the single entity in combination with other antiretroviral drugs or as DOR/3TC/TDF, is demonstrated in this Summary of Clinical Efficacy by the following parameters, as measured at Week 48 in the pivotal Phase 3 trials:

- Proportion of subjects achieving HIV-1 RNA <50 copies/mL;
- Proportion of subjects achieving HIV-1 RNA <40 copies/mL;
- Proportion of subjects achieving HIV-1 RNA <200 copies/mL;
- Time to loss of virologic response (TLVOR);
- Change from baseline in $CD4^+$ T-cell count;
- Protocol-defined virologic failure (PDVF) and viral drug resistance.

Data from the Phase 2b trial (P007) demonstrate the efficacy of DOR 100 mg through Week 96 and support the choice of the 100-mg dose based on the above parameters as well as additional considerations.

The efficacy endpoints for the analysis of pooled data are provided in the Integrated Statistical Analysis Plan [Ref. 5.3.5.3: 04LVBJ] and summarized below; those for individual trials are summarized in [Table 2.7.3-trtmtnve48wk: 3].

1.4.1.1 Antiretroviral Efficacy

Proportion of Subjects With Virologic Response

Three HIV-1 RNA thresholds were used in evaluating antiretroviral efficacy: <50, <40, and <200 copies/mL. The threshold of <50 copies/mL, commonly used in clinical trials of HIV therapies, was used for the primary analyses in the Phase 3 trials. The threshold of <40 copies/mL reflects the lower limit of quantification of the assay used in the Phase 2b and 3 trials that support this application. The threshold of <200 copies/mL has also been frequently used in clinical trials as well as in clinical practice, particularly in defining virologic failure.

In 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 and proportions of subjects with HIV-1 RNA <200 copies/mL at each of these timepoints. The proportion of subjects with HIV-1 RNA <50 copies/mL was also assessed as a supportive analysis in this trial.

In 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.

Time to Loss of Virologic Response (TLOVR)

In P007, TLOVR was defined, for subjects who had achieved HIV-1 RNA <40 copies/mL and subsequently had 2 consecutive measurements (≥1 week apart) of HIV-1 RNA ≥40 copies/mL, as the time between Day 1 and the first of the 2 consecutive values ≥40 copies/mL. For subjects who achieved and sustained HIV-1 RNA levels of <40 copies/mL, TLOVR was censored at the time of the last available measurement. For subjects who did not achieve HIV-1 RNA <40 copies/mL, TLOVR was defined as 0 weeks. TLOVR in P007 was also summarized using a threshold of 200 copies/mL.

In P018 and P021, TLOVR was defined as it was in P007 but with an HIV-1 RNA threshold of 50 copies/mL.

1.4.1.2 Immunologic Efficacy

Immunologic efficacy was assessed, as a secondary efficacy endpoint, by the change in $CD4^+$ T-cell count from baseline to various timepoints during each trial.

In P007, change in $CD4^+$ T-cell count from baseline was assessed at Weeks 24, 48 and 96. In P018 and P021, this variable was assessed at Week 48.

1.4.1.3 Protocol-Defined Virologic Failure (PDVF)

In P007, 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 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.

An HIV-1 RNA threshold of 200 copies/mL was also used to assess virologic failure in P007.

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.

This change in the PDVF definition for Phase 3 reflects an updated understanding of the kinetics of viral load response with NNRTIs, including that observed for DOR in the Phase 2b trial (P007).

1.4.1.4 Evaluation of Viral Drug Resistance

Genotypic and phenotypic data for viral drug resistance to DOR, and to each comparator and each background nucleos(t)ide reverse transcriptase inhibitor (NRTI), were assessed in P007, P018, and P021 for subjects with PDVF. Viral resistance testing was also conducted in P018 and P021 for subjects who discontinued study treatment for other reasons. The methods used by the central laboratory ([redacted]) for evaluating genotypic and phenotypic viral resistance in all 3 trials are summarized in [Ref. 5.3.5.1: P018V01MK1439: 9.5.1.1].

Postbaseline genotypic resistance to DOR was defined, for the purpose of the Phase 2b and Phase 3 trials, as any of the following mutations, based on in vitro testing performed by the Sponsor: RT L100I, K101E, V106A, V106I, V106M, V108I, E138K, Y188L, G190A, G190S, H221Y, P225H, F227C, F227L, F227V, M230I, M230L, L234I, P236L, and Y318F. While no threshold for phenotypic resistance to DOR has yet been clinically defined, the central laboratory used a 2.5-fold change in IC_{50} versus wild-type virus as a broad assay-reproducibility cut-off for potential phenotypic resistance to DOR (commonly done for other

antiretrovirals in development before sufficient data are available to define a clinically relevant cut-off).

1.4.2 Statistical Methodology

1.4.2.1 Definitions of Analysis Populations

Efficacy analyses were based on the Full Analysis Set (FAS) for the individual trials (P007, P018, P021) and for the analysis of pooled data from P018 and P021. The FAS consists of all subjects who received at least 1 dose of study treatment and had baseline data (for those analyses that required baseline data). Subjects are included in the treatment group to which they were randomized. (The rationale for pooling data from P018 and P021, but not from P007, is found in [Sec. 2.7.3.3.1-trtmtnve48wk].)

Analysis of key efficacy endpoints in P018 and P021, ie, the proportions of subjects with HIV-1 RNA <50 copies/mL and <40 copies/mL at Week 48, was also carried out using the Per-Protocol (PP) population. The PP consists of subjects in the FAS population who had no reported major protocol deviation that could potentially affect or confound the efficacy results. The results of the analyses on the PP population are found in the study reports [Ref. 5.3.5.1: P018V01MK1439]; [Ref. 5.3.5.1: P021V01MK1439A] and described briefly in the results of individual trials.

1.4.2.2 Missing Data Approaches

For P007, the primary missing data approach was the non-completer = failure (NC=F) approach, in which all subjects with missing data were considered to be failures, regardless of reason, except for an intermittent missing value flanked by two successes (ie, HIV-1 RNA <40 copies/mL). The Observed Failure (OF) approach, described below, and an additional approach (treatment-related discontinuation = failure [TRD=F]) were used as sensitivity analyses. The FDA snapshot approach, also described below, was added as a post-hoc analysis to facilitate comparison with the analyses for P018 and P021. Further details are provided in the study report [Ref. 5.3.5.1: P018V01MK1439].

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

- FDA Snapshot: In this approach, all subjects with missing data are considered to be failures, regardless of reason.

- Observed Failure (OF): In this approach, subjects with non-intermittent missing data who prematurely discontinued study treatment due to lack of efficacy were considered to be failures.

The FDA snapshot approach was the primary method for analysis of the proportion of subjects achieving various levels of virologic suppression (ie, HIV-1 RNA levels <40, <50 and <200 copies/mL), while the OF approach was used as a sensitivity analysis. Each approach provides a frame of reference for efficacy analysis: the FDA snapshot approach considers a study failure endpoint, which depends on the conduct of the trial, while the OF approach focuses on antiretroviral efficacy of the treatment.

Analysis of immunologic response (change in $CD4^+$ T-cell count from baseline) in each of the individual trials (P007, P018, P021) and in the pooled analysis of P018 and P021 used the OF approach for missing data, as did subgroup analyses of antiretroviral and immunologic efficacy. The OF approach to missing data was used for the subgroup analyses because it provides an evaluation that focuses on virologic factors and not administrative factors such as missing visits or visits outside of pre-specified time windows.

Although some missing-data approaches exclude subjects from analyses for those timepoints at which their data are missing, all efficacy analyses except for the PP analyses are based on the FAS population.

Approaches used to address missing values are summarized in [Table 2.7.3-trtmtnve48wk: 2].

Table 2.7.3-trtmtnve48wk: 2

Summary of the Approaches to Missing Data

		Non-Intermittent Missing Values† Not Related to Treatment		Non-Intermittent Missing Values Related to Treatment	
Approach	**Intermittent Missing Values**	**Success at Study Therapy Discontinuation**	**Failure at Study Therapy Discontinuation**	**Study Therapy D/C Due to Clinical or Lab AE**	**Study Therapy D/C Due to Lack of Efficacy**
FDA Snapshot	Failure	Failure	Failure	Failure	Failure
OF	Excluded‡	Excluded	Failure	Excluded	Failure
NC=F (P007 only)	Failure[a]	Failure	Failure	Failure	Failure
TRD=F (P007 only)	Excluded	Excluded	Failure	Failure	Failure

† Values missing due to permanent discontinuation from the trial.

‡ 'Excluded' refers to exclusion of missing data value from a given subject at a given time point being excluded. .

Abbreviations: D/C: discontinuation; NC=F: non-completer = failure; OF: observed failure; TRD=F: treatment-related discontinuation = failure.

Note: FDA snapshot approach was the primary approach for P018 and P021 analyses.

a: Unless flanked by 2 successes (HIV-1 RNA <40 copies/mL).

1.4.2.3 Other Statistical Methods

The statistical methods applied to each efficacy endpoint in the individual trials are found in the respective CSRs [Ref. 5.3.5.1: P007V01MK1439], [Ref. 5.3.5.1: P018V01MK1439], [Ref. 5.3.5.1: P021V01MK1439A]. Pooled data in the integrated analysis of P018 and P021 are summarized with descriptive statistics only; the Integrated Statistical Analysis Plan is found in [Ref. 5.3.5.3: 04LVBJ].

2 SUMMARY OF RESULTS OF INDIVIDUAL STUDIES

Results of the individual Phase 2b (P007) and Phase 3 (P018, P021) trials are summarized in [Table 2.7.3-trtmtnve48wk: 3] and described in this section. Detailed results from each trial are available in the respective CSRs [Ref. 5.3.5.1: P007V01MK1439], [Ref. 5.3.5.1: P018V01MK1439], [Ref. 5.3.5.1: P021V01MK1439A]. This application is based on data from the first 48 weeks of treatment in the ongoing Phase 3 trials (P018 and P021) and from 96 weeks of treatment in the completed Phase 2b trial (P007), including the 24-week dose-selection phase.

Table 2.7.3-trtmtnve48wk: 3
Summary of DOR and DOR/3TC/TDF Efficacy Data Supporting the Current Application

Trial Number [Link]	Study Design Countries with Subjects Status	No. of Subjects (Treated) by Treatment Group	Subject Sex and Median Age (Range)	Efficacy Objectives and Endpoints Evaluated in This Summary	Major Efficacy Findings Regarding DOR or DOR/3TC/TDF
007[ ]	Multicenter, double-blind (in-house blinding), randomized, active-comparator-controlled, 2-part, dose-ranging (Part I) efficacy, pharmacokinetics and safety study in treatment-naïve, HIV-1-infected adults. Australia, Belgium, Canada, France, Germany, the Netherlands, Poland, Puerto Rico, Romania, Russian Federation, Spain, United States Completed	Part I DOR 25 mg N=40 DOR 50 mg N=43 DOR 100 mg N=42 DOR 200 mg N=41 EFV 600 mg N=43 Parts I/II Combined DOR 100 mg N=108 EFV 600 mg N=108 Each treatment above was administered in combination with FTC/TDF. Note: Efficacy data were analyzed for Part I and for Parts I+ II combined; there was no separate analysis for Part II data.	**Part I** DOR 25 mg 38 M / 2 F 36.5 yrs (21-69) DOR 50 mg 37 M / 6 F 36 yrs (25-66) DOR 100 mg 36 M / 6 F 36.5 yrs (19-67) DOR 200 mg 40 M / 1 F 32 yrs (21-50) EFV 600 mg 38 M / 4 F 34 yrs (22-54) **Parts I+II** DOR 100 mg 99 M / 9 F 35 yrs (19-67) EFV 600 mg 101 M / 7 F 34 yrs (20-57 yrs)	**Primary** Part I: Evaluate antiretroviral activity of DOR, at each dose, compared with EFV, each in combination with FTC/TDF, as measured by proportion of subjects with HIV-1 RNA <40 copies/mL at Week (Wk) 24. Parts I/II combined: Same as for Part I but for selected DOR dose only. **Secondary** Part I: Evaluate antiretroviral activity and immunological effect of DOR, at each dose, compared with EFV, each in combination with FTC/TDF, as measured by, respectively, proportion of subjects with HIV-1 RNA <200 copies/mL at Wk 24 and change from baseline in $CD4^+$ T-cell count at Wk 24. Parts I/II combined: Same as for Part I but for selected DOR dose only, compared with EFV, each in combination with FTC/TDF, for 48 and 96 weeks. **Exploratory** Assess the development of resistance to DOR in subjects with virologic failure. Time to loss of virologic response (TLOVR) **Additional Analysis** Supportive analysis of the proportion of subjects achieving HIV-1 RNA <50 copies/mL.	**Results (Part I and Parts I/II combined)** Antiretroviral efficacy: ▪ [Part I]: At Week 24, antiretroviral efficacy of each dose of DOR was robust (71.4% - 80.5% of subjects with HIV-1 RNA <40 copies/mL) with no functional distinction among doses, and comparable to that of EFV (64.3%), regardless of missing data approach (results here based on FDA snapshot approach). ▪ [Parts I/II combined]: At Week 24, antiretroviral efficacy of DOR 100 mg was robust (72.2% of subjects with HIV-1 RNA <40 copies/mL) and comparable to that of EFV (73.1%), regardless of missing data approach. ▪ [Parts I/II combined]: At both Week 48 and Week 96, antiretroviral efficacy of DOR 100 mg was robust and durable (77.8% at Week 48 and 75.0% at Week 96 of subjects with HIV-1 RNA <40 copies/mL), and comparable to that of EFV (78.7% and 75.9%), regardless of missing data approach. ▪ All efficacy results using the thresholds of HIV-1 RNA <50 and <200 copies/mL were consistent with those seen for the threshold of <40 copies/mL. Immunologic response: ▪ [Part I]: At Week 24, immunological efficacy of each studied dose of DOR was robust and comparable to that of EFV (mean increase from baseline in $CD4^+$ T-cell count of 152 and 146 cells/mm^3, respectively). ▪ [Parts I/II combined]: At both Week 48 and Week 96, immunological efficacy of DOR 100 mg was robust (mean increase of 192 cells/mm^3 at Week 48 and 259 cells/mm^3 at Week 96) and comparable to that of EFV (195 and 264 cells/mm^3, respectively).

Trial Number [Link]	Study Design Countries with Subjects Status	No. of Subjects (Treated) by Treatment Group	Subject Sex and Median Age (Range)	Efficacy Objectives and Endpoints Evaluated in This Summary	Major Efficacy Findings Regarding DOR or DOR/3TC/TDF
018 [ ]	Multicenter, double-blind, randomized, active-comparator-controlled, randomized trial in HIV-1-infected, treatment-naïve adults Argentina, Australia, Austria, Canada, Chile, Denmark, France, Germany, Italy, Romania, Russian Federation, South Africa, Spain, United Kingdom, United States (including Puerto Rico) Ongoing	DOR 100 mg QD N=383 DRV+r 800/100 mg N=383	DOR 100 mg 319 M / 64 F 34.8 yrs (18-68) DRV+r, 800/100 mg 326 M / 57 F 35.7 yrs (18-69)	**Primary** Evaluate whether the antiretroviral activity of DOR 100 mg QD is non-inferior to that of DRV+r (800mg/100mg QD), each in combination with FTC/TDF or ABC/3TC, as measured by the proportion of subjects with HIV-1 RNA <50 copies/mL at Wk 48. If non-inferiority is established, evaluate superiority of DOR to DRV+r with respect to antiretroviral activity. **Secondary** Evaluate the immunologic effect of DOR 100 mg QD, compared with DRV+r, each in combination with FTC/TDF or ABC/3TC, as measured by change from baseline in $CD4^+$ T-cell count at Week 48. Evaluate the antiretroviral activity of DOR 100 mg QD, compared with DRV+r, each in combination with FTC/TDF or ABC/3TC, as measured by the proportion of subjects with HIV-1 RNA <40 copies/mL at Wk 48. **Exploratory** Evaluate the antiretroviral activity of DOR 100 mg QD, compared with DRV+r, each in combination with FTC/TDF or ABC/3TC, as measured by the proportion of subjects with HIV-1 RNA <200 copies/mL at Wk 48. Evaluate the antiretroviral activity of DOR 100 mg QD, compared with DRV+r, each in combination with FTC/TDF or ABC/3TC, as measured by TLOVR. Assess the development of resistance to DOR in subjects with virologic failure.	Antiretroviral Efficacy: ▪ At Week 48, antiretroviral efficacy of DOR 100 mg was robust (83.8% of subjects with HIV-1 RNA <50 copies/mL) and non-inferior to that of DRV+r (79.9%), with a treatment difference (DOR-DRV+r) of 3.9% (95% CI: -1.6, 9.4). ▪ Consistent efficacy results were also observed with regard to proportions of subjects with HIV-1 RNA <40 and <200 copies/mL, regardless of the approach to missing data. Immunologic response: ▪ At Week 48, immunologic efficacy of DOR was robust and comparable to that of DRV+r (mean change from baseline of 193 and 186 $CD4^+$ T-cells/mm^3, respectively).

Trial Number [Link]	Study Design Countries with Subjects Status	No. of Subjects (Treated) by Treatment Group	Subject Sex and Median Age (Range)	Efficacy Objectives and Endpoints Evaluated in This Summary	Major Efficacy Findings Regarding DOR or DOR/3TC/TDF
021 [ ]	Multicenter, double-blind, randomized, active-comparator-controlled, randomized trial in HIV-1-infected, treatment-naïve adults Australia, Belgium, Canada, Chile, Colombia, Denmark, Germany, Guatemala, Honduras, Israel, Mexico, New Zealand, Peru, Portugal, Russian Federation, South Africa, Spain, Switzerland, Taiwan, Thailand, United Kingdom, United States Ongoing	DOR/3TC/TDF (DOR 100 mg) N=364 EFV/FTC/TDF N=364	DOR/3TC/TDF 305 M / 59 F 33.6 yrs (18-70 yrs) EFV/FTC/TDF 311 M / 53 F 32.7 yrs (18-69 yrs)	**Primary** Evaluate whether the antiretroviral activity of DOR/3TC/TDF QD is non-inferior to that of EFV/FTC/TDF QD, as measured by the proportion of subjects with HIV-1 RNA <50 copies/mL at Wk 48. **Secondary** Evaluate the immunologic effect of DOR/3TC/TDF QD, compared with EFV/FTC/TDF QD, as measured by change from baseline in $CD4^+$ T-cell count at Week 48. Evaluate whether the antiretroviral activity of DOR/3TC/TDF QD is superior to that of EFV/FTC/TDF QD, as measured by the proportion of subjects with HIV-1 RNA <50 copies/mL at Wk 48 Evaluate the antiretroviral activity of DOR/3TC/TDF QD, compared with EFV/FTC/TDF QD, as measured by the proportion of subjects with HIV-1 RNA <40 copies/mL at Wk 48. **Exploratory** Evaluate the antiretroviral activity of DOR/3TC/TDF QD, compared with EFV/FTC/TDF QD, as measured by the proportion of subjects with HIV-1 RNA <200 copies/mL at Wk 48. Evaluate the antiretroviral activity of DOR/3TC/TDF QD, compared with EFV/FTC/TDF QD, as measured by TLOVR. Assess the development of resistance to DOR in subjects with virologic failure.	Antiretroviral Efficacy: ▪ At Week 48, the antiretroviral efficacy of DOR/3TC/TDF (assessed as the proportion of subjects with HIV-1 RNA <50 copies/mL) was robust (84.3% of subjects with HIV-1 RNA <50 copies/mL) and non-inferior to that of EFV/FTC/TDF, with a treatment difference (DOR/3TC/TDF - EFV/FTC/TDF) of 3.5% (95% CI: -2.0, 9.0). ▪ Consistent antiretroviral efficacy results were also seen for DOR/3TC/TDF and EFV/FTC/TDF using thresholds of <40 and <200 copies/mL. Immunologic response: ▪ At Week 48, immunologic efficacy (assessed as the mean change from baseline in $CD4^+$ T-cell count) of DOR/3TC/TDF was robust and comparable to that of EFV/FTC/TDF (mean change from baseline of 198 and 188 $CD4^+$ T-cells/mm^3, respectively).

2.1 Protocol 007: Phase 2b Dose-Ranging Trial - Comparison With Efavirenz

2.1.1 Protocol 007 Study Design

P007 was a 2-part, multicenter, double-blind (in-house blinding), randomized, dose-ranging Phase 2b trial in HIV-1-infected, treatment-naïve men and women, 18 years of age or older, with an HIV-1 RNA level of ≥1,000 copies/mL and a $CD4^+$ T-cell count of ≥100 cells/mm^3 at screening. Subjects were stratified by their screening HIV-1 RNA level (≤ or >100,000 copies/mL). The trial design is shown in [Figure 2.7.3-trtmtnve48wk: 1].

Part I used a dose-ranging approach to assess the efficacy, pharmacokinetics, safety and tolerability of DOR at 25, 50, 100, or 200 mg QD, compared with EFV 600 mg QD, each in combination with TDF/FTC (administered as TRUVADA), to support dose selection for further study. Subjects (N=210; approximately 40 subjects per treatment group) were randomized to DOR 25, 50, 100, or 200 mg QD or EFV 600 mg QD. The primary efficacy objective for Part I was to evaluate, for each dose of DOR in comparison with EFV, the suppression of HIV-1 at Week 24. After the analysis of Week 24 data leading to the selection of the 100-mg dose for further development, subjects enrolled in Part I continued to receive either DOR or EFV, as blinded treatment, through Week 96. Subjects randomized to DOR 100 mg continued with that treatment; subjects randomized to DOR 25, 50 or 200 mg were switched to 100 mg at their next scheduled visit between Weeks 36 and 72, with the majority switching between Weeks 48 and 72.

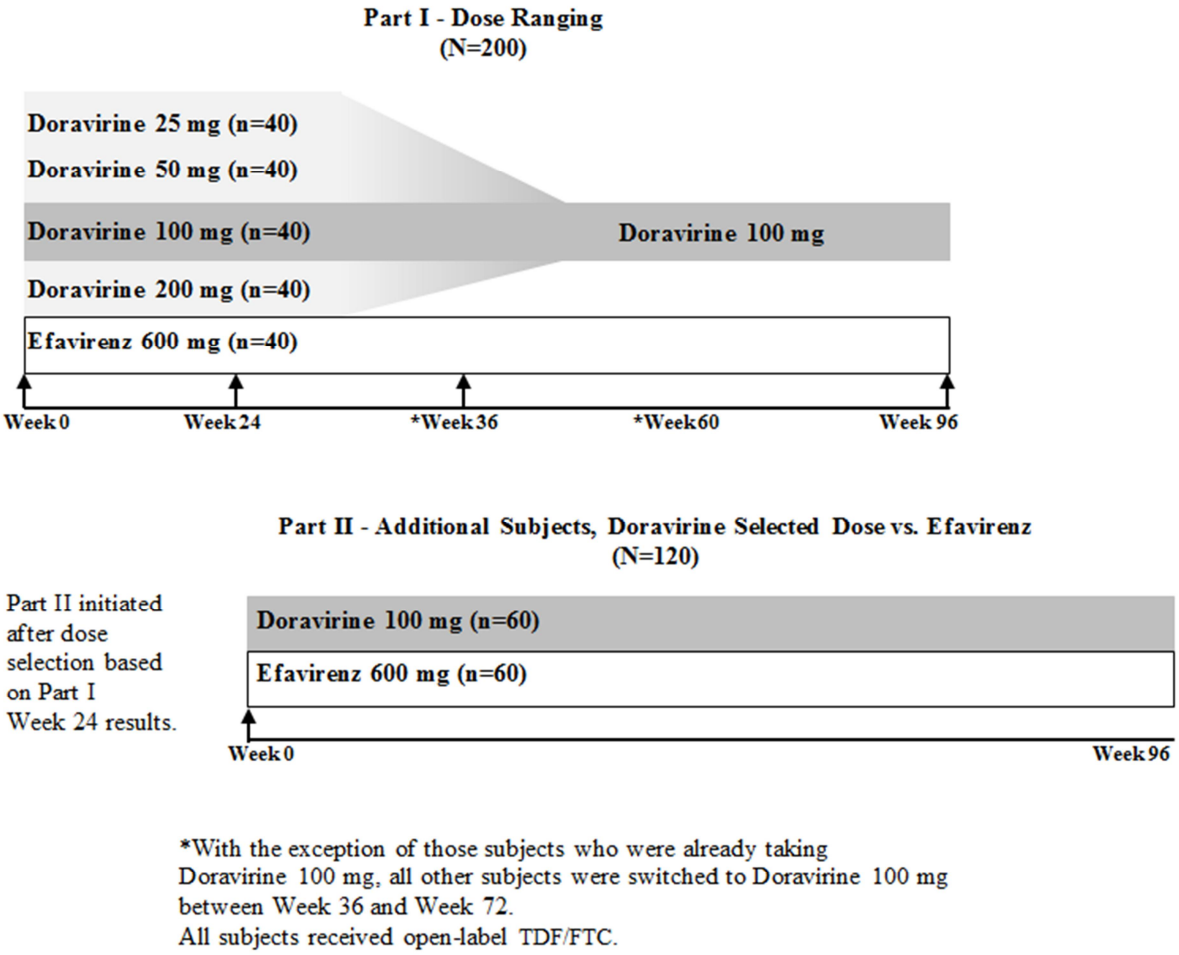
Part II was designed to provide safety and efficacy data in approximately 120 additional subjects (actual N=132), with all subjects randomized to blinded treatment with either the dose of DOR selected in Part I (100 mg) or EFV 600 mg QD. The sample size was chosen to provide sufficient power for testing the hypothesis that the proportions of subjects with CNS AEs by Week 8 and Week 24 would be lower in the DOR group than in the EFV group. Other objectives were intended to confirm the efficacy and safety of the selected dose of DOR in comparison with EFV 600 mg.

In Parts I and II, virologic and immunologic responses were assessed at Weeks 2, 4, 8, 12, 16, 24, 36, 48, 60, 72, 84 and 96.

The primary efficacy endpoint in P007 was the proportion of subjects with HIV-1 RNA <40 copies/mL; the primary missing-data approach was NC=F. In order to facilitate comparison with results from P018 and P021, 2 post-hoc analyses were carried out: (1) the endpoint of the proportion of subjects with HIV-1 RNA <50 copies/mL was added and (2) endpoints for all of the HIV-1 RNA thresholds (40, 50 and 200 copies/mL) were analyzed using the FDA snapshot approach to missing data. Analyses using both the FDA snapshot and the OF approach are presented below. Analyses using additional missing-data approaches can be found in the CSR [Ref. 5.3.5.1: P007V01MK1439].

Figure 2.7.3-trtmtnve48wk: 1

Protocol 007 Study Design



*With the exception of those subjects who were already taking Doravirine 100 mg, all other subjects were switched to Doravirine 100 mg between Week 36 and Week 72.
All subjects received open-label TDF/FTC.

2.1.2 Protocol 007 Key Efficacy Results

Efficacy results for P007 are reported for Part I alone for each of the DOR dose groups separately and combined; in addition, results are reported for Parts I and II combined. There was no separate analysis of data for Part II alone. Results are presented as described below:

- Part I: Subjects in each of the 4 DOR dose groups (25, 50, 100 and 200 mg; n≈40 subjects each) separately; subjects who received any dose of DOR (referred to as the 'DOR-combined group', n=166); and subjects who received EFV 600 mg (n=42).

- Parts I+II (combined):

  (a) Subjects who were randomized to and received 100 mg DOR throughout either Part I or Part II (n=108); and subjects who received EFV 600 mg in either Part I or Part II (n=109).

(b) Same groups as above bullet plus subjects in the additional DOR dose groups separately (25-, 50-, and 200-mg groups in Part I) and combined ('DOR-combined' group who received DOR in either Part I or Part II; n=232).

Note that 'the 100-mg group' refers to only those subjects who received the 100-mg dose of DOR throughout Part I or Part II of the trial; subjects who were switched to that dose after initial treatment with one of the other DOR doses are not included.

2.1.2.1 Demographic and Prognostic Characteristics at Baseline

The DOR-combined group (consisting of subjects who received any dose of DOR, N=232) and the EFV group (N=108) were generally well balanced with respect to demographic and prognostic characteristics at baseline [Ref. 5.3.5.1: P007V01MK1439: 10.5]. Most subjects were male (92.2% and 93.5%, respectively) and white (73.7% and 80.6%, respectively). The median age was 35 years and 34 years, respectively, with 4 subjects and 0 subjects aged 65 years or older in the DOR and EFV groups, respectively. Mean baseline $CD4^+$ T-cell counts were 432 and 448 cells/mm^3 in the DOR-combined and EFV groups, respectively, and most subjects (59.9% and 67.6%, respectively) had baseline $CD4^+$ T-cell counts >350 cells/mm^3. The mean baseline plasma HIV-1 RNA value was 4.6 $\log_{10}$ copies/mL in each group; the proportions of subjects with baseline HIV-1 RNA >100,000 copies/mL were 31.9% and 37.0% in the DOR-combined and EFV groups, respectively.

2.1.2.2 Antiretroviral Efficacy Summary: Week 24, Week 48 and Week 96

Antiretroviral Response at Week 24

Comparable efficacy was seen for all treatment groups in both Part I, comparing each dose of DOR and the DOR-combined group with EFV 600 mg, and Parts I/II combined, comparing the selected dose of DOR (100 mg) with EFV 600 mg, as detailed below. This result was seen regardless of whether the HIV-1 RNA threshold was <50 copies/mL, <40 copies/mL (the primary endpoint), or <200 copies/mL and regardless of the approach to missing data. Results presented below were calculated using the FDA snapshot approach.

Part I: The efficacy of each DOR dose was robust at Week 24 and comparable to that of EFV 600 mg: HIV-1 RNA <50 copies/mL was achieved by 76.2% to 82.9% of subjects who received any dose of DOR and by 69.0% of subjects who received EFV 600 mg [Table 2.7.3-trtmtnve48wk: 4]. Similarly, HIV-1 RNA <40 copies/mL was achieved by 71.4% to 80.5% of subjects who received any dose of DOR and by 64.3% of subjects who received EFV 600 mg [Table 2.7.3-trtmtnve48wk: 5].

Parts I/II combined: The efficacy of the selected dose of DOR 100 mg was robust and comparable to that of EFV 600 mg at Week 24: HIV-1 RNA <50 copies/mL was achieved by 76.9% of subjects who received DOR 100 mg (beginning on Day 1) and 77.8% of subjects

who received EFV 600 mg [Ref. 5.3.5.1: P007V01MK1439: Table 11-12]. Consistent with those results, 72.2% and 73.1% of subjects, respectively, achieved HIV-1 RNA <40 copies/mL [Ref. 5.3.5.1: P007V01MK1439: Table 11-2]. (Recall that results for the DOR 100-mg group refer only to subjects randomized to the 100-mg dose; subjects randomized to the 25-, 50-, or 200-mg doses of DOR were switched to the 100-mg dose between Weeks 36 and 72.)

Table 2.7.3-trtmtnve48wk: 4

P007: Proportion of Subjects with HIV-1 RNA <50 copies/mL at Week 24
Part I (Doravirine All Doses vs. Efavirenz)
Full Analysis Set

Missing Data Approach	Treatment	Proportion of Subjects With HIV-1 RNA <50 copies/mL		Difference in Percent Response [Doravirine minus Efavirenz][†] (95% CI)[††]
		n/N	% (95% CI)	
FDA Snapshot Approach	Doravirine 25 mg	32/40	80.0 (64.4, 90.9)	11.0 (-8.3, 29.5)
	Doravirine 50 mg	34/43	79.1 (64.0, 90.0)	9.9 (-8.9, 28.4)
	Doravirine 100 mg	32/42	76.2 (60.5, 87.9)	6.9 (-12.4, 25.8)
	Doravirine 200 mg	34/41	82.9 (67.9, 92.8)	13.7 (-5.0, 31.8)
	Doravirine Combined	132/166	79.5 (72.6, 85.4)	10.3 (-3.5, 26.5)
	Efavirenz 600 mg	29/42	69.0 (52.9, 82.4)	
Observed Failure (OF)	Doravirine 25 mg	32/37	86.5 (71.2, 95.5)	13.9 (-4.7, 31.8)
	Doravirine 50 mg	34/41	82.9 (67.9, 92.8)	10.3 (-8.0, 28.4)
	Doravirine 100 mg	32/41	78.0 (62.4, 89.4)	5.0 (-13.9, 23.9)
	Doravirine 200 mg	34/40	85.0 (70.2, 94.3)	12.1 (-6.0, 30.2)
	Doravirine Combined	132/159	83.0 (76.3, 88.5)	10.2 (-2.9, 26.4)
	Efavirenz 600 mg	29/40	72.5 (56.1, 85.4)	

[†] 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™.

Source: [Ref. 5.3.5.1: P007V01MK1439: Table 11-11]

Table 2.7.3-trtmtnve48wk: 5

P007: Proportion of Subjects with HIV-1 RNA <40 copies/mL at Week 24
Part I (Doravirine All Doses vs. Efavirenz)
Full Analysis Set

Missing Data Approach	Treatment	Proportion of Subjects With HIV-1 RNA <40 copies/mL		Difference in Percent Response [Doravirine minus Efavirenz][†]
		n/N	% (95% CI)	(95% CI)[††]
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)	
Observed Failure (OF)	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)	

[†] 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™.

Source: [Ref. 5.3.5.1: P007V01MK1439: Table 11-1]

Antiretroviral 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 at each HIV-1 RNA threshold (<40, <50, and <200 copies/mL) and with each approach to missing data. Results presented below were calculated using data from Parts I/II and the FDA snapshot approach. (Recall that results for the DOR 100-mg group refer only to subjects randomized to the 100-mg dose; subjects randomized to the 25-, 50-, or 200-mg doses of DOR were switched to the 100-mg dose between Weeks 36 and 72.)

- 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 [Ref. 5.3.5.1: P007V01MK1439: Table 11-13], while 77.8% and 78.7% of subjects, respectively, achieved HIV-1 RNA <40 copies/mL [Ref. 5.3.5.1: P007V01MK1439: Table 11-3]. Consistently durable antiretroviral efficacy was observed with the HIV-1 RNA thresholds of <40 [Ref. 5.3.5.1: P007V01MK1439: Figure 14.2-7] and <200 copies/mL [Ref. 5.3.5.1: P007V01MK1439: Figure 14.2-14].

- Week 96: 75.9% of subjects in both groups achieved HIV-1 RNA <50 copies/mL [Ref. 5.3.5.1: P007V01MK1439: Table 11-14], while 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 11-4], [Ref. 5.3.5.1: P007V01MK1439: Figure 14.2-27].

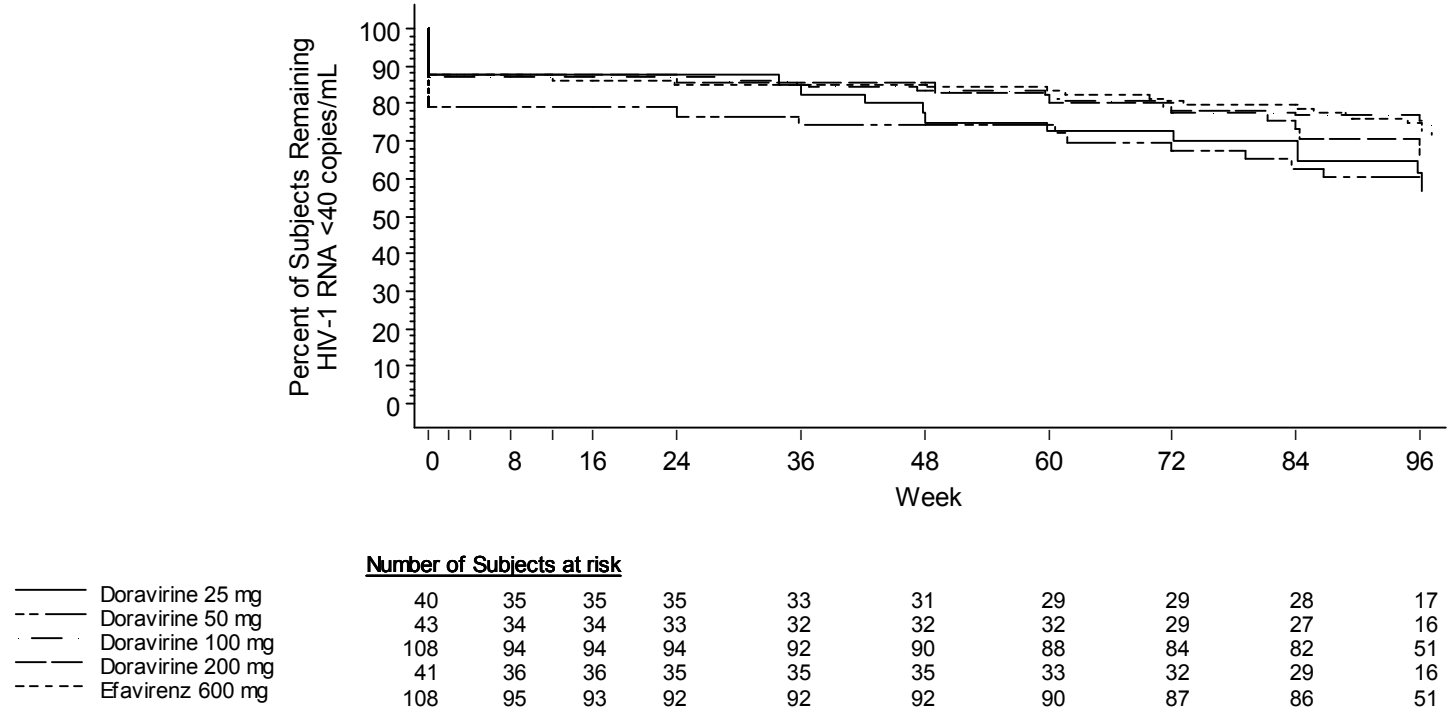
2.1.2.3 Time to Loss of Virologic Response

TLOVR was analyzed for each DOR dose group and the EFV group, in Parts I/II combined, using a threshold of 40 copies/mL HIV-1 RNA as well as a threshold of 200 copies/mL as specified by the protocol. The risk of loss-of-response was comparable in each of the DOR dose groups and the EFV group [Figure 2.7.3-trtmtnve48wk: 2]. (Recall that results for the DOR 100-mg group refer only to subjects randomized to the 100-mg dose; subjects randomized to the 25-, 50-, or 200-mg doses of DOR were switched to the 100-mg dose between Weeks 36 and 72.)

Comparable results were seen when the DOR-combined group was compared with the EFV group [Ref. 5.3.5.1: P007V01MK1439: Figure 14.2-16]. In addition, consistent results were seen (ie, comparable risk of loss-of-response in the DOR and EFV groups) regardless of whether the 40 or 200 copies/mL HIV-1 RNA threshold was used (comparing [Ref. 5.3.5.1: P007V01MK1439: Figure 14.2-16] and [Ref. 5.3.5.1: P007V01MK1439: Figure 14.2-19]). In the comparison between the DOR-combined and EFV groups using a threshold of 40 copies/mL, 31.5% of subjects (73/232) and 25.9% of subjects (28/108) experienced an event of loss of virologic response; log-rank test p=0.293 [Ref. 5.3.5.1: P007V01MK1439: Table 14.2-20]. Additional results are found in the study report [Ref. 5.3.5.1: P007V01MK1439: Table 14.2-21, Table 14.2-22, Table 14.2-23].

Figure 2.7.3-trtmtnve48wk: 2

P007: Kaplan-Meier Plot of Time-to-Loss-Of-Virologic-Response (TLOVR) by HIV-1 RNA ≥40 copies/mL
Parts I/II Combined (Doravirine 4 Doses vs. Efavirenz)
Full Analysis Set



Source: [P007V01MK1439: analysis-adtte]

C Confidential

2.1.2.4 Immunologic Efficacy Summary: Week 24, Week 48 and Week 96

At Week 24, the immunologic efficacy (assessed as change from baseline in $CD4^+$ T-cell count) of DOR was comparable to that of EFV 600 mg in both Part I and Parts I/II combined.

- Part I: mean $CD4^+$ T-cell counts in the DOR-combined and EFV groups increased by 135 and 121 cells/mm^3, respectively [Ref. 5.3.5.1: P007V01MK1439: Table 11-7];

- Parts I+II: mean $CD4^+$ T-cell counts in the DOR 100-mg and EFV groups increased by 152 and 146 cells/mm^3, respectively [Ref. 5.3.5.1: P007V01MK1439: Table 11-8].

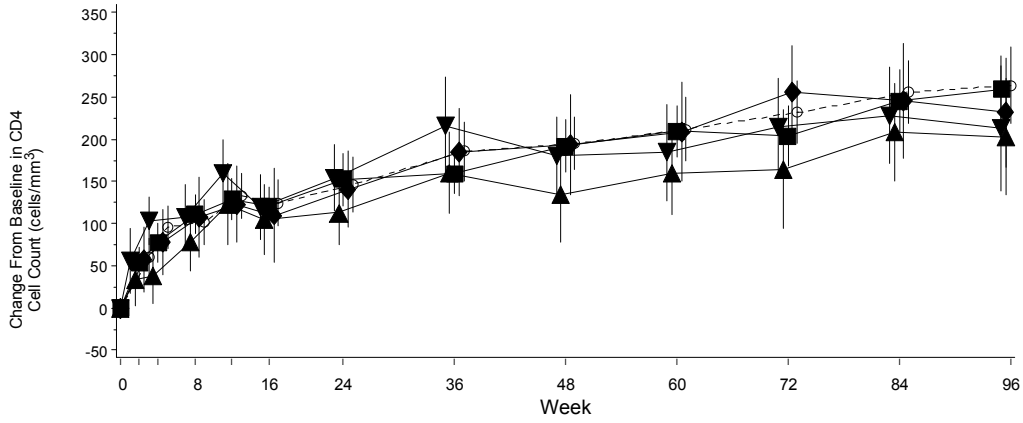
The mean change from baseline in $CD4^+$ T-cell counts for each DOR dose group increased through Week 36, with smaller increases through approximately Week 84; thereafter, no distinguishable changes were evident through Week 96 [Figure 2.7.3-trtmtnve48wk: 3]. This response pattern was comparable to that observed for EFV 600 mg. At both Week 48 and Week 96 (using data from Parts I+II), comparable levels of immunologic efficacy were seen for DOR 100 mg (ie, subjects randomized to receive DOR 100 mg) and EFV 600 mg [Ref. 5.3.5.1: P007V01MK1439: Table 11-9, Table 11-10].

- Week 48: mean $CD4^+$ T-cell counts in the DOR 100-mg and EFV groups increased by 192 and 195 cells/mm^3, respectively.

- Week 96: mean $CD4^+$ T-cell counts in the DOR 100-mg and EFV groups increased by 259 and 264 cells/mm^3, respectively.

Figure 2.7.3-trtmtnve48wk: 3

PN007: Change From Baseline in CD4 Cell Count (cells/mm^3) Over Time
Observed Failure Approach
Parts I/II Combined (Doravirine 4 Doses vs. Efavirenz)
Full Analysis Set



Number of Contributing Subjects										
Doravirine 25 mg	40	38	34	38	38	36	36	35	35	33
Doravirine 50 mg	43	42	41	41	39	38	38	36	36	32
Doravirine 100 mg	108	105	106	106	105	102	102	98	97	95
Doravirine 200 mg	41	41	37	40	39	39	39	39	37	36
Efavirenz 600 mg	108	101	99	101	100	100	99	97	95	93

Source: [P007V01MK1439: analysis-adcd4]

2.1.2.5 Protocol-Defined Virologic Failure and Evaluation of Viral Drug Resistance

Protocol-defined Virologic Failure (PDVF)

Genotypic and phenotypic resistance tests were carried out for HIV-1 isolates from subjects who met PDVF criteria and had HIV-1 RNA >400 copies/mL. Viral resistance to DOR and EFV, as well as to the background NRTIs FTC and TDF, was summarized.

PDVF criteria, based on an HIV-1 RNA threshold of 40 copies/mL [Sec. 2.7.3.1.4.1.3-trtmtnve48wk], were met by 43 subjects (18.5%) in the DOR-combined group (26 non-responders and 17 rebounders) and by 14 subjects (13.0%) in the EFV group (10 non-responders and 4 rebounders) through Week 96 [Ref. 5.3.5.1: P007V01MK1439: Table 14.2-37]. In P007 (unlike in P018 or P021), investigators were to decide whether or not a subject who met PDVF criteria would be withdrawn from the trial; this provided an opportunity to observe virologic response to continued treatment with study drug following PDVF. Approximately half of the non-responders at Week 24 in each treatment group achieved viral

suppression (HIV-1 RNA <40 copies/mL) at Week 48, and over half (16 of 26 in the DOR-combined group and 8 of 10 in the EFV group) did so at Week 96. This suggests that the stringent definition of PDVF in the P007 protocol was applied to subjects who were in fact responding to study therapy, but had not yet achieved full virologic suppression by Week 24.

Viral Drug Resistance

Of the 57 subjects with PDVF (43 in the DOR-combined group and 14 in the EFV group), samples from 18 subjects (15 and 3, respectively) met the viral load criterion for genotypic and phenotypic resistance testing. Of these 15 DOR-treated subjects, 13 had genotype results reported, and 14 had phenotype results reported, while all 3 subjects in the EFV group had both genotype and phenotype results reported.

HIV-1 from 3 of 232 subjects (1.3%) treated with any dose of DOR (2 in the 25-mg group and 1 in the 100-mg group) developed mutations associated with NNRTI resistance, with genotypic and phenotypic resistance to DOR noted in only 1 of these subjects (in the DOR 25-mg group). Isolates from 2 subjects in the DOR 25-mg group showed genotypic resistance (RT K101K/E, P236P/L in 1 subject and V106V/I, F227C in 1 subject); of these, only the V106V/I, F227C mutant was associated with phenotypic resistance (66-fold higher IC_{50} relative to wild-type virus for DOR). The remaining subject, in the DOR 100-mg group, had an isolate that showed mutations (E138E/G, V179D) previously associated with resistance to certain NNRTIs (including RPV and EFV); it is possible this subject had the NNRTI-resistant variants in minority HIV-1 populations that were not detected in the screening samples. Brief summaries of viral drug resistance in these subjects and detailed listings of resistance data for subjects in all treatment groups are provided in the CSR [Ref. 5.3.5.1: P007V01MK1439: 11.2].

HIV-1 from 2 of 108 subjects (1.9%) treated with EFV developed mutations associated with resistance to EFV. In one case, RT K101K/Q and G190S mutations were identified at the Week 60 visit (Day 433), with a >70.9-fold higher IC_{50} relative to wild-type virus for EFV and a 6.1-fold higher IC_{50} for DOR. In the other case, RT K103N and N348I were identified at Week 96, with a 13.0-fold higher IC_{50} for EFV (and no change in susceptibility to DOR). In both viral isolates, no genotypic or phenotypic resistance to FTC or tenofovir was noted.

2.1.2.6 Dose Selection for Phase 2 and 3

The DOR dose for additional Phase 2 and Phase 3 trials was selected based on the efficacy and safety data at Week 24 in P007. Because both efficacy and safety findings [Sec. 2.7.4] were comparable across all tested DOR doses (25, 50, 100 and 200 mg), the selection of the 100-mg dose was based on the following additional considerations (details in [Sec. 2.7.2.1.5.1]):

- As a CYP3A substrate, the 100-mg QD dose of DOR resulted in plasma concentrations sufficient to achieve efficacy, even when co-administered with drugs anticipated to decrease DOR exposure.

- The safety profile of DOR remained favorable in the presence of CYP3A inhibitors anticipated to increase DOR exposure.

- The 100-mg QD dose resulted in plasma concentrations predicted (based on in vitro data and modeling and simulation) to be efficacious against virus harboring several common HIV-1 mutations that confer resistance to other NNRTIs, specifically, RT K103N, Y181C, K103N/Y181C, and G190A.

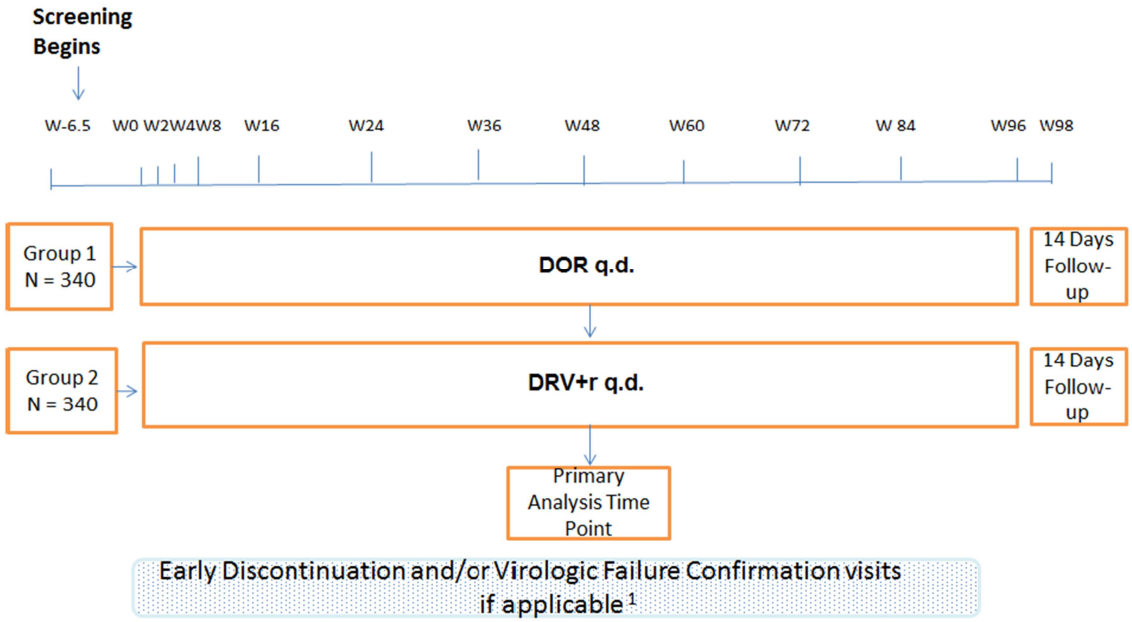
2.2 Protocol 018: Phase 3 Trial – Comparison With Darunavir+Ritonavir

2.2.1 Protocol 018 Study Design

P018 is a Phase 3, multicenter, double-blind, randomized, active-controlled trial in HIV-1-infected, treatment-naïve men and women, 18 years of age or older, with an HIV-1 RNA level of ≥1,000 copies/mL at screening. A total of 769 subjects were randomized to receive DOR 100 mg QD or ritonavir-boosted darunavir (DRV+r) 800 mg/100 mg QD, each in combination with NRTI therapy. One of two NRTI therapies was chosen by the investigator: FTC/TDF, supplied as TRUVADA (TDF 300 mg/FTC 200 mg), or ABC/3TC, supplied as either EPZICOM or KIVEXA (ABC 600 mg/3TC 300 mg). Subjects were stratified by HIV-1 RNA level at screening (≤ or >100,000 copies/mL) and investigator-chosen NRTI therapy. Subjects will receive blinded treatment for 96 weeks in the base study, and, if eligible, may choose to enter an optional 96-week study extension. No subject had completed the base study at the time of the database lock for the primary endpoint analysis (Week 48). The design of the base study is shown in [Figure 2.7.3-trtmtnve48wk: 4], and objectives relevant to the Week 48 timepoint are listed in [Table 2.7.3-trtmtnve48wk: 3].

Figure 2.7.3-trtmtnve48wk: 4

Protocol 018 Study Design



DOR = doravirine (MK-1439) 100 mg q.d ; DRV+r = darunavir (800 mg) boosted with ritonavir (100 mg); q.d = once daily

[1] Virologic failure or relapse is confirmed with 2 consecutive measurements of HIV-1RNA at least 1 week apart

2.2.2 Protocol 018 Key Efficacy Results

2.2.2.1 Demographic and Prognostic Characteristics at Baseline

The DOR and DRV+r treatment groups were generally well balanced with respect to demographic and prognostic characteristics at baseline [Ref. 5.3.5.1: P018V01MK1439: 10.5]. Most subjects were male (83.3% and 85.1% in the DOR and DRV+r groups, respectively) and white (73.1% in each group). The median age was 33 years and 34 years in the DOR and DRV+r groups, respectively; each group had 4 or fewer subjects aged 65 years or older. Baseline $CD4^+$ T-cell counts were >200 cells/mm^3 in most subjects: 89.0% and 82.5% in the DOR and DRV+r groups, respectively. Baseline mean plasma HIV-1 RNA was 4.4 $\log_{10}$ copies/mL in each group; the proportions of subjects with baseline HIV-1 RNA >100,000 copies/mL were 21.7% and 19.3% in the DOR and DRV+r groups, respectively. The background NRTI regimen for the majority of subjects in both groups was FTC/TDF (86.9% and 87.5% of subjects in the DOR and DRV+r groups, respectively).

2.2.2.2 Efficacy Summary at Week 48: Virologic and Immunologic Responses

Antiretroviral Efficacy at Week 48

The antiretroviral efficacy of DOR 100 mg at Week 48, as measured by the proportion of subjects with HIV-1 RNA <50 copies/mL, was non-inferior to that of DRV+r [Table 2.7.3-trtmtnve48wk: 6]. Using the FDA snapshot approach, 83.8% and 79.9% of subjects in the DOR and DRV+r groups, respectively, achieved HIV-1 RNA <50 copies/mL. The treatment difference (DOR – DRV+r) was 3.9% (95% confidence interval [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, was comparable to that of DRV+r. Specifically, 83.3% and 79.1% of subjects in the DOR and DRV+r groups, respectively, using the FDA snapshot approach, achieved HIV-1 RNA <40 copies/mL, with a treatment difference of 4.2% (95% CI: -1.4, 9.7).

Comparable antiretroviral efficacy results in the DOR and DRV+r groups were also seen with a threshold of <200 copies/mL.

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.

Immunologic Efficacy at Week 48

The immunologic efficacy of DOR 100 mg, as measured by the change from baseline to Week 48 in $CD4^+$ T-cell count (using the OF approach), was comparable to that of DRV+r: mean increases from baseline were 193 and 186 cells/mm^3, respectively [Table 2.7.3-trtmtnve48wk: 6].

Table 2.7.3-trtmtnve48wk: 6

P018: 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/mm3)	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]

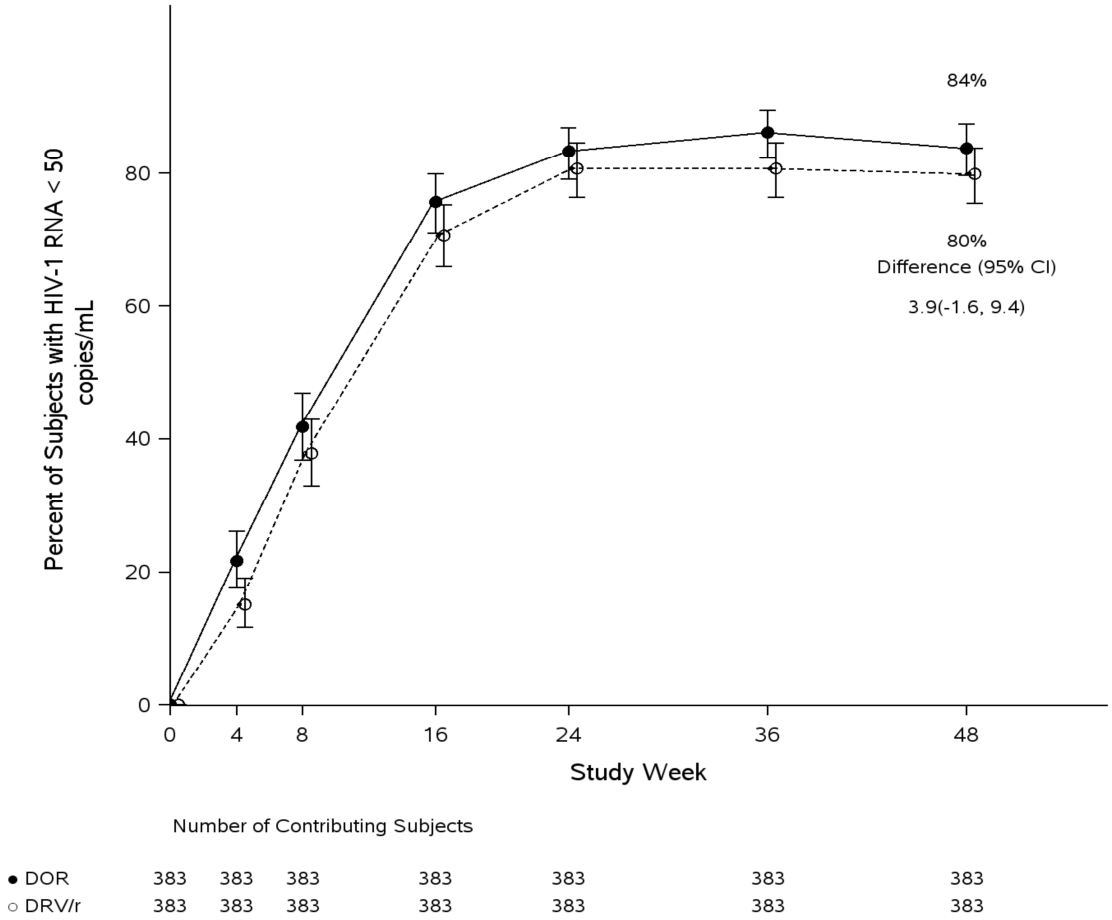
2.2.2.3 Antiretroviral Efficacy Through Week 48

The proportion of subjects in the DOR group who achieved HIV-1 RNA <50 copies/mL increased from baseline through Week 24, demonstrating a response that was robust and comparable to that of DRV+r. Proportions of subjects with HIV-1 RNA <50 copies/mL then remained generally consistent through Week 48, demonstrating the sustainability of the response in both treatment groups [Figure 2.7.3-trtmtnve48wk: 5]. Additional details are available in the CSR [Ref. 5.3.5.1: P018V01MK1439: 11.1.2.1].

Comparable antiretroviral efficacy over time in the DOR and DRV+r groups was also seen when HIV-1 RNA thresholds of <40 copies/mL and <200 copies/mL were used [Ref. 5.3.5.1: P018V01MK1439: 11.1.2.1].

Figure 2.7.3-trtmtnve48wk: 5

P018: Proportion of Subjects With HIV-1 RNA < 50 copies/mL Over Time
FDA Snapshot Approach

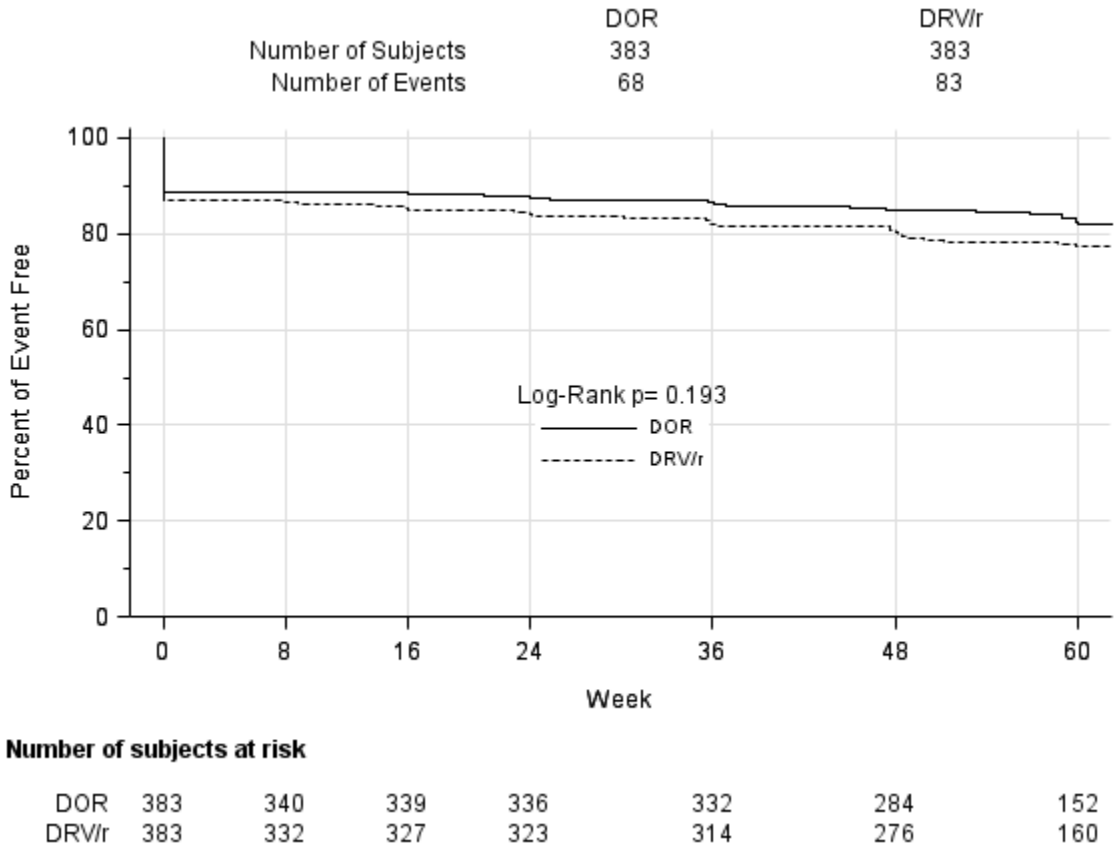


2.2.2.4 Time to Loss of Virologic Response (TLOVR)

Time to loss of virologic response (TLOVR), using an HIV-1 RNA threshold of 50 copies/mL, is presented in a Kaplan-Meier plot, including a non-multiplicity-adjusted p-value. The risk of loss-of-response was similar in the DOR and DRV+r groups through Week 48 and, for subjects with data past that timepoint, through Week 60 [Figure 2.7.3-trtmtnve48wk: 6]. In the DOR group, 17.8% of subjects (68/383) and 21.7% of subjects (83/383) had events of TLOVR; log-rank test p=0.193 [Ref. 5.3.5.1: P018V01MK1439: Table 14.2-6].

Figure 2.7.3-trtmtnve48wk: 6

P018: Kaplan-Meier Plot for Time to Loss of Virologic Response



Number of subjects at risk

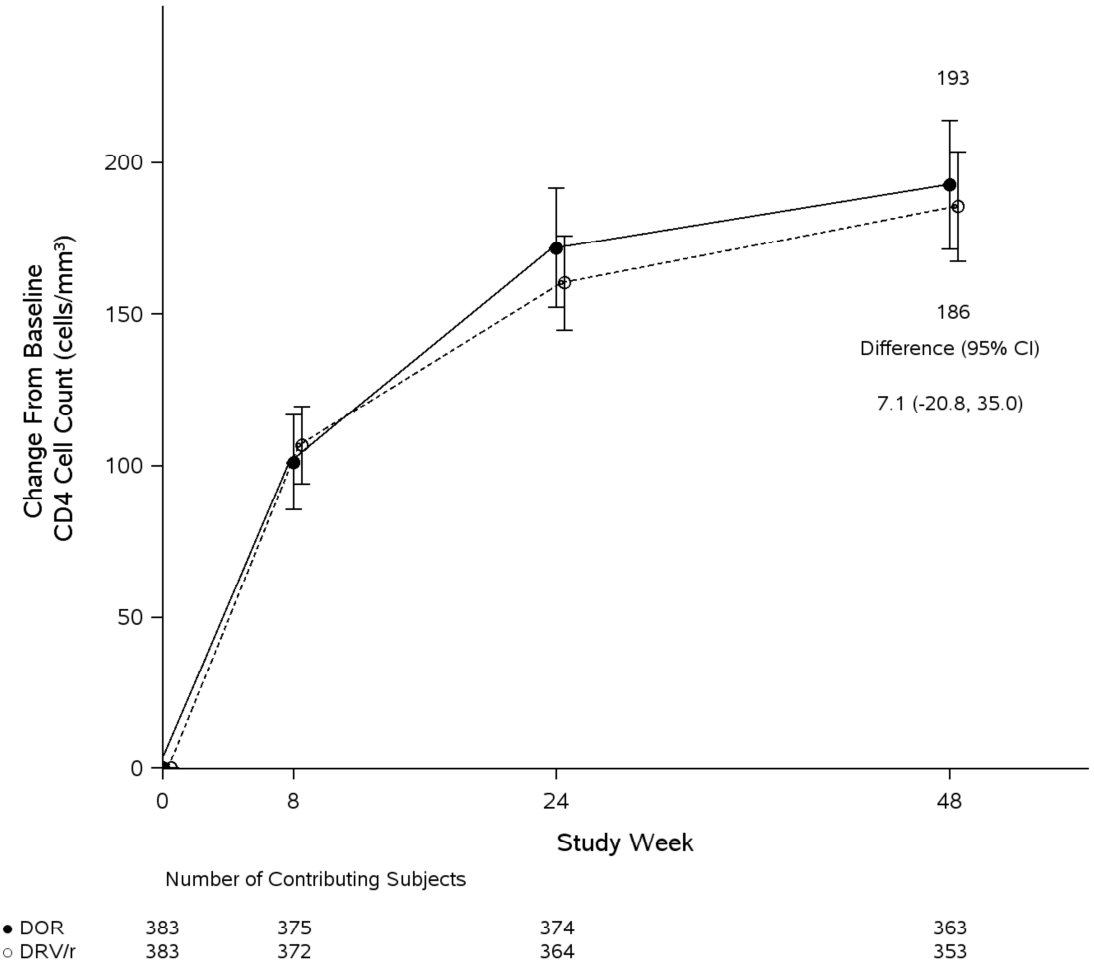
DOR	383	340	339	336	332	284	152
DRV/r	383	332	327	323	314	276	160

2.2.2.5 Immunologic Response Through Week 48

The immunologic response to DOR 100 mg and to DRV+r at Week 48 was presented above [Sec. 2.7.3.2.2.2.2-trtmtnve48wk] . The mean change from baseline in $CD4^+$ T-cell counts among subjects in both the DOR and DRV+r groups increased rapidly through Week 8, with further increases through Week 48 [Figure 2.7.3-trtmtnve48wk: 7].

Figure 2.7.3-trtmtnve48wk: 7

P018: Change From Baseline in $CD4^+$ T-Cell Count (cells/mm³) Over Time
Observed Failure Approach



2.2.2.6 Protocol-Defined Virologic Failure (PDVF) and Development of Viral Drug Resistance Through Week 48

Numbers of subjects with PDVF (with subjects classified as rebounders or non-responders) are summarized below; the majority of subjects in both the DOR and DRV+r groups who met PDVF criteria were rebounders. For subjects who were required to discontinue study drug due to PDVF and for subjects who discontinued for other reasons (and had HIV-1 RNA >400 copies/mL at the PDVF confirmation or discontinuation visit), details of genotypic and phenotypic assessments of viral drug resistance are summarized below; further details on resistance data are provided in the study report [Ref. 5.3.5.1: P018V01MK1439: 11.1.4.2].

Subjects With Protocol-Defined Virologic Failure (PDVF)

Through Week 48, rates of PDVF were low and comparable in the DOR and DRV+r treatment groups: 19 subjects (4.9%) and 24 subjects (6.3%), respectively. The majority of subjects with PDVF in each treatment group were rebounders who had initially responded to treatment (17 subjects [4.4%] and 19 subjects [5.0%], respectively), while few were non-responders (2 subjects [0.5%] and 5 subjects [1.3%], respectively) [Table 2.7.3-trtmtnve48wk: 7].

More than half the subjects who met either rebound or non-response PDVF criteria in each treatment group had HIV-1 RNA <200 copies/mL at the time of virologic failure confirmation (12/19 [63%] in the DOR group and 14/24 [58%] in the DRV+r group). In the majority of subjects who met the rebound definition of PDVF in both treatment groups, HIV-1 RNA levels decreased between the viral failure visit and the viral failure confirmation visit [Ref. 5.3.5.1: P018V01MK1439: 16.2.6.1].

Table 2.7.3-trtmtnve48wk: 7

P018: Number of Subjects with Protocol Defined Virologic Failure (Weeks 0-48)

	Doravirine 100 mg QD N=(383) n (%)			Darunavir/ritonavir 800/100 mg QD N=(383) n (%)		
	Confirmation HIV-1 RNA ≥50 and ≤200 copies/mL	Confirmation HIV-1 RNA >200 copies/mL	Total	Confirmation HIV-1 RNA ≥50 and ≤200 copies/mL	Confirmation HIV-1 RNA >200 copies/mL	Total
Virologic Failure (confirmed)† by Week 24						
Non-Responder	0 (0.0)	1 (0.3)	1 (0.3)	0 (0.0)	2 (0.5)	2 (0.5)
Rebounder	7 (1.8)	2 (0.5)	9 (2.3)	4 (1.0)	2 (0.5)	6 (1.6)
Virologic Failure (confirmed)† by Week 36						
Non-Responder	0 (0.0)	1 (0.3)	1 (0.3)	0 (0.0)	3 (0.8)	3 (0.8)
Rebounder	9 (2.3)	4 (1.0)	13 (3.4)	10 (2.6)	4 (1.0)	14 (3.7)
Virologic Failure (confirmed)† by Week 48						
Non-Responder	0 (0.0)	2 (0.5)	2 (0.5)	1 (0.3)	4 (1.0)	5 (1.3)
Rebounder	12 (3.1)	5 (1.3)	17 (4.4)	13 (3.4)	6 (1.6)	19 (5.0)

† Protocol defined virologic failure (PDVF) for this study is defined as one of the following: 1) Rebounder: Confirmed (two consecutive measures at least one week apart) HIV-1 RNA ≥ 50 copies/mL after initial response of HIV-1 RNA <50 copies/mL at any time during the study; Or 2) Non responder: Confirmed (two consecutive measures at least one week apart) HIV -1 RNA ≥ 200 copies/mL at Week 24 or Week 36; OR Confirmed (two consecutive measures at least one week apart) HIV-1 RNA ≥ 50 copies/mL at Week 48.

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; advf]

C Confidential

Viral Drug Resistance in Subjects With PDVF

Of the 19 subjects in the DOR group who met criteria for PDVF, 7 had successful genotype testing and 6 had successful phenotype testing; of the 24 subjects in the DRV+r group, 8 had successful testing for both genotype and phenotype. Detailed listings by subject are found in the CSR [Ref. 5.3.5.1: P018V01MK1439: 16.2.6].

No HIV-1 genotypic mutation known to be associated with resistance to currently licensed NNRTIs or to DOR (although its resistance profile has yet to be fully defined) was identified among the 7 DOR-treated subjects with PDVF and successfully tested viral isolates, and no phenotypic resistance to DOR was observed.

No HIV-1 genotypic primary mutation associated with DRV resistance was identified among the 8 DRV+r-treated subjects with PDVF and successfully tested viral isolates. While secondary polymorphic PI resistance mutations were seen in viral isolates from 3 subjects, no decrease in phenotypic susceptibility to DRV was observed.

Resistance to each of the NRTIs administered was also summarized. Briefly, no genotypic resistance or decrease in phenotypic susceptibility to FTC, 3TC, TDF or ABC was seen in either the DOR or DRV+r group.

Viral Drug Resistance in Subjects Who Discontinued for Reasons Other Than PDVF

Viral isolates from subjects who discontinued from study treatment for reasons other than meeting PDVF criteria (and who had HIV-1 RNA >400 copies/mL at the discontinuation visit) were also assessed for genotypic and phenotypic drug resistance. Of the 40 subjects in the DOR group and the 53 subjects in the DRV+r group, who discontinued for reasons other than PDVF, 2 and 3 subjects, respectively, had resistance testing successfully performed.

Descriptions of resistance data for each of the 2 DOR-treated subjects, as well as detailed listings of resistance data, by subject, for both treatment groups, are found in the CSR [Ref. 5.3.5.1: P018V01MK1439: 11.1.4.2.2], [Ref. 5.3.5.1: P018V01MK1439: 16.2.6]. Among subjects treated with DRV+r who discontinued for reasons other than meeting PDVF criteria, no primary genotypic resistance mutation and no phenotypic resistance to DRV or to the NRTI components was identified.

2.2.2.7 Efficacy in Subgroups by Demographic and Prognostic Factors

When efficacy in P018 at Week 48 was assessed *across* treatment groups by various baseline demographic and prognostic factors, specifically age, gender, region, race and ethnicity, screening and baseline HIV-1 RNA (≤ or >100,000 copies/mL), baseline $CD4^+$ T-cell count, chronic hepatitis B/C status, and viral subtype, comparable efficacy was seen in the DOR and DRV+r groups for each of the sub-populations defined by these factors [Ref. 5.3.5.1: P018V01MK1439: Table 11-7].

Within each treatment group, lower efficacy was observed among subjects 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. For

example, when comparing subgroups having baseline $CD4^+$ T-cell counts >50 and ≤200 cells/mm^3 and >200 cells/mm^3, the proportions of subjects in the DOR group who achieved HIV-1 RNA <50 copies/mL at Week 48 was 82.9% and 88.9%, respectively, while for the DRV+r group, it was 89.1% and 74.4%, respectively.

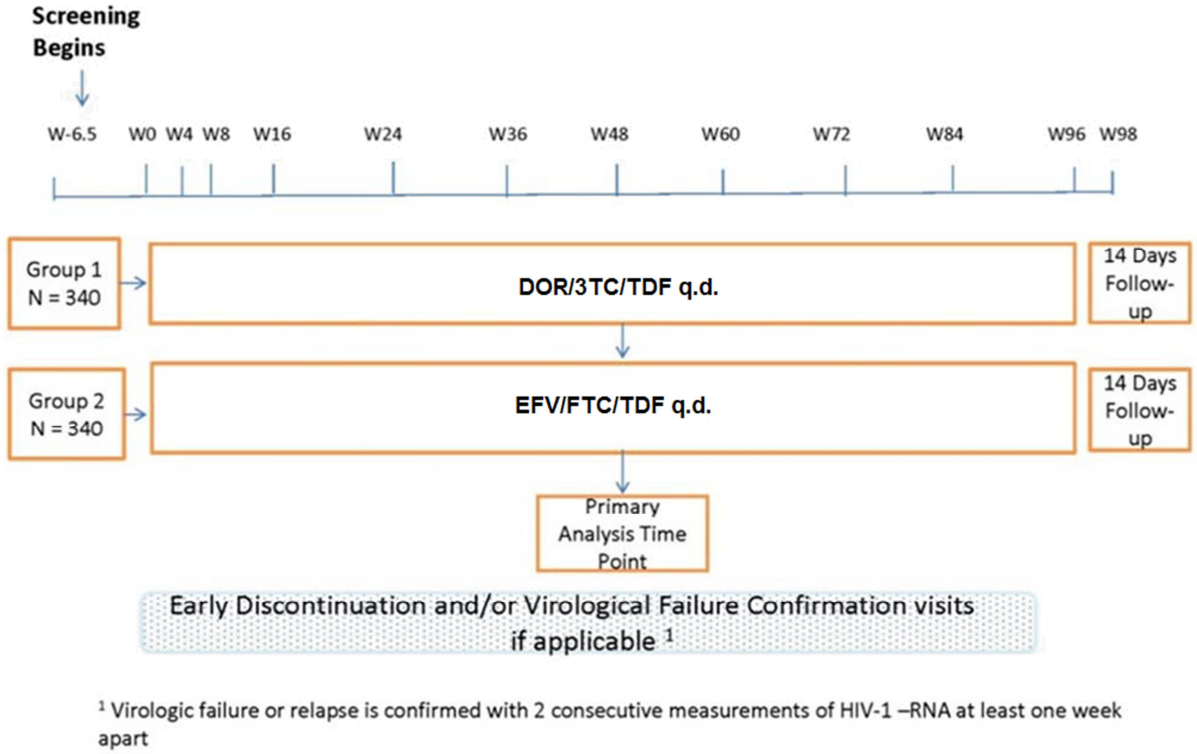
2.3 Protocol 021: Phase 3 Trial – Comparison With EFV/TDF/FTC

2.3.1 Protocol 021 Study Design

P021 is a Phase 3, multicenter, double-blind, randomized, active-controlled trial in HIV-1-infected, treatment-naïve men and women, 18 years of age or older, with an HIV-1 RNA level of ≥1,000 copies/mL at screening. A total of 734 subjects were stratified by screening HIV-1 RNA level (≤ or > 100,000 copies/mL) and hepatitis B and/or C co-infection status (yes or no) and randomized within each of the 4 strata to DOR/3TC/TDF or EFV/FTC/TDF (supplied as ATRIPLA). Subjects will receive blinded treatment for 96 weeks in the base study, and, if eligible, may choose to enter an optional 96-week study extension. No subject had completed the 96-week base study by the time of the database lock for the primary endpoint analysis (Week 48). The design of the base study is shown in [Figure 2.7.3-trtmtnve48wk: 8], and objectives relevant to the Week 48 timepoint are listed in [Table 2.7.3-trtmtnve48wk: 3].

Figure 2.7.3-trtmtnve48wk: 8

Protocol 021 Study Design



[1] Virologic failure or relapse is confirmed with 2 consecutive measurements of HIV-1 –RNA at least one week apart

2.3.2 Protocol 021 Key Efficacy Results

2.3.2.1 Demographic and Prognostic Characteristics at Baseline

The DOR/3TC/TDF and EFV/FTC/TDF treatment groups were generally well balanced with respect to demographic and prognostic characteristics at baseline [Ref. 5.3.5.1: P021V01MK1439A: 10.5]. Overall, the subject population comprised 616 (84.6%) men and 112 (15.4%) women, was predominantly white (47.7%), and had a median age of 31 years (range: 18 to 70 years). Within the DOR/3TC/TDF and EFV/FTC/TDF groups, median ages were 32 years and 30 years, respectively; each group had 2 subjects aged 65 years or older.

Baseline $CD4^+$ T-cell counts were >200 cells/mm^3 for most subjects in the DOR/3TC/TDF (87.9%) and EFV/FTC/TDF (87.4%) groups. Similarly, baseline mean plasma HIV-1 RNA levels were comparable for subjects in the DOR/3TC/TDF (4.4 $\log_{10}$ copies/mL) and EFV/FTC/TDF (4.5 $\log_{10}$ copies/mL) groups; the proportions of subjects with baseline HIV-1 RNA >100,000 copies/mL were 20.1% and 22.5%, respectively.

2.3.2.2 Efficacy Summary at Week 48: Virologic and Immunologic Responses

Antiretroviral Efficacy at Week 48

The antiretroviral efficacy of DOR/3TC/TDF at Week 48, as measured by the proportion of subjects with HIV-1 RNA <50 copies/mL, was non-inferior to that of EFV/FTC/TDF [Table 2.7.3-trtmtnve48wk: 8].

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 of 3.5% (95% CI: -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 threshold of HIV-1 RNA <40 copies/mL (a secondary endpoint), DOR/3TC/TDF continued to demonstrate antiretroviral efficacy comparable to that of EFV/FTC/TDF at Week 48. Specifically, 83.3% and 79.7% of subjects in the DOR/3TC/TDF and EFV/FTC/TDF groups, respectively, achieved HIV-1 RNA <40 copies/mL using the FDA snapshot approach; the treatment difference was 4.1% (95% CI: -1.5, 9.7).

Comparable 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 (86.0% and 82.7%, respectively; difference: 3.3% [95% CI: -2.0, 8.6]) at Week 48.

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 results are consistent with the results for the FAS population [Ref. 5.3.5.1: P021V01MK1439A: Table 14.2-2].

Immunologic Efficacy at Week 48

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; mean increases from baseline were 198 and 188 cells/mm^3 among subjects in the DOR/3TC/TDF and EFV/FTC/TDF groups, respectively [Table 2.7.3-trtmtnve48wk: 8].

Table 2.7.3-trtmtnve48wk: 8

PN021: 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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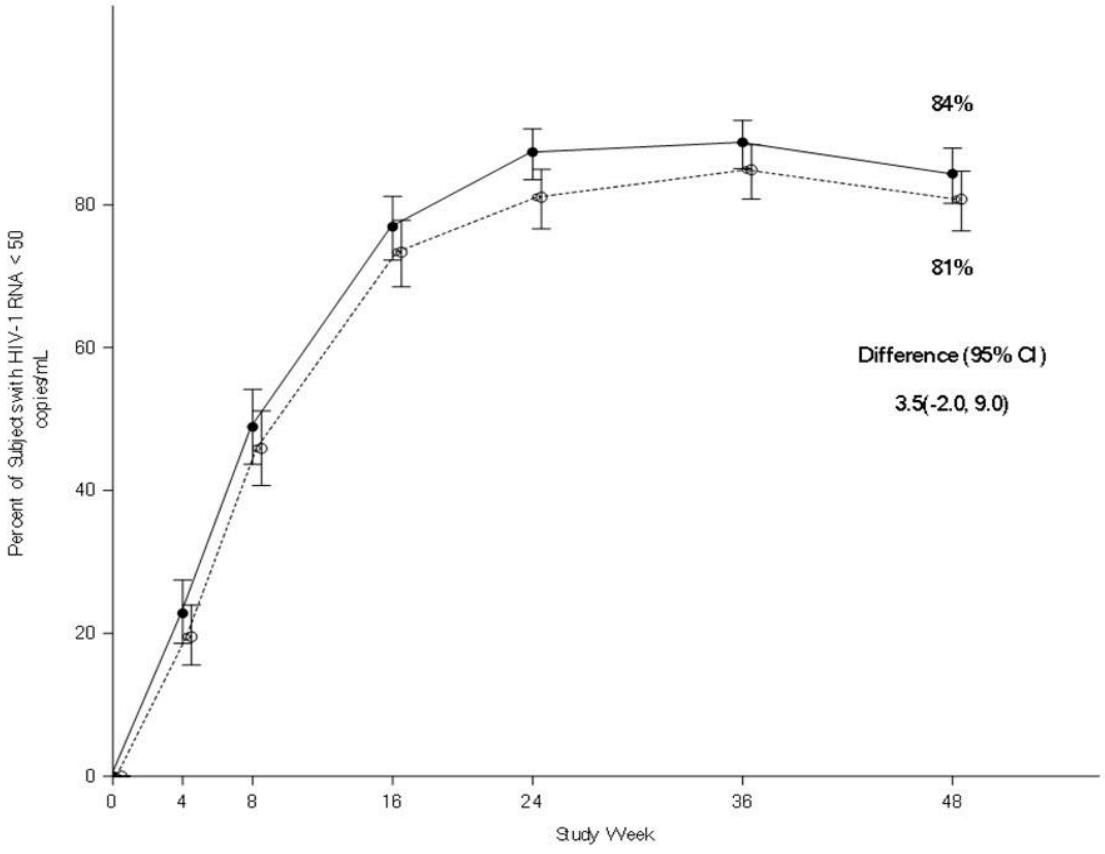
2.3.2.3 Antiretroviral Efficacy Through Week 48

The proportion of subjects in the DOR/3TC/TDF group who achieved HIV-1 RNA <50 copies/mL increased from baseline through Week 24, demonstrating a response that was robust and comparable to that of EFV/FTC/TDF. Thereafter, the proportions of subjects with HIV-1 RNA <50 copies/mL remained consistent through Week 48, demonstrating the sustainability of the response in both treatment groups [Figure 2.7.3-trtmtnve48wk: 9].

Comparable antiretroviral efficacy over time was seen in the 2 treatment groups when HIV-1 RNA thresholds of <40 copies/mL and <200 copies/mL were used [Ref. 5.3.5.1: P021V01MK1439A: 11.1.2.1].

Figure 2.7.3-trtmtnve48wk: 9

PN021: Proportion of Subjects With HIV-1 RNA < 50 copies/mL Over Time
FDA Snapshot Approach



Number of Contributing Subjects

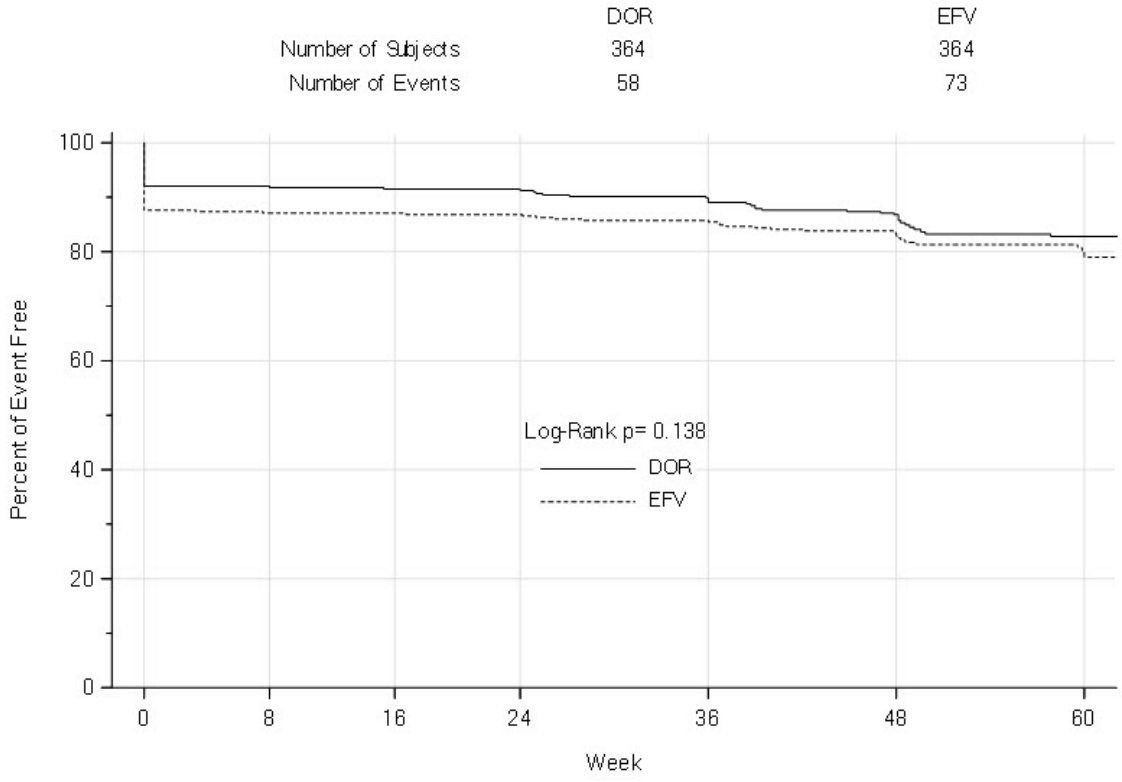
• DOR	364	364	364	364	364	364	364
○ EFV	364	364	364	364	364	364	364

2.3.2.4 Time to Loss of Virologic Response (TLOVR)

TLOVR – using an HIV-1 RNA threshold of 50 copies/mL – was assessed by Kaplan-Meier product-limit estimates and by the log-rank test (non-multiplicity-adjusted p-value) and Cox models. The risk of loss-of-response was comparable in the DOR/3TC/TDF and EFV/FTC/TDF treatment groups through Week 48 and, for subjects with data past that timepoint, through Week 60 [Figure 2.7.3-trtmtnve48wk: 10]. In the DOR/3TC/TDF and EFV/FTC/TDF groups, using a threshold of 50 copies/mL, 15.9% of subjects (58/364) and 20.1% of subjects (73/364) experienced an event of loss of virologic response; log-rank test p=0.138 [Ref. 5.3.5.1: P021V01MK1439A: Table 14.2-7].

Figure 2.7.3-trtmtnve48wk: 10

PN021: Kaplan-Meier Plot for Time to Loss of Virologic Response



Number of subjects at risk

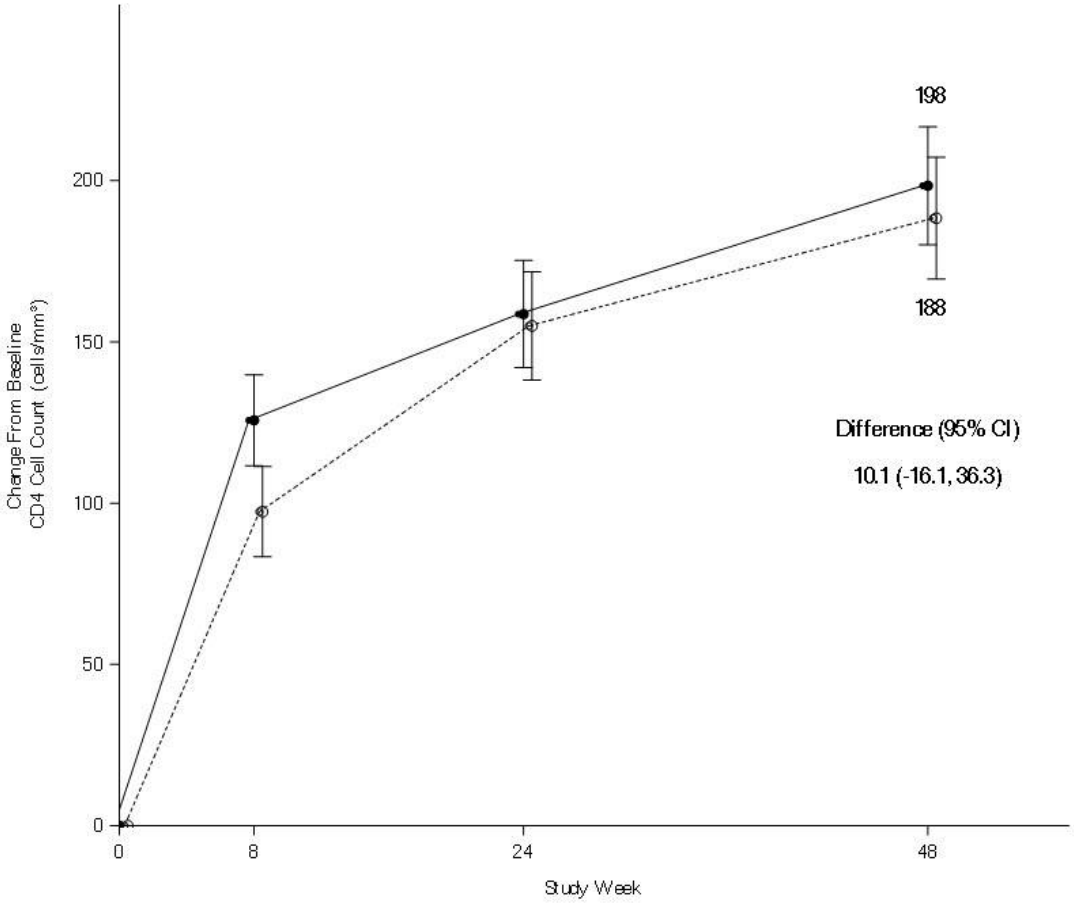
DOR	364	335	333	333	327	275	153
EFV	364	317	317	316	312	265	136

2.3.2.5 Immunologic Response Through Week 48

$CD4^+$ T-cell counts increased rapidly through Week 8, where an observed difference between treatment groups was noted, with subsequent increases through Week 48 [Figure 2.7.3-trtmtnve48wk: 11]. At Weeks 24 and 48, increases from baseline were comparable in the two treatment groups.

Figure 2.7.3-trtmtnve48wk: 11

P021: Change From Baseline in $CD4^+$ T-Cell Count (cells/mm³) Over Time
Observed Failure Approach



Number of Contributing Subjects

● DOR	364	359	357	344
○ EFV	364	347	338	329

2.3.2.6 Protocol-Defined Virologic Failure and Evaluation of Viral Drug Resistance

Numbers of subjects with PDVF (with subjects classified as rebounders or non-responders) are summarized below; the majority of subjects in both the DOR/3TC/TDF group and EFV/FTC/TDF group who met PDVF criteria were rebounders (16 of 22 and 10 of 14 subjects, respectively). For subjects who were required to discontinue study drug due to PDVF and for subjects who discontinued for other reasons (and had HIV-1 RNA >400 copies/mL at the PDVF confirmation or discontinuation visit), details of genotypic and phenotypic assessments of viral drug resistance are summarized below; further details are provided in the study report [Ref. 5.3.5.1: P021V01MK1439A: 11.1.4].

Subjects With Protocol-Defined Virologic Failure (PDVF)

Through Week 48, rates of PDVF were low and comparable in the DOR/3TC/TDF (6.0%; 22 subjects) and EFV/FTC/TDF (3.8%; 14 subjects) treatment groups. The majority of subjects with PDVF in each treatment group (DOR/3TC/TDF; EFV/FTC/TDF) were rebounders who had initially responded to treatment (16 subjects [4.4%]; 10 subjects [2.7%]); few subjects were non-responders (6 subjects [1.6%]; 4 subjects [1.1%]) [Table 2.7.3-trtmtnve48wk: 9].

All subjects who met the non-response PDVF criteria (6 of 6 in the DOR/3TC/TDF group; 4 of 4 in the EFV/FTC/TDF group) had HIV-1 RNA >200 copies/mL at the time of virologic failure confirmation [Ref. 5.3.5.1: P021V01MK1439A: Table 11-10]. In both groups, the majority of subjects who met the rebound definition of PDVF had HIV-1 RNA levels that decreased between the viral failure visit and the viral failure confirmation visit.

Table 2.7.3-trtmtnve48wk: 9

P021: Number of Subjects with Protocol Defined Virologic Failure (Weeks 0-48)

	DOR/3TC/TDF QD N=(364) n (%)			EFV/FTC/TDF QD N=(364) n (%)		
	Confirmation HIV-1 RNA ≥50 and ≤200 copies/mL	Confirmation HIV-1 RNA >200 copies/mL	Total	Confirmation HIV-1 RNA ≥50 and ≤200 copies/mL	Confirmation HIV-1 RNA >200 copies/mL	Total
Virologic Failure (confirmed)† by Week 24						
Non-Responder	0 (0.0)	5 (1.4)	5 (1.4)	0 (0.0)	4 (1.1)	4 (1.1)
Rebounder	3 (0.8)	2 (0.5)	5 (1.4)	1 (0.3)	3 (0.8)	4 (1.1)
Virologic Failure (confirmed)† by Week 36						
Non-Responder	0 (0.0)	6 (1.6)	6 (1.6)	0 (0.0)	4 (1.1)	4 (1.1)
Rebounder	5 (1.4)	3 (0.8)	8 (2.2)	3 (0.8)	3 (0.8)	6 (1.6)
Virologic Failure (confirmed)† by Week 48						
Non-Responder	0 (0.0)	6 (1.6)	6 (1.6)	0 (0.0)	4 (1.1)	4 (1.1)
Rebounder	10 (2.7)	6 (1.6)	16 (4.4)	4 (1.1)	6 (1.6)	10 (2.7)

† Protocol defined virologic failure (PDVF) for this study is defined as one of the following: 1) Rebounder: Confirmed (two consecutive measures at least one week apart) HIV-1 RNA ≥ 50 copies/mL after initial response of HIV-1 RNA <50 copies/mL at any time during the study; Or 2) Non responder: Confirmed (two consecutive measures at least one week apart) HIV -1 RNA ≥ 200 copies/mL at Week 24 or Week 36; OR Confirmed (two consecutive measures at least one week apart) HIV-1 RNA ≥ 50 copies/mL at Week 48.

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; advf]

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Viral Drug Resistance in Subjects With PDVF

Of the 22 subjects in the DOR/3TC/TDF group who met PDVF criteria, results from viral drug resistance testing (both genotyping and phenotyping) are available for 13 subjects. Of the 14 subjects in the EFV/FTC/TDF group who met PDVF criteria, results from viral drug resistance testing are available for 10 subjects for genotyping and for 9 of those subjects for phenotyping. Detailed listings by subject, for both treatment groups, are found in the CSR [Ref. 5.3.5.1: P021V01MK1439A: 16.2.6.1].

Among subjects in the DOR/3TC/TDF group with PDVF, genotypic mutations associated with DOR resistance were identified in viral isolates from 7 subjects, with phenotypic resistance to DOR identified in 6 of these subjects. Phenotypic resistance to EFV was also demonstrated in each of these 6 subjects. Genotypic and phenotypic resistance to the NRTI 3TC was seen in 5 of these subjects; none of these subjects' isolates had phenotypic resistance to tenofovir except for a single case of partial susceptibility to tenofovir. None of the genotypic mutations noted below were present at baseline, and no phenotypic resistance to any study drug was seen at baseline except as noted (ie, IC_{50} relative to wild-type virus <2.0 for both DOR and EFV and <1.5 for the NRTIs FTC, tenofovir, 3TC). Brief summaries of viral drug resistance in these subjects are found in the study report [Ref. 5.3.5.1: P021V01MK1439A: 11.1.4.2.1.1].

Among subjects in the EFV/FTC/TDF group with PDVF, genotypic mutations associated with viral EFV resistance were seen in 9 subjects, with phenotypic resistance to EFV observed in all 8 of the subjects for whom phenotyping results were available (phenotyping failed in 1 subject). In the majority (6 of 8) of these EFV-treated subjects, no phenotypic resistance to DOR was demonstrated; the K103N mutation (alone or in combination with E138E/G or V108V/I+T369T/A/I/V) was observed in 5 of 5 cases of genotypic and phenotypic resistance to EFV and no phenotypic resistance to DOR. In 4 of these subjects, genotypic and phenotypic resistance to FTC was seen; none of these subjects' isolates demonstrated phenotypic resistance to tenofovir. Additional details are found in [Ref. 5.3.5.1: P021V01MK1439A: 11.1.4.2.1.2].

Viral Drug Resistance in Subjects Who Discontinued for Reasons Other Than PDVF

Viral isolates from subjects who discontinued from study treatment for reasons other than meeting PDVF criteria (and who had HIV-1 RNA >400 copies/mL at the discontinuation visit) were also assessed for genotypic and phenotypic drug resistance. Of the 35 subjects in the DOR/3TC/TDF group who discontinued without meeting criteria for PDVF, 9 subjects had results from resistance testing available for both genotyping and phenotyping; of the 50 subjects in the EFV/FTC/TDF group who did so, 13 had results reported for genotyping and 12 of those subjects also had results reported for phenotyping.

None of the 9 DOR/3TC/TDF-treated subjects with results available had HIV-1 with a genotypic resistance mutation or phenotypic resistance to DOR.

Five of the 13 EFV/FTC/TDF-treated subjects with results available had virus with a genetic mutation associated with EFV resistance, although 2 had mutations (either T369T/I or

K101Q) that did not alone confer genotypic resistance to EFV, and did not have phenotypic resistance to EFV. Among the 3 EFV/FTC/TDF-treated subjects with phenotypic resistance to EFV, the mutations identified were RT K103N alone in 2 cases and K101K/N+P225P/H in the third.. HIV-1 from one of these subjects was also identified by the central lab as phenotypically resistant to DOR based on a 2.9-fold higher IC_{50} relative to wild-type virus; however, based on the lack of known genotypic mutations to DOR, minimal change in IC_{50} from the baseline value (1.7-fold), and insufficient clinical data to define a clinical cutoff for DOR phenotypic resistance, it is considered that this subject did not develop resistance to DOR.

Detailed listings by subject are found in the CSR [Ref. 5.3.5.1: P021V01MK1439A: 16.2.6.4; 16.2.6.5].

2.3.2.7 Efficacy in Subgroups by Demographic and Prognostic Factors

Efficacy at Week 48 (proportions of subjects with HIV-1 RNA <50 copies/mL) was assessed by various baseline demographic and prognostic factors – age, gender, region, race/ethnicity, screening/baseline HIV-1 RNA (≤ or >100,000 copies/mL), baseline $CD4^+$ T-cell count, chronic hepatitis B/C status, and viral subtype). Comparable results (based on 95% CIs around the differences between treatment groups that include 0) were observed in the DOR/3TC/TDF and the EFV/FTC/TDF treatment groups across most of the subgroups [Ref. 5.3.5.1: P021V01MK1439A: Table 11-7]. While the 95% CIs for the differences in response between treatment groups for subgroups of subjects aged ≤ or > median age (31 yrs) excluded 0, there is no biological explanation for this observation.

Of note, among subjects with a high baseline HIV-1 RNA level (>100,000 copies/mL), comparable proportions of subjects achieved HIV-1 RNA <50 copies/mL at Week 48 (81.2% and 80.8% for the DOR/3TC/TDF and EFV/FTC/TDF groups, respectively). Among subjects with baseline $CD4^+$ T-cell counts ≤50 cells/mm^3, the proportions of subjects who achieved HIV-RNA <50 copies/mL at Week 48 were comparable 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 (although the 95% CI excluded 0) achieved HIV-RNA <50 copies/mL at Week 48 (70.6% and 88.2% [95% CI: -37.1, 1.9]), although the numbers of subjects in each of these baseline-$CD4^+$ subgroups were too small to be clinically meaningful.

3 COMPARISON AND ANALYSES OF RESULTS ACROSS STUDIES

This section provides integrated data and analyses from the pivotal Phase 3 trials, P018 and P021, in which a pooled DOR group (referred to as the DOR Regimen group) is compared with the DRV+r group from P018 and with the EFV/FTC/TDF group from P021. Results and analyses from the Phase 2b trial, P007, are presented as supportive findings that demonstrate the durability of the efficacy response [Sec. 2.7.3.2.1.2-trtmtnve48wk] and are referred to below where relevant.

The rationale behind the pooling strategy is described in [Sec. 2.7.3.3.1-trtmtnve48wk], a definition of the analysis population and data summarizing subject disposition and baseline

demographic and prognostic factors are found in [Sec. 2.7.3.3.2-trtmtnve48wk], the efficacy results for the integrated analysis are found in [Sec. 2.7.3.3.3-trtmtnve48wk], and efficacy results for subpopulations defined by various demographic and prognostic characteristics are found in [Sec. 2.7.3.3.4-trtmtnve48wk].

3.1 Rationale for Pooling Strategy for Efficacy Analyses

The two Phase 3 trials, P018 and P021, are similar in design and have the same efficacy endpoints, definition of PDVF, and approach to handling subjects with PDVF, thus justifying the pooling of their data, as described in the Integrated Statistical Analysis Plan [Ref. 5.3.5.3: 04LVBJ].

P007 data were not pooled with those of the Phase 3 trials because critical aspects of their study designs were different. Specifically, in P018 and P021, subjects who met the criteria for PDVF were required to be discontinued from the trial, and were counted as failures in the FDA snapshot analysis at later timepoints; in P007, in contrast, discontinuation was at the investigator's discretion. This differential handling of PDVF in the analyses could cause different patterns of missing data and thus affect the interpretation of the efficacy analyses if results were integrated. Another difference between the Phase 2b and Phase 3 trials that supports pooling efficacy data from only P018 and P021 is related to the inclusion criteria: only P007 specified an inclusion criterion related to $CD4^+$ T-cell count at screening (subjects were required to have $CD4^+$ T-cell count $\geq$100 cells/mm^3). $CD4^+$ T-cell count at therapy initiation is known to have an effect on treatment outcome.

Subjects in P018 and P021 are referred to as the 'pooled efficacy population'. Subjects who received DOR in P018 or DOR/3TC/TDF in P021 are referred to as the 'DOR Regimen' group.

3.2 Trial Populations

3.2.1 Subject Disposition in the Pooled Efficacy Population

Comparable proportions of subjects across treatment groups discontinued from the trial for any reason by the Week 48 visit window [Table 2.7.3-trtmtnve48wk: 10]. While overall proportions of subjects who discontinued were generally balanced across treatment groups (15.8% to 19.8%), an approximately 3-fold greater proportion of subjects discontinued due to an AE in the EFV/FTC/TDF group than in the DOR Regimen group. (Data showing subject status through the data cutoff date are found in [Table 5.3.5.3.2-trtmtnve48wk: 2].)

Table 2.7.3-trtmtnve48wk: 10

Disposition of Subjects
Efficacy Pool (P018 and P021 Combined)
All Data Available

	DOR Regimen (P018, P021)		DRV+r (P018)		EFV/FTC/TDF (P021)	
	n	(%)	n	(%)	n	(%)
Total Randomized	753		384		366	
Not Treated	6	(0.8)	1	(0.3)	2	(0.5)
Treated	747	(99.2)	383	(99.7)	364	(99.5)
Discontinued Study	119	(15.8)	76	(19.8)	70	(19.1)
Adverse Event	16	(2.1)	12	(3.1)	23	(6.3)
Death	2	(0.3)	0	(0.0)	3	(0.8)
Lack Of Efficacy	33	(4.4)	19	(4.9)	14	(3.8)
Lost To Follow-Up	23	(3.1)	19	(4.9)	7	(1.9)
Non-Compliance With Study Drug	8	(1.1)	4	(1.0)	2	(0.5)
Physician Decision	6	(0.8)	3	(0.8)	2	(0.5)
Pregnancy	3	(0.4)	0	(0.0)	2	(0.5)
Protocol Deviation	5	(0.7)	6	(1.6)	2	(0.5)
Withdrawal By Subject	23	(3.1)	13	(3.4)	15	(4.1)

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

Source: [ISE: analysis-adsl; dsplus]

3.2.2 Baseline Demographic and Prognostic Characteristics in the Pooled Efficacy Population

The pooled efficacy population reflects the enrollment of the pivotal trials, with a subject population representative of the global target population in regard to geographic, racial, ethnic, gender and age characteristics. Both P018 and P021 are being carried out in North America, South America, Europe and Russia, South Africa, and Australia/New Zealand, although with different levels of enrollment in each region. The overall subject population also reflects the target population with regard to virologic and other baseline factors such as HIV-1 subtype and baseline viral load and $CD4^+$ T-cell level.

Demographic and prognostic characteristics were comparable across the DOR Regimen group and both comparator groups with the exception of various racial and regional subgroups [Table 2.7.3-trtmtnve48wk: 11]. Because data from the DRV+r and EFV/FTC/TDF groups for this integrated analysis were each from a single trial, the differences noted reflect differences in regional enrollment between the trials.

Across treatment groups, most subjects were male (83.5% – 85.4%); the racial group with the largest proportion of subjects in each treatment group was white (61.2% in DOR Regimen, 73.1% in DRV+r, 46.7% in EFV/FTC/TDF). The median age was between 30 and 34 years (range: 18-70 years).

Mean baseline HIV-1 RNA was between 4.4 and 4.5 $\log_{10}$ copies/mL, and the mean $CD4^+$ T-cell count at baseline was between 412 and 434 cells/mm^3. The HIV-1 subtype present in most subjects was B (66.7 % to 71.0%).

Most subjects (95.3% to 97.5%) were *not* co-infected with either hepatitis B virus (HBV) or hepatitis C virus (HCV). More subjects were co-infected with HBV (1.7% to 3.1%) than with HCV (0.3% to 1.6%); none were co-infected with both HBV and HCV.

P018 and P021 each had two stratification factors for randomization; the common factor was screening HIV-1 RNA of ≤ or >100,000 copies/mL. Approximately 75% of subjects in each treatment group were in the stratum of screening HIV-1 RNA ≤100,000 copies/mL. The additional stratification factor in P018 was the investigator-chosen NRTI regimen and, in P021, co-infection with HBV and/or HCV.

Table 2.7.3-trtmtnve48wk: 11

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]

3.3 Results From Pooled Efficacy Population

There were no hypotheses associated with the efficacy analyses for the pooled efficacy population. In both P018 and P021, the primary efficacy hypothesis evaluated the non-inferiority of DOR to the active comparator at Week 48 with respect to antiretroviral efficacy, as measured by the proportion of subjects with HIV-1 RNA <50 copies/mL. Results from P018 and P021 showed that DOR and DOR/3TC/TDF, respectively, met the non-inferiority criterion for the efficacy hypothesis; results are provided in [Sec. 2.7.3.2.2.2-trtmtnve48wk] and [Sec. 2.7.3.2.3.2-trtmtnve48wk], respectively.

3.3.1 Efficacy Summary at Week 48: Virologic and Immunologic Responses

Antiretroviral efficacy was comparable across the DOR Regimen group and the comparator groups with respect to the primary endpoint (proportion of subjects with HIV-1 RNA <50 copies/mL at Week 48 using the FDA snapshot approach): 84.1%, 79.9% and 80.8% in the DOR Regimen, DRV+r and EFV/FTC/TDF groups, respectively [Table 2.7.3-trtmtnve48wk: 12]. Antiretroviral efficacy was also comparable across the 3 treatment groups with respect to related secondary and exploratory endpoints (proportions of subjects with HIV-1 RNA <40 and <200 copies/mL at Week 48). Efficacy results were consistent across the different missing-data approaches used (FDA snapshot approach and OF approach).

Immunologic efficacy at Week 48 was also comparable across the DOR Regimen group and the comparator groups: mean change from baseline in $CD4^+$ T-cell count was 196, 186 and 188 cells/mm^3 in the DOR Regimen, DRV+r and EFV/FTC/TDF groups, respectively [Table 2.7.3-trtmtnve48wk: 12].

Table 2.7.3-trtmtnve48wk: 12

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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Virologic outcome at Week 48 is based on the FDA snapshot algorithm and uses an HIV-1 RNA threshold of 50 copies/mL. Among subjects who did *not* achieve HIV-1 RNA <50 copies/mL, comparable proportions of subjects across the treatment groups either had HIV-1 RNA data at Week 48 but did not reach the virologic threshold or had no data at Week 48 (15.9%, 20.1% and 19.2% in the DOR Regimen, DRV+r and EFV/FTC/TDF groups, respectively). Among those with no data at Week 48, a higher proportion of subjects who discontinued due to an AE was observed in the EFV group compared with the DOR and DRV+r groups.

Table 2.7.3-trtmtnve48wk: 13

Virologic Outcome at Week 48
Efficacy Pool (P018 and P021 Combined)
FDA Snapshot Approach

Outcome	DOR Regimen (P018, P021) (N=747) n	(%)	DRV+r (P018) (N=383) n	(%)	EFV/FTC/TDF (P021) (N=364) n	(%)
HIV-1 RNA <50 copies/mL	628	(84.1)	306	(79.9)	294	(80.8)
HIV-1 RNA ≥ 50 copies/mL[†]	82	(11.0)	50	(13.1)	37	(10.2)
No Virologic Data at Week 48 Window	37	(5.0)	27	(7.0)	33	(9.1)
Reasons						
Discontinued study due to AE or Death[‡]	14	(1.9)	11	(2.9)	24	(6.6)
Discontinued study for Other Reasons[§]	20	(2.7)	15	(3.9)	8	(2.2)
On study but missing data in window	3	(0.4)	1	(0.3)	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 adverse event (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.
n (%) = Number (Percent) of subjects in each category.

Source: [ISE: analysis-adsl; adrna]

3.3.2 Antiretroviral Efficacy Through Week 48

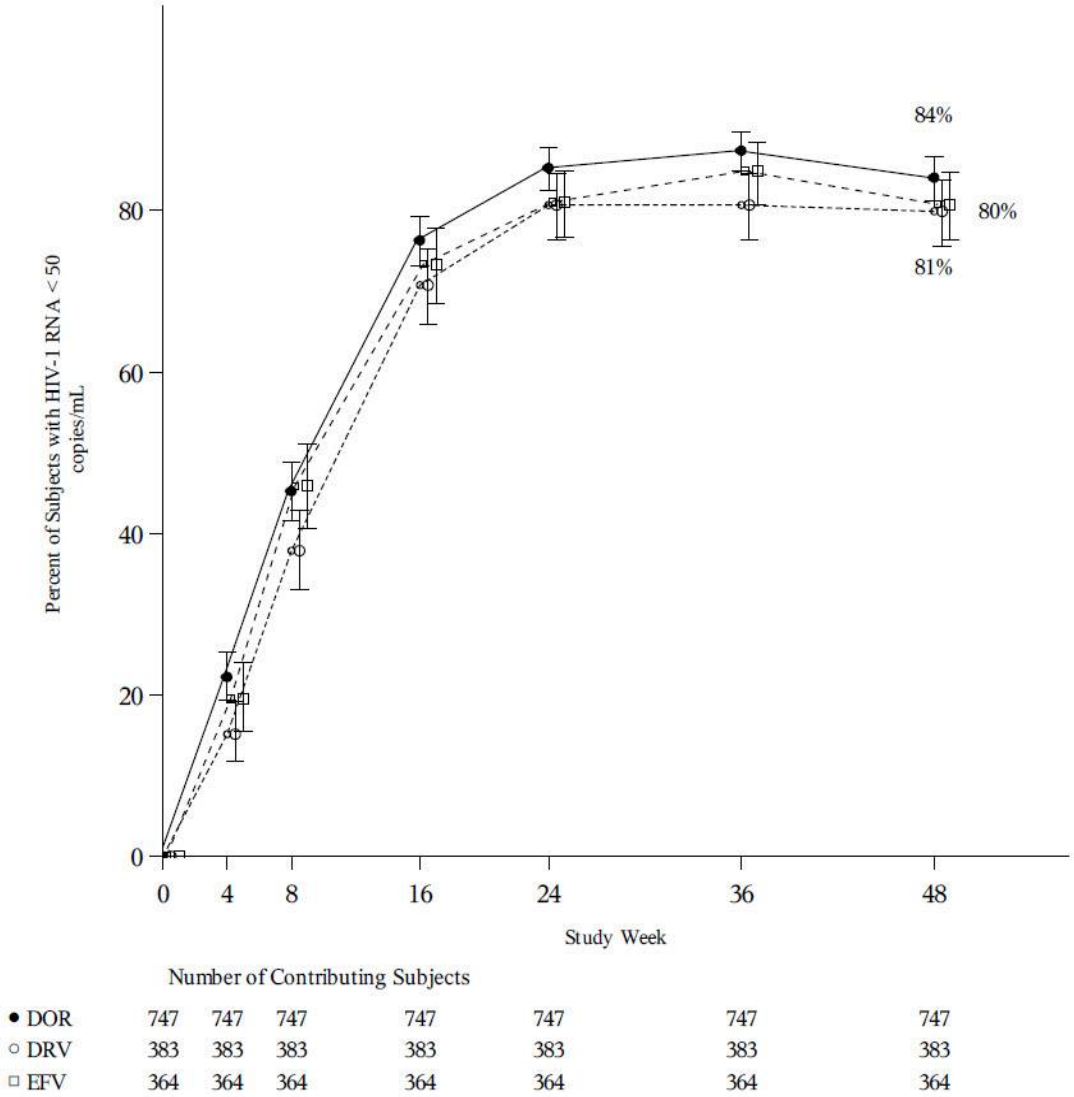
Using the FDA snapshot approach and the threshold of HIV-1 RNA <50 copies/mL, the response in all groups approached a plateau at Week 24 that carried through Week 48. Responses were comparable across groups at each timepoint.

A consistent pattern of antiretroviral efficacy over time was seen across all groups when HIV-1 RNA thresholds of <40 and <200 copies/mL were used. Analyses using the OF approach to missing data with each of these thresholds also showed a consistent pattern of antiretroviral efficacy over time [Sec. 5.3.5.3.2.3.3.2-trtmtnve48wk].

These data are supported by a summary of proportions of subjects with HIV-1 RNA in various categories at each timepoint, including <40 copies/mL with detectable HIV-1 RNA and <40 copies/mL with undetectable HIV-1 RNA [Table 2.7.3-trtmtnve48wk: 14]. Notably, among subjects who did not achieve HIV-1 RNA <50 copies/mL at Week 48, most had HIV-1 RNA <200 copies/mL, the threshold used as a measure of viral failure in various guidelines [Ref. 5.4: 04LV4N].

Figure 2.7.3-trtmtnve48wk: 12

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

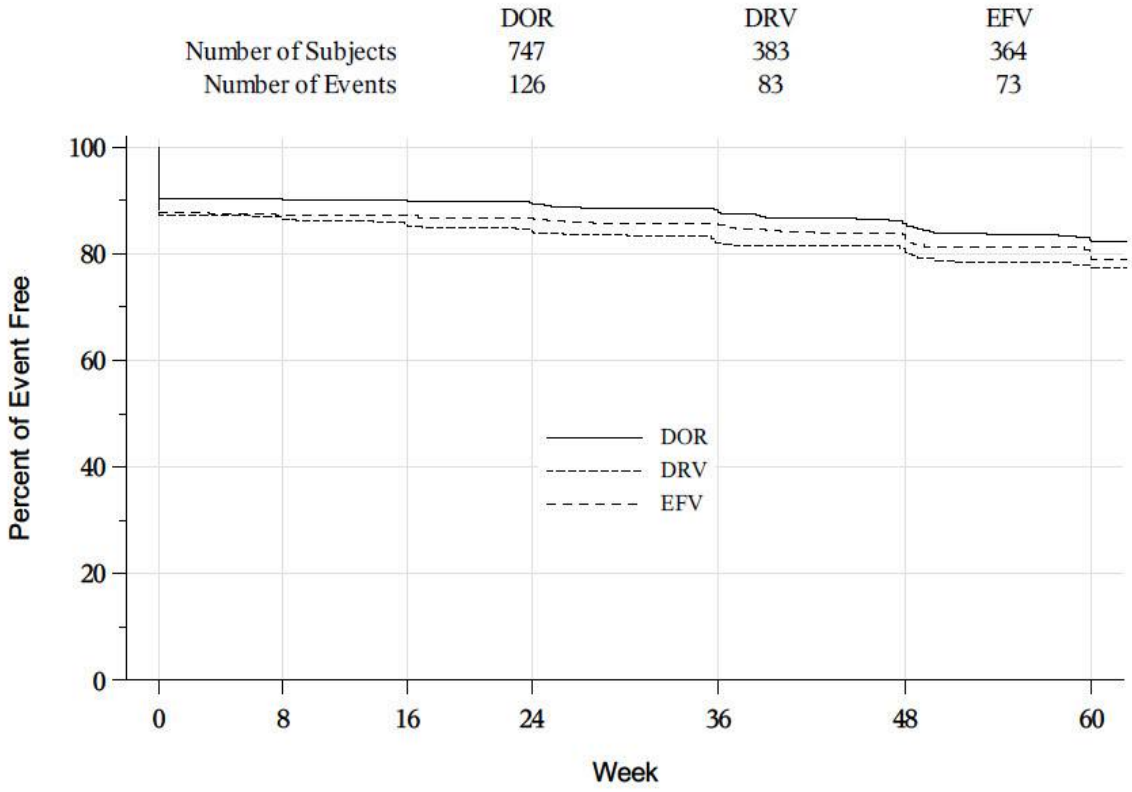


3.3.3 Time to Loss of Virologic Response (TLOVR)

As seen in the Kaplan-Meier plot of TLOVR, the risk of loss-of-response was comparable across the DOR Regimen, DRV+r, and EFV/FTC/TDF treatment groups, with no clinically meaningful difference seen across the groups [Figure 2.7.3-trtmtnve48wk: 13].

Figure 2.7.3-trtmtnve48wk: 13

Kaplan-Meier Plot for Time to Loss of Virologic Response
Efficacy Pool (Protocols 018 and 021 Combined)



Number of subjects at risk

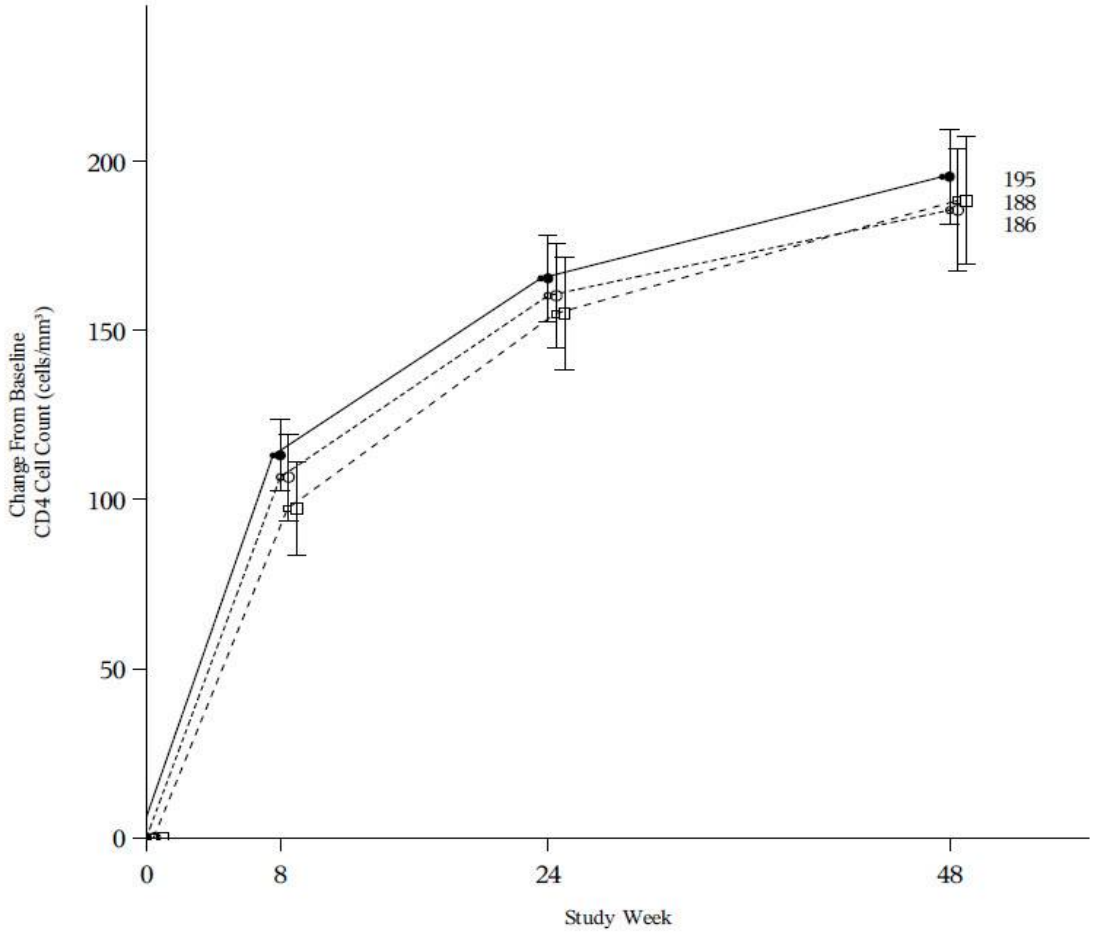
DOR	747	675	672	669	659	559	305
DRV	383	332	327	323	314	276	160
EFV	364	317	317	316	312	265	136

3.3.4 Immunologic Response Through Week 48

Immunologic efficacy, as measured by change from baseline in $CD4^+$ T-cell count at Weeks 8, 24 and 48, was comparable across the DOR Regimen group, the DRV+r group and the EFV/FTC/TDF group. Specifically, a clinically meaningful change from baseline was seen by Week 8 in each group (113, 107, and 97 cells/mm^3, respectively), with further increases at Weeks 24 and 48 [Figure 2.7.3-trtmtnve48wk: 14].

Figure 2.7.3-trtmtnve48wk: 14

Change from Baseline in $CD4^+$ T-Cell Count (cells/mm^3) Over Time
Efficacy Pool (Protocols 018 and 021 Combined)
Observed Failure Approach



Number of Contributing Subjects

● DOR	747	734	731	707
○ DRV	383	372	364	353
□ EFV	364	347	338	329

3.3.5 Protocol-Defined Virologic Failure and Evaluation of Viral Drug Resistance

Subjects With Protocol-Defined Virologic Failure (PDVF)

Numbers of subjects with PDVF are summarized below for the pooled efficacy population. For this integrated analysis, subjects with PDVF were defined as either rebounders or non-responders, with the same definitions as in the individual P018 and P021 trials [Sec. 2.7.3.1.4.1.3-trtmtnve48wk].

Proportions of subjects who met the criterion for PDVF by Week 48 were low and comparable across the DOR Regimen group, the DRV+r group and the EFV/FTC/TDF group (5.5%, 6.3%, and 3.8%, respectively) [Table 2.7.3-trtmtnve48wk: 14]. A majority of subjects in all 3 groups were rebounders who had initially responded to treatment. It is notable that approximately two-thirds of subjects with PDVF in the DOR Regimen and DRV+r groups had low-level viremia, ie, HIV-1 RNA between 50 and 200 copies/mL, at the time of virologic failure confirmation, as did approximately half of subjects with PDVF in the EFV/FTC/TDF group [Table 2.7.3-trtmtnve48wk: 14]. This observation is consistent with the possibility that the viremia meeting PDVF criteria was due to non-compliance with study medication, and that the subsequent lower viral load reflected increased compliance that, had it continued, would have resulted in re-suppression.

Further characterization of levels of HIV-1 RNA among subjects who met PDVF criteria are provided in the individual study reports [Ref. 5.3.5.1: P018V01MK1439: 16.2.6], [Ref. 5.3.5.1: P021V01MK1439A: 16.2.6].

Table 2.7.3-trtmtnve48wk: 14

Number of Subjects with Protocol Defined Virologic Failure
Efficacy Pool (P018 and P021 Combined)
(Weeks 0-48)

	DOR Regimen (P018, P021) N=(747) n (%)			DRV+r (P018) N=(383) n (%)			EFV/FTC/TDF (P021) N=(364) n (%)		
	Confirmation HIV-1 RNA ≥50 and ≤200 copies/mL	Confirmation HIV-1 RNA >200 copies/mL	Total	Confirmation HIV-1 RNA ≥50 and ≤200 copies/mL	Confirmation HIV-1 RNA >200 copies/mL	Total	Confirmation HIV-1 RNA ≥50 and ≤200 copies/mL	Confirmation HIV-1 RNA >200 copies/mL	Total
Virologic Failure (confirmed)† by Week 24									
Non-Responder	0 (0.0)	6 (0.8)	6 (0.8)	0 (0.0)	2 (0.5)	2 (0.5)	0 (0.0)	4 (1.1)	4 (1.1)
Rebounder	10 (1.3)	4 (0.5)	14 (1.9)	4 (1.0)	2 (0.5)	6 (1.6)	1 (0.3)	3 (0.8)	4 (1.1)
Virologic Failure (confirmed)† by Week 36									
Non-Responder	0 (0.0)	7 (0.9)	7 (0.9)	0 (0.0)	3 (0.8)	3 (0.8)	0 (0.0)	4 (1.1)	4 (1.1)
Rebounder	14 (1.9)	7 (0.9)	21 (2.8)	10 (2.6)	4 (1.0)	14 (3.7)	3 (0.8)	3 (0.8)	6 (1.6)
Virologic Failure (confirmed)† by Week 48									
Non-Responder	0 (0.0)	8 (1.1)	8 (1.1)	1 (0.3)	4 (1.0)	5 (1.3)	0 (0.0)	4 (1.1)	4 (1.1)
Rebounder	22 (2.9)	11 (1.5)	33 (4.4)	13 (3.4)	6 (1.6)	19 (5.0)	4 (1.1)	6 (1.6)	10 (2.7)

† Protocol defined virologic failure (PDVF) for this study is defined as one of the following: 1) Rebounder: Confirmed (two consecutive measures at least one week apart) HIV-1 RNA ≥ 50 copies/mL after initial response of HIV-1 RNA <50 copies/mL at any time during the study; Or 2) Non responder: Confirmed (two consecutive measures at least one week apart) HIV -1 RNA ≥ 200 copies/mL at Week 24 or Week 36; OR Confirmed (two consecutive measures at least one week apart) HIV-1 RNA ≥ 50 copies/mL at Week 48.

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; advf]

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Development of Viral Drug Resistance

Viral drug resistance was assessed for subjects in P018 and P021 who met PDVF criteria (41 subjects), or who discontinued for a reason other than PDVF, and had an HIV-1 RNA level >400 copies/mL. Among subjects in P018 and P021 treated with 100 mg DOR (as a single entity in combination with 2 NRTIs or as DOR/3TC/TDF), 30 subjects had both genotype and phenotype data reported; an additional subject had only genotype data reported. Viral drug resistance was also assessed for subjects in P007 who met that trial's definition of PDVF. Among subjects in P007 treated with DOR 100 mg, 5 subjects had genotype data reported, of whom 4 had both genotype and phenotype data reported; among subjects treated with any dose of DOR, 14 subjects had genotype data reported, of whom 12 had both genotype and phenotype data reported.

Viral resistance data from HIV-1 isolates collected during the treatment period are described within the individual trial summaries above [Sec. 2.7.3.2-trtmtnve48wk]. A listing of post-baseline viral resistance data, for each subject who developed genotypic resistance to any study drug in his/her treatment regimen, is provided below [Table 2.7.3-trtmtnve48wk: 15]. For subjects with resistance data at more than one timepoint and the same resistance-related mutation(s) at each timepoint, the table includes only the latest on-treatment timepoint. A listing by subject of resistance-related data from both baseline (screening) and post-baseline timepoints, including polymorphisms not considered related to viral resistance, is provided in each of the study reports for all subjects with genotypic and/or phenotypic resistance to DOR or to EFV [Ref. 5.3.5.1: P007V01MK1439: 11.2], [Ref. 5.3.5.1: P018V01MK1439: 16.2.6], [Ref. 5.3.5.1: P021V01MK1439A: 16.2.6].

Among 747 subjects in P018 and P021 treated with 100 mg DOR (as a single entity in combination with 2 NRTIs or as DOR/3TC/TDF), a low frequency of RT mutations known to be associated with DOR resistance was observed. HIV-1 isolates from 8 (1.1%) subjects had at least 1 genetic resistance mutation, with phenotypic resistance to DOR observed in 7 (0.9%) of these [Figure 2.7.3-trtmtnve48wk: 15]. When subjects in the DOR 100-mg group of P007 are included, no additional subjects had mutations known to be associated with DOR resistance, thus 8 of 855 subjects (0.9%) had genotypic resistance and 7 (0.8%) had phenotypic resistance to DOR. Among the 232 subjects in P007 who received any dose of DOR, 2 subjects in the 25-mg group, but no subject in the 50-, 100- or 200-mg groups, developed genotypic resistance to DOR; only 1 of these was associated with phenotypic resistance to DOR. (One subject in the DOR 100-mg group in P007 developed genotypic and phenotypic resistance to EFV.) Of the 7 subjects in P007, P018 or P021 who received any dose of DOR and developed post-baseline mutations associated with phenotypic resistance to DOR, 6 were found to have phenotypic resistance to both DOR and EFV; the seventh subject (who discontinued from P018 for a reason other than PDVF) was found to be phenotypically resistant to DOR but susceptible to EFV.

The RT amino acid position that was most frequently observed to have a resistance-associated substitution among DOR-treated subjects (6 of 11 isolates) was V106 (with a majority having the V106I substitution). This substitution was often seen in combination with F227C (5 of 6 cases).

Among 472 subjects in P007 and P021 treated with EFV (as a single entity in combination with 2 NRTIs or as EFV/FTC/TDF), the observed frequency of mutations in HIV-1 RT associated with EFV resistance was low, but higher than that observed in subjects treated with DOR or DOR/3TC/TDF. HIV-1 from 14 subjects (3.0%) had a genetic resistance mutation, with phenotypic resistance to EFV observed in 13 (2.8%) of these isolates. Notably, among the 13 isolates from EFV-treated subjects with phenotypic resistance to EFV, only 4 demonstrated phenotypic resistance to DOR. Note that no threshold for defining phenotypic resistance to DOR has yet been clinically defined; the central laboratory used a 2.5-fold change in IC_{50} versus wild-type virus as a broad assay-reproducibility cut-off for potential phenotypic resistance to DOR (commonly done for other antiretrovirals in development before sufficient data are available to define a clinically relevant cut-off).

None of the 383 subjects treated with DRV+r in P018 was found to have HIV-1 with a primary genotypic resistance mutation or with phenotypic resistance to DRV.

Figure 2.7.3-trtmtnve48wk: 15

Resistance Among Doravirine-Treated Subjects in P018 and P021

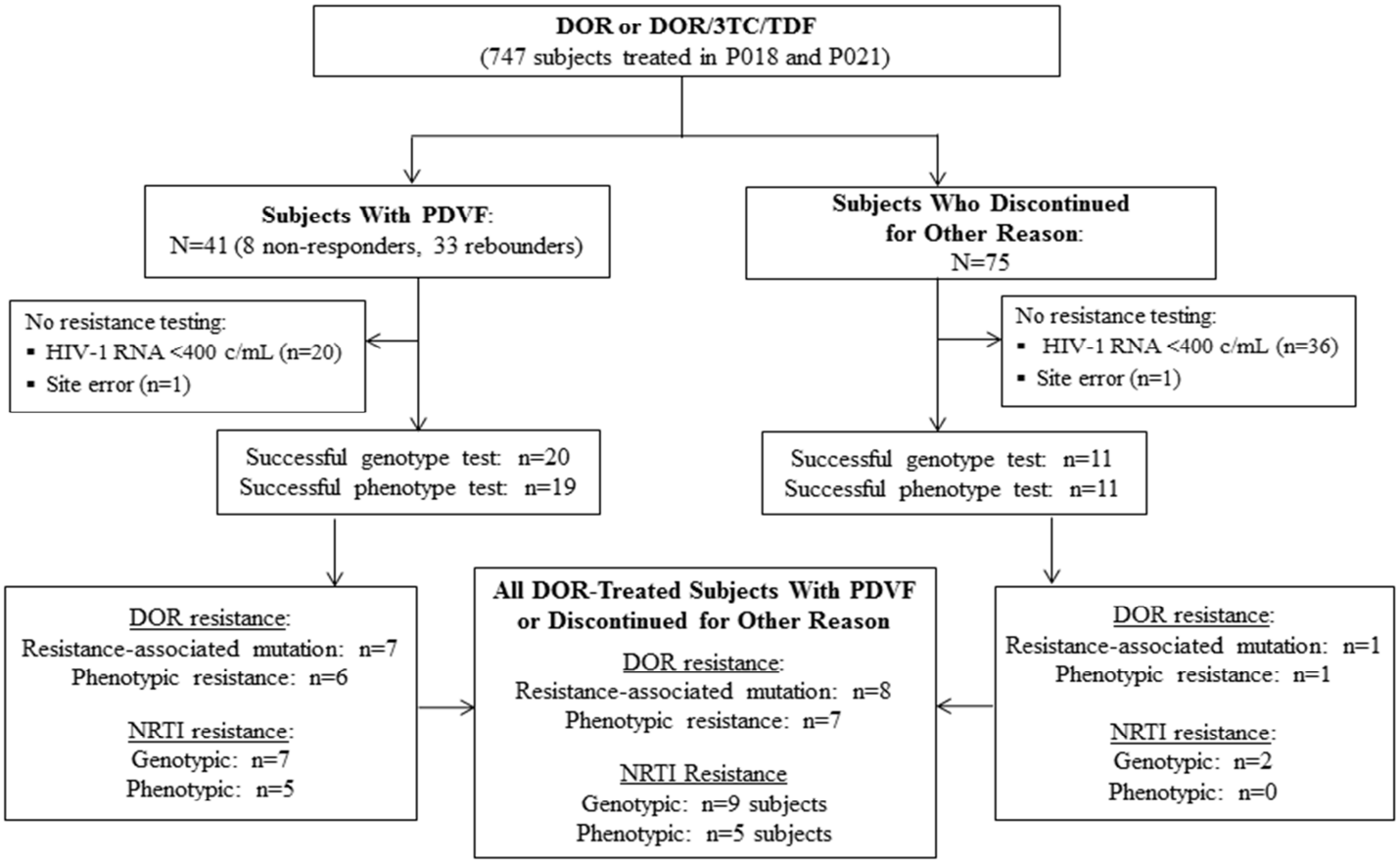


Table 2.7.3-trtmtnve48wk: 15

Postbaseline Resistance Data: Protocols 007, 018 and 021

Subject [Trial] Treatment[a] HIV-1 Subtype	PDVF Type or D/C (Reason): Week of PDVF-VFC or D/C Visit	Day Sample Collected (Visit Type)[b] Viral Load[c]	**DOR Susceptibility** [Subjects Treated w/DOR] Genotypic Resistance [RT Mutation]	**DOR Susceptibility** [Subjects Treated w/DOR] Phenotypic Resistance IC_{50} Fold Diff.[d]	**Comparator Susceptibility** [Subjects Treated w/EFV or DRV+r] Genotypic Resistance	**Comparator Susceptibility** [Subjects Treated w/EFV or DRV+r] Phenotypic Resistance IC_{50} Fold Diff.[d]	**NRTI Susceptibility**[e] Genotypic Resistance [RT Mutation]	**NRTI Susceptibility**[e] Phenotypic Resistance
Subjects Treated With DOR or DOR/3TC/TDF: Trials P007, P018, P021[f]								
A (P007) DOR 25 mg Subtype B	Rebound PDVF: Wk 24	D.255 (Wk 36) 17,814 c/mL	K101K/E	S (0.6, 0.7)[g]			FTC: None TDF: None	S S
	D/C (noncompliance): Wk 60	D.507 (Wk 72) [Not avail.]	P236P/L	S (0.8)			FTC: None TDF: None	S S
B (P007) DOR 25 mg Subtype B	Rebound PDVF: Wk 48	D.427 (VFC) 533 c/mL	V106V/I, F227C	R (66.0)			FTC: M184V TDF: None	R S
C (P007) DOR 100 mg Subtype A	Non-response PDVF: Wk 24	D.171 (VFC)	E138E/G, V179D	S (0.9)			FTC: A62V TDF: A62V	S S
	D/C (noncompliance): Wk 24	D.197 (D/C)	E138E/G, V179D	S (0.8)			FTC: A62V TDF: A62V	S S
D (P018) Subtype B	D/C (noncompliance): Wk 24	D.169 (D/C) 55,708 c/mL	V106I, H221Y, F227C	R (>96.6)			FTC: M184V TDF: None	R S
E (P021) Subtype AE	Rebound PDVF: Wk 48	D.366 (D/C) 1,256 c/mL	Y188L	R (>181.6)			3TC: M41L, M184V TDF: M41L	R S
F (P021) Subtype C	Non-response PDVF: Wk 36	D.338 (D/C) 7,498 c/mL	Y318Y/F	S (0.4)			FTC: A62V TDF: A62V	S S

Subject [Trial] Treatment[a] HIV-1 Subtype	PDVF Type or D/C (Reason): Week of PDVF-VFC or D/C Visit	Day Sample Collected (Visit Type)[b] Viral Load[c]	**DOR Susceptibility** [Subjects Treated w/DOR] Genotypic Resistance [RT Mutation]	DOR Susceptibility Phenotypic Resistance IC_{50} Fold Diff.[d]	**Comparator Susceptibility** [Subjects Treated w/EFV or DRV+r] Genotypic Resistance	Comparator Susceptibility Phenotypic Resistance IC_{50} Fold Diff.[d]	**NRTI Susceptibility**[e] Genotypic Resistance [RT Mutation]	NRTI Susceptibility Phenotypic Resistance
G (P021) Subtype B	Non-response PDVF: Wk 24	D.195 (VFC) 12,691 c/mL	V106I, F227C	R (>105.5)			3TC: None TDF: None	S S
H (P021) Subtype B	Non-response PDVF: Wk 24	D.169 (VF) 33,250 c/mL	H221H/Y, F227C	R (>88.4)			3TC: M184V TDF: None	R S
		D.182 (VFC) 34,944 c/mL	V106V/I, H221H/Y, F227C	R (>109.9)			3TC: M184V TDF: None	R S
I (P021) Subtype B	Non-response PDVF: Wk 24	D.251 (VFC)	F227C	R (>93.3)			3TC: M184V TDF: None	R S
J (P021) Subtype B	Non-response PDVF: Wk 24	D.176 (VF) 80,038 c/mL	V106V/A, P225P/H	R (32.0)			3TC: None TDF: None	S S
		D.212 (D/C) 106,092 c/mL	V106A, P225H, Y318Y/F	R (>210.8)			3TC: K65R TDF: K65R	R PS
K (P021) Subtype C	Non-response PDVF: Wk 24	D.170 (VF) 71,727 c/mL	V106M, V108V/I, F227F/C	R (103.3)			3TC: None TDF: None	S S
		D.196 (VFC) 32,799 c/mL	V106M/T, F227C/R	R (>98.2)			3TC: K65K/R, M184V TDF: K65K/R	R S
Subjects Treated With Efavirenz (EFV): Trials P007, P021								
					RT Mutation		RT Mutation	
L (P007) Subtype B	Rebound PDVF: Wk 60	D.433 (Wk 60) 11,801 c/mL			K101K/Q, G190S	R (>70.9)	FTC: None TDF: None	S S
M (P007) Subtype B	Rebound PDVF: Wk 72	D.680 (Wk 96) 11,801 c/mL			K103N, N348I	R (13.0)	FTC: None TDF: None	S S
N (P021) Subtype B	Rebound PDVF: Wk 48	D.366 (VF) 407 c/mL			K103N	R (6.4)	FTC: None TDF: None	S S
O (P021) Subtype B	Rebound PDVF: Wk 48	D.374 (VFC) 4,909 c/mL			K103N, E138E/G	R (11.0)	FTC: None TDF: None	S S

Subject [Trial] Treatment[a] HIV-1 Subtype	PDVF Type or D/C (Reason): Week of PDVF-VFC or D/C Visit	Day Sample Collected (Visit Type)[b] Viral Load[c]	**DOR Susceptibility** [Subjects Treated w/DOR]		**Comparator Susceptibility** [Subjects Treated w/EFV or DRV+r]		**NRTI Susceptibility**[e]	
			Genotypic Resistance [RT Mutation]	Phenotypic Resistance IC_{50} Fold Diff.[d]	Genotypic Resistance	Phenotypic Resistance IC_{50} Fold Diff.[d]	Genotypic Resistance [RT Mutation]	Phenotypic Resistance
P (P021) Subtype Complex	Rebound PDVF: Wk 24	D.240 (Wk 36) 3,459 c/mL			K103N	R (5.3)	FTC: None TDF: None	S S
Q (P021) Subtype C	Rebound PDVF: Wk 16	D.186 (Wk 24) 16,960 c/mL			K103N	R (11.0)	FTC: None TDF: None	S S
R (P021) Subtype B	Rebound PDVF: Wk 48	D.188 (Wk 24) 9,566 c/mL			G190E	(Test failed)	FTC: V118I, M184V TDF: None	(Test failed) (Test failed)
S (P021) Subtype B	Non-response PDVF: Wk 24	D.188 (Wk 24) 4,017 c/mL			K103N	R (6.8)	FTC: M184V TDF: None	R S
T (P021) Subtype B	Non-response PDVF: Wk 24	D.232 (Wk 36) 585 c/mL			K103N, M230L	R (>91.8)	FTC: M184V TDF: None	R S
U (P021) Subtype B	Non-response PDVF: Wk 24	D.178 (Wk 24) 57,519 c/mL			G190E	R (>112.5)	FTC: M184I, K219K/E TDF: None	R S
V (P021) Subtype B	Non-response PDVF: Wk 24	D.172 (Wk 24) 952 c/mL			K103N	R (12.0)	FTC: None TDF: None	S S
		D.212 (Wk 36) 11,224 c/mL			K103N, V108V/I, T369T/A/I/V	R (22.0)	FTC: K65K/R, M184M/I TDF: K65K/R	R S
W (P021) Subtype B	D/C (LFUp): Wk 16	D.173 (Wk 24) 1,610 c/mL			K103N	R (32.0)	FTC: None TDF: None	S S
X (P021) Subtype B	D/C (LoE): Wk 8	D.118 (Wk 16) 9,264 c/mL			K103N	R (20.0)	FTC: None TDF: None	S S
Y (P021) Subtype AE	D/C (SubjWD): Wk 36	D.276 (Wk 24) 136,633 c/mL			K101K/N, K103N, P225P/H	R (24.0)	FTC: None TDF: None	S S

Subject [Trial] Treatment[a] HIV-1 Subtype	PDVF Type or D/C (Reason): Week of PDVF-VFC or D/C Visit	Day Sample Collected (Visit Type)[b] Viral Load[c]	**DOR Susceptibility** [Subjects Treated w/DOR]		**Comparator Susceptibility** [Subjects Treated w/EFV or DRV+r]		**NRTI Susceptibility**[e]	
			Genotypic Resistance [RT Mutation]	Phenotypic Resistance IC_{50} Fold Diff.[d]	Genotypic Resistance	Phenotypic Resistance IC_{50} Fold Diff.[d]	Genotypic Resistance [RT Mutation]	Phenotypic Resistance
Subjects Treated With Darunavir + ritonavir (DRV+r): Trial P018								
					PI Mutation		PI Susceptibility	
None								

Abbreviations: LFUp = lost to follow-up; LoE = lack of efficacy; PI = protease inhibitor; PS = partially susceptible; SCR = screening visit (Days -45 through -1 for P007, P018 and P021); SubjWD = withdrawal by subject; VFC = viral failure confirmation visit.

a: The DOR dose is shown for only subjects in P007; all subjects in P018 and P021 received 100 mg DOR. All subjects in P007 received FTC/TDF as background therapy; all subjects in P018 listed in this table received FTC/TDF as background therapy, and all subjects in P021 received either DOR/3TC/TDF or EFV/FTC/TDF.

b: For subjects who met PDVF criteria, the sample reported here was collected at the viral failure confirmation (VFC) visit; for subjects who discontinued due to a reason other than PDVF, the sample was collected at the discontinuation visit.

c: Viral load is measured as HIV-1 RNA copies/mL.

d: If the fold difference in IC_{50} with respect to wild-type virus for a given study drug was less than the threshold used to define phenotypic resistance, the virus was considered susceptible to that drug ('S').

e: Data on NRTI susceptibility are provided for only the NRTIs in each subject's treatment regimen.

f: One DOR-treated subject described in the P018 study report is excluded from this table because the subject's HIV-1 isolate is not considered to have developed resistance to DOR for the purposes of this pooled analysis. The subject with observed phenotypic resistance to DOR (2.8-fold change at Day 29 relative to wild-type virus) is not considered to have developed resistance to DOR based on the observed virologic response, lack of genotypic mutations associated with DOR resistance, minimal change in IC_{50} from baseline (baseline IC_{50} FC was 2.2) and insufficient clinical data to define a clinical cutoff for DOR phenotypic resistance [Ref. 5.3.5.1: P018V01MK1439: 11.1.4.2.2]. In addition, a subject in P021with an RT V179D mutation at baseline as well as at discontinuation at Week 24 is not considered to have developed resistance to DOR based on observed susceptibility to DOR at both baseline and Day 169 and resistance to EFV at baseline (4.7 FC) and Day 169 (4.3 FC), and is excluded from this table.

g: Subject 'A' had 2 samples from Day 255 tested for phenotypic resistance.

Note: Subjects in P007 were not necessarily discontinued if they met criteria for protocol-defined viral failure (PDVF) – this was left to the clinical judgment of the investigator; subjects in P018 and P021 were required to be discontinued from the trial if they met PDVF criteria.

Note: The screening period was Days -45 through -1 for P007, P018 and P021.

3.4 Analyses of Results in Subpopulations of the Pooled Efficacy Population

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 various demographic and prognostic factors [Table 2.7.3-trtmtnve48wk: 16]. 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 comparable across the DOR Regimen and DRV+r groups but slightly higher in the EFV/FTC/TDF group (75.9%, 72.1%, 83.7%, respectively).

When thresholds of HIV-1 RNA 40 and 200 copies/mL were used to evaluate antiretroviral response, results were consistent with those for the 50 copies/mL threshold, ie, there was a lack of meaningful differences across subgroups [Table 5.3.5.3.2-trtmtnve48wk: 24], [Table 5.3.5.3.2-trtmtnve48wk: 25].

Similarly, there were no meaningful differences in immunologic efficacy observed across treatment groups for all demographic and prognostic factors [Table 5.3.5.3.2-trtmtnve48wk: 26].

Analyses of efficacy at Week 48 by subgroup (including estimates of treatment differences) are presented as forest plots (as well as in tables) in the individual CSRs [Ref. 5.3.5.1: P018V01MK1439: 11.1.3], [Ref. 5.3.5.1: P021V01MK1439A: 11.1.3].

Table 2.7.3-trtmtnve48wk: 16

Proportion of Subjects with Plasma HIV-1 RNA <50 Copies/mL at Week 48 by Prognostic and Demographic Factors Efficacy Pool (P018 and P021 Combined) Observed Failure Approach

Prognostic and Demographic Factors	Response					
	DOR Regimen (P018, P021)		DRV+r (P018)		EFV/FTC/TDF (P021)	
	n/N	% (95% CI)	n/N	% (95% CI)	n/N	% (95% CI)
Total	628/710	88.5 (85.9, 90.7)	306/355	86.2 (82.2, 89.6)	294/331	88.8 (84.9, 92.0)
Baseline Plasma HIV-1 RNA (copies/mL)						
≤100,000 copies/mL	508/562	90.4 (87.6, 92.7)	250/282	88.7 (84.4, 92.1)	235/258	91.1 (86.9, 94.3)
>100,000 copies/mL	120/148	81.1 (73.8, 87.0)	55/72	76.4 (64.9, 85.6)	59/73	80.8 (69.9, 89.1)
Baseline Plasma HIV-1 RNA (copies/mL)						
≤500,000 copies/mL	608/684	88.9 (86.3, 91.1)	299/342	87.4 (83.4, 90.7)	282/314	89.8 (85.9, 92.9)
>500,000 copies/mL	20/26	76.9 (56.4, 91.0)	6/12	50.0 (21.1, 78.9)	12/17	70.6 (44.0, 89.7)
Screening Plasma HIV-1 RNA (copies/mL)						
≤100,000 copies/mL	490/540	90.7 (88.0, 93.0)	233/264	88.3 (83.7, 91.9)	229/250	91.6 (87.4, 94.7)
>100,000 copies/mL	138/170	81.2 (74.5, 86.8)	73/91	80.2 (70.6, 87.8)	65/81	80.2 (69.9, 88.3)
Baseline CD4 Cell Counts (cells/mm^3)						
≤50 cells/mm^3	10/14	71.4 (41.9, 91.6)	12/18	66.7 (41.0, 86.7)	6/9	66.7 (29.9, 92.5)
>50 cells/mm^3 and ≤200 cells/mm^3	53/69	76.8 (65.1, 86.1)	32/43	74.4 (58.8, 86.5)	30/34	88.2 (72.5, 96.7)
>200 cells/mm^3	565/627	90.1 (87.5, 92.3)	262/294	89.1 (85.0, 92.4)	258/288	89.6 (85.5, 92.9)
Hepatitis Status[†]						
Hepatitis B and/or C Positive	17/19	89.5 (66.9, 98.7)	13/17	76.5 (50.1, 93.2)	8/8	100.0 (63.1, 100.0)
Both Hepatitis B and C Negative	611/691	88.4 (85.8, 90.7)	293/338	86.7 (82.6, 90.1)	286/323	88.5 (84.6, 91.8)
Age (years)						
18 to 64	624/706	88.4 (85.8, 90.7)	303/352	86.1 (82.0, 89.5)	293/330	88.8 (84.9, 92.0)
≥65	4/4	100.0 (39.8, 100.0)	3/3	100.0 (29.2, 100.0)	1/1	100.0 (2.5, 100.0)
Age (years)						
≤Median (32 yrs)	310/366	84.7 (80.6, 88.2)	138/160	86.3 (79.9, 91.2)	179/197	90.9 (85.9, 94.5)

Prognostic and Demographic Factors	Response					
	DOR Regimen (P018, P021)		DRV+r (P018)		EFV/FTC/TDF (P021)	
	n/N	% (95% CI)	n/N	% (95% CI)	n/N	% (95% CI)
>Median (32 yrs)	318/344	92.4 (89.1, 95.0)	168/195	86.2 (80.5, 90.7)	115/134	85.8 (78.7, 91.2)
Gender						
Male	526/592	88.9 (86.0, 91.3)	268/304	88.2 (84.0, 91.6)	250/283	88.3 (84.0, 91.8)
Female	102/118	86.4 (78.9, 92.0)	38/51	74.5 (60.4, 85.7)	44/48	91.7 (80.0, 97.7)
Race						
American Indian or Alaska Native	9/13	69.2 (38.6, 90.9)	2/2	100.0 (15.8, 100.0)	6/6	100.0 (54.1, 100.0)
Asian	63/65	96.9 (89.3, 99.6)	6/7	85.7 (42.1, 99.6)	54/60	90.0 (79.5, 96.2)
Black or African American	115/144	79.9 (72.4, 86.1)	63/79	79.7 (69.2, 88.0)	51/63	81.0 (69.1, 89.8)
Multiple	48/55	87.3 (75.5, 94.7)	1/1	100.0 (2.5, 100.0)	45/48	93.8 (82.8, 98.7)
Native Hawaiian or Other Pacific Islander	0/0	N/A	2/2	100.0 (15.8, 100.0)	0/0	N/A
White	393/433	90.8 (87.6, 93.3)	232/264	87.9 (83.3, 91.6)	138/154	89.6 (83.7, 93.9)
Ethnicity						
Hispanic or Latino	187/213	87.8 (82.6, 91.9)	70/81	86.4 (77.0, 93.0)	101/110	91.8 (85.0, 96.2)
Not Hispanic or Latino	433/489	88.5 (85.4, 91.2)	230/268	85.8 (81.1, 89.8)	189/217	87.1 (81.9, 91.3)
Unknown	8/8	100.0 (63.1, 100.0)	6/6	100.0 (54.1, 100.0)	4/4	100.0 (39.8, 100.0)
Region						
Africa	48/55	87.3 (75.5, 94.7)	15/19	78.9 (54.4, 93.9)	22/27	81.5 (61.9, 93.7)
Asia/Pacific	65/70	92.9 (84.1, 97.6)	2/3	66.7 (9.4, 99.2)	51/57	89.5 (78.5, 96.0)
Europe	224/245	91.4 (87.2, 94.6)	149/168	88.7 (82.9, 93.1)	79/85	92.9 (85.3, 97.4)
Latin America	114/127	89.8 (83.1, 94.4)	28/33	84.8 (68.1, 94.9)	75/80	93.8 (86.0, 97.9)
North America	177/213	83.1 (77.4, 87.9)	112/132	84.8 (77.6, 90.5)	67/82	81.7 (71.6, 89.4)
Viral Subtype						
Clade B	419/476	88.0 (84.8, 90.8)	222/255	87.1 (82.3, 90.9)	202/226	89.4 (84.6, 93.1)
Non-Clade B	207/232	89.2 (84.5, 92.9)	84/100	84.0 (75.3, 90.6)	92/105	87.6 (79.8, 93.2)
Missing	2/2	100.0 (15.8, 100.0)	0/0	N/A	0/0	N/A

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

4 ANALYSIS OF CLINICAL INFORMATION RELEVANT TO DOSING RECOMMENDATIONS

The proposed dose of DOR in HIV-1-infected, treatment-naive individuals aged 18 or older, for both the single-entity tablet (given in combination with other antiretroviral agents) and the FDC tablet (DOR/3TC/TDF), is 100 mg QD. No dose adjustment is needed in patients with renal impairment, mild or moderate hepatic impairment, or other intrinsic factors.

This recommendation is based on the comprehensive analysis of the efficacy and safety profile of DOR at the 100-mg dose and additional doses, based on data from the Phase 2b P007 trial, and the overall efficacy and safety profile of DOR and DOR/3TC/TDF, as presented in this document and the summary of safety [Sec. 2.7.4]. The dosing recommendation is also supported by a population pharmacokinetic (PK)-based evaluation of intrinsic factor effects on DOR PK and an exposure-response analysis for key efficacy and safety endpoints.

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 DOR with rifabutin is projected to maintain therapeutic exposures at steady state (ie, comparable 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. Because the magnitude of induction associated with CYP3A moderate inducers varies across compounds and is substrate-dependent, 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.

DOR may be administered without regard to food.

Sections 4.1 and 4.2 below summarize the data supporting the Sponsor's recommendation of the 100-mg dose of DOR for the treatment of HIV-1 infection; details are found in [Sec. 2.7.2.1.5]. (The rationale for selection of the 100-mg dose for further clinical development, based on analysis of results in P007, is summarized above in [Sec. 2.7.3.2.1.2.6-trtmtnve48wk]).

4.1 Clinical Data Supporting Dosing Recommendations for Commercial Use

Prior to Phase 3 initiation, the 100-mg dose of DOR was selected for further development based on efficacy and safety results of the dose-finding part of the Phase 2b trial (P007), in which subjects were treated for 24 weeks with 25, 50, 100, or 200 mg DOR QD [Sec. 2.7.3.2.1.2.6-trtmtnve48wk], as well as on considerations of potential drug-drug interactions and efficacy coverage for common HIV-1 mutations associated with NNRTI resistance [Sec. 2.7.2.1.5]. Further support for the recommendation of the 100-mg dose of

DOR for marketed use comes from efficacy and safety data from P007 beyond Week 24, safety and efficacy results from the Phase 3 trials (P018 and P021), and an extensive exposure-response analysis of data from P018 and P021 and P007, summarized below.

Analyses of efficacy data from the Phase 2b trial (P007) and Phase 3 trials (P018, P021) demonstrate the robust efficacy of the 100-mg dose of DOR with respect to antiretroviral and immunologic efficacy. Additional support for the 100-mg dose is found in the exposure-response analyses for efficacy endpoints described in [Sec. 2.7.2.1.5.2]. The relationship between DOR PK and virologic response was flat over the exposures achieved over the range of doses used in P007 (25 to 200 mg), indicating that these doses are on the plateau of the exposure-response curve for efficacy, and suggesting little additional benefit of a higher dose. In the Phase 3 trials, the exposure-response relationships between DOR C_{24} and the proportion of subjects achieving HIV-1 RNA <50 or <40 copies/mL at Week 48, using either the FDA snapshot or OF approach, are generally flat over the range of exposures achieved at the 100-mg dose, with only a slight decrease in efficacy in subjects in the lowest decile of steady-state DOR C_{24} values.

Analyses of safety data from the Phase 2b and Phase 3 trials, including the 200-mg dose in P007, indicate a favorable safety profile [Sec. 2.7.4]. Exposure-response analysis of pre-specified safety data from the Phase 2b and Phase 3 trials [Sec. 2.7.2.1.5.3] also did not identify any association between DOR PK and either the incidence of neuropsychiatric AEs or the concentration of fasting low-density lipoprotein cholesterol (LDL-C). While a significant relationship was identified for DOR exposure and non-HDL-C, non-HDL-C levels over the range of exposures associated with the 100-mg QD dose were below baseline levels of non-HLD-C, consistent with an overall decrease in non-HDL-C levels relative to baseline. Therefore, the exposure-response relationship is not clinically meaningful. In addition, favorable safety profiles of DOR and DOR/3TC/TDF with respect to comparators have been demonstrated for neuropsychiatric adverse events (in comparison with EFV), changes in specific lipids from baseline (in comparison with both EFV and DRV+r), and discontinuation due to adverse events (in comparison with both EFV and DRV+r) at the 100-mg QD dose. Taken together, the favorable safety profile and lack of dose-limiting toxicities observed across the Phase 2b and Phase 3 trials and the lack of meaningful exposure-response relationships for key safety endpoints support the appropriateness of the 100-mg QD dose of DOR from a safety perspective.

4.2 Intrinsic and Extrinsic Factors Related to Dosing Recommendations

Intrinsic Factors

As determined from Phase 1 trials and/or population PK analyses, there are no clinically meaningful effects of age, gender, weight, BMI, race, ethnicity, renal impairment (mild, moderate and severe), or mild/moderate hepatic impairment on DOR PK. As such, no dose adjustment for DOR is required based on these factors [Sec. 2.7.2.3.1.1.5].

Based on the lack of effect of moderate hepatic impairment on DOR PK and the low intrinsic clearance of DOR, 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 dedicated Phase 1 PK trial or in Phase 3 trials.

Extrinsic Factors

DOR is not a perpetrator of clinically meaningful drug-drug interactions, based on in vitro data and clinical drug-drug interaction trials, which supports its use as part of combination antiretroviral therapy and its use in the presence of medications administered to treat comorbid conditions [Sec. 2.7.2.3.1.1.6.3].

Because DOR is metabolized primarily by CYP3A [Sec. 2.7.2.1.4.2], DOR is anticipated to be a victim of CYP3A-mediated drug-drug interactions. Concomitant use of strong CYP3A4 inhibitors was permitted in Phase 3 trials. In these trials (P018, P021), 67 subjects were co-administered moderate or strong CYP3A inhibitors for at least 7 days (with 13 subjects co-administered strong CYP3A inhibitors, and 16 subjects moderate CYP3A inhibitors, for 30 days or longer); no meaningful differences in this population's safety profile were seen in comparison to that of subjects not using concomitant strong or moderate CYP3A inhibitors [Sec. 2.7.4.5.3]. Consequently, DOR 100 mg may be co-administered with CYP3A inhibitors without dose adjustment [Sec. 2.7.2.2.5.3].

Moderate and strong CYP3A inducers have a clinically meaningful effect on the PK of DOR. DOR is contraindicated with use of strong CYP3A inducers. In addition, DOR 100 mg should be administered BID when it is co-administered with the more moderate CYP3A inducer rifabutin, in order to provide C_{24} values comparable to those observed for the 100-mg dose without co-administration of inducers. The magnitude of the effect on DOR PK of other moderate CYP3A inducers, which may be co-administered with DOR, is unknown [Sec. 2.7.2.3.1.1.6]. DOR may be administered without regard to food or gastric acid modifying agents (eg, antacids, proton pump inhibitors, H_2-antagonists) [Sec. 2.7.2.2.3.1.7].

Dosing Recommendations Relevant to DOR/3TC/TDF

The FDC tablet DOR/3TC/TDF contains 100 mg of DOR, the recommended dose for DOR as a single-entity tablet, and the marketed doses of 3TC and TDF (300 mg each). Because the efficacy and safety profiles of DOR as a single entity and as the FDC are similar, and because no clinically meaningful differences in PK of any of the FDC components was seen when co-administered as individual components or as the FDC tablet, the dose recommendations for DOR are applicable to DOR when administered as part of the FDC.

The efficacy of DOR/3TC/TDF was demonstrated in P021, as detailed above [Sec. 2.7.3.2.3-trtmtnve48wk]. In addition, in the exposure-response analysis, no clinically meaningful differences in the exposure-response relationships were observed for DOR when administered as either the single-entity tablet or the FDC [Sec. 2.7.2.3.2].

Intrinsic Factors:

No dosage adjustment is required for the DOR/3TC/TDF FDC based on age, gender, race, weight, BMI, or mild/moderate hepatic impairment.

Dose adjustment is required for both 3TC and TDF in patients with estimated creatinine clearance below 50 mL/min [ ]; given that dose adjustments from the 300-mg doses of 3TC and TDF are not possible with DOR/3TC/TDF, the FDC should not be used in this population.

Extrinsic Factors:

The DDI profiles and recommendations for the individual components also apply to DOR/3TC/TDF [Sec. 2.7.2.3.1.1.6], [Sec. 2.7.2.3.1.3.3], [Sec. 2.7.2.3.1.2.3]. Due to the DOR component, the FDC is contraindicated for use with strong CYP3A4 inducers; DOR/3TC/TDF may be co-administered with the more moderate inducer, rifabutin, with an additional dose of 100 mg DOR separated by approximately 12 hours.

Due to the TDF component of the FDC, in the treatment of chronic hepatitis B, the FDC should not be administered with adefovir dipivoxil. Furthermore, co-administration of TDF and ledipasvir/sofosbuvir has been shown to increase tenofovir exposure, and patients should be monitored for tenofovir associated AEs. Co-administration of TDF with drugs that reduce renal function or compete for active tubular secretion may increase serum concentrations of tenofovir and/or increase the concentrations of other renally eliminated drugs and AEs associated with these agents should be monitored [Sec. 2.7.2.3.1.2.3]. In addition, the FDC should not be used 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.

Administration of DOR/3TC/TDF with a high-fat meal did not have a clinically meaningful effect on the PK of any of the components [Sec. 2.7.1.3.3.1]. Therefore, DOR/3TC/TDF may be administered without regard to food [Sec. 2.7.2.3.1], as it was in P021.

5 PERSISTENCE OF EFFICACY AND/OR TOLERANCE EFFECTS

DOR and DOR/3TC/TDF demonstrated robust antiretroviral and immunologic responses that were non-inferior to those of DRV+r and EFV (each in combination with other antiretroviral drugs). This response was sustained through 48 weeks of treatment based on data from P018 [Sec. 2.7.3.2.2.2.3-trtmtnve48wk] and P021 [Sec. 2.7.3.2.3.2.3-trtmtnve48wk], [Sec. 2.7.3.3.3.2-trtmtnve48wk]. In P007, both virologic and immunologic responses were durable through 96 weeks of treatment.

5.1 Sustained Response Through Week 48 (P018 and P021)

Robust antiretroviral efficacy of DOR at Week 48 was seen in the integrated (P018 + P021) data, as evidenced by the proportions of subjects in the DOR Regimen group who achieved HIV-1 RNA <50 copies/mL (using the FDA snapshot approach to missing data). Proportions of subjects with virologic response reached a plateau at Week 24, with no clinically meaningful change seen thereafter through Week 48 [Figure 2.7.3-trtmtnve48wk: 12].

Consistent evidence of sustained robust antiretroviral efficacy through Week 48 was seen when HIV-1 RNA thresholds of <40 copies/mL and <200 copies/mL were used [Table 2.7.3-trtmtnve48wk: 16], [Table 5.3.5.3.2-trtmtnve48wk: 17]. There were no notable differences in antiretroviral efficacy over time between the DOR Regimen group and the control groups (DRV+r and EFV/FTC/TDF), regardless of HIV-1 RNA threshold.

Results of the TLOVR analysis at Week 48 are consistent with the results for antiretroviral efficacy. The sustained antiretroviral efficacy of DOR and DOR/3TC/TDF is further supported by the TLOVR analysis using additional data through Week 60 for between 37% and 41% of subjects in each of the treatment groups in the pooled efficacy population [Sec. 2.7.3.3.3.3-trtmtnve48wk].

The change from baseline in $CD4^+$ T-cell count (using the OF approach to missing data) increased over time for the DOR Regimen group [Figure 2.7.3-trtmtnve48wk: 14] in both P018 and P021. The time course of this change from baseline in $CD4^+$ T-cell count was comparable to that seen in each of the control groups (DRV+r and EFV/FTC/TDF, respectively).

5.2 Durability of Response Through Week 96 (P007)

Efficacy data from the final Week 96 visit in P007, as well as from Weeks 24 and 48 in that trial, are summarized in [Sec. 2.7.3.3.3-trtmtnve48wk], with additional data found in the CSR [Ref. 5.3.5.1: P007V01MK1439]. Among subjects in Parts I+II randomized to the 100-mg dose of DOR (as well as to the other DOR doses), proportions of subjects with HIV-1 RNA <40 copies/mL (the primary efficacy endpoint in P007) increased from baseline through Week 24, then remained generally stable from Weeks 24 through 96. Consistent evidence of durable antiretroviral efficacy through Week 96 was seen when using the HIV-1 RNA thresholds of <50 copies/mL [Ref. 5.3.5.1: P007V01MK1439; Figure 14.2-27] and <200 copies/mL [Ref. 5.3.5.1: P007V01MK1439; Figure 14.2-14]. In addition, results of TLOVR analysis at Week 96 are consistent with results for antiretroviral efficacy. These data indicate the durability of the antiretroviral efficacy of DOR through 96 weeks of treatment, with a pattern comparable to that of EFV 600 mg.

Immunologic efficacy of DOR 100 mg was also shown to be durable through Week 96. Mean changes from baseline in $CD4^+$ T-cell count at Week 96 were, in fact, larger than at Week 48 [Ref. 5.3.5.1: P007V01MK1439; Table 14.2-19]. The time course of this change from baseline in $CD4^+$ T-cell count was comparable to that seen in the EFV group.

6 CONCLUSIONS

DOR 100 mg QD, as a single entity (administered in combination therapy 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 efficacy comparable to that of 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.

  - By Week 48 of therapy, approximately 1% of DOR-treated subjects developed genotypic resistance to DOR, compared with 3% of EFV-treated subjects who developed genotypic resistance to EFV; none of the subjects treated with DRV+r developed resistance to DRV.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The List of Abbreviations serves as the first use/definition of the terms used in this Summary of Clinical Efficacy. The following terms may be used interchangeably within the document:

- Participant / subject
- Study / trial
- Intervention / treatment / medication / study drug
- Adverse event / adverse experience
- MK-1439A / doravirine/lamivudine/tenofovir disoproxil fumarate (DOR/3TC/TDF)

Abbreviation	Definition
3TC	Lamivudine
ATV	Atazanavir
CI	Confidence interval
DOR	Doravirine (MK-1439, PIFELTRO™)
DOR/3TC/TDF	Fixed-dose combination of doravirine, lamivudine and tenofovir disoproxil fumarate (MK-1439A, DELSTRIGO™)
DRV	Darunavir
DSG	Delayed Switch Group
EFV	Efavirenz
EVG	Elvitegravir
FDA	Food and Drug Administration
HIV-1	human immunodeficiency virus type 1
InSTI	integrase strand-transfer inhibitor
ISG	Immediate Switch Group
LPV	Lopinavir
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
NVP	Nevirapine
OF	Observed failure
PD	Pharmacodynamics
PDVF	Protocol-Defined Virologic Failure
PI	protease inhibitor
PK	Pharmacokinetics
QD	once daily
RNA	Ribonucleic acid
RPV	Rilpivirine
TDF	Tenofovir disoproxil fumarate

1 BACKGROUND AND OVERVIEW OF CLINICAL EFFICACY

This Summary of Clinical Efficacy provides an overview of the clinical efficacy profile of DOR/3TC/TDF from a Phase 3 Switch trial (P024) in HIV-1 infected virologically suppressed adults switching treatment from a stable baseline antiretroviral regimen to DOR/3TC/TDF.

P024 is an ongoing, Phase 3, multicenter, multinational, randomized, open-label, active-controlled trial, being conducted to evaluate a switch to treatment with DOR/3TC/TDF in HIV-1 infected individuals who are virologically suppressed on a stable (minimum 6 months at baseline) antiretroviral regimen. The baseline antiretroviral regimen included a ritonavir- or cobicistat-boosted PI (specifically, ATV, DRV, or LPV), cobicistat-boosted EVG (an integrase strand-transfer inhibitor), or an NNRTI (specifically EFV, NVP, or RPV), each administered with 2 NRTIs. Participants were randomized in a 2:1 ratio to either the Immediate Switch Group (ISG) who received DOR/3TC/TDF on Study Day 1, or the Delayed Switch Group (DSG) who remained on their baseline regimen until Study Week 24, when they began treatment with DOR/3TC/TDF. Efficacy results for the 48-week base study are presented in this Summary of Clinical Efficacy.

A total of 852 participants were screened, 673 were randomized to study treatment, and 670 were treated. Of those treated, 447 were treated with DOR/3TC/TDF in the ISG and 223 continued baseline regimen in the DSG from Day 1 to Study Week 24. Of the 223 DSG participants who continued their baseline regimen, 209 (93.7%) switched to DOR/3TC/TDF at Study Week 24. Most participants (90.4% for ISG and 90.6% for DSG) completed their treatment regimen through Study Week 48 (the base study). [Ref. 5.3.5.1: P024MK1439A: 10.1]

This Module provides an overview of the clinical efficacy data of DOR/3TC/TDF from P024. The efficacy and safety results are provided in the clinical study report (CSR) [Ref. 5.3.5.1: P024MK1439A].

2 SUMMARY OF RESULTS OF INDIVIDUAL STUDIES

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Table 2.7.3-switch48wk: 1

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]

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Table 2.7.3-switch48wk: 2

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]

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Table 2.7.3-switch48wk: 3

Virologic Outcome
FDA Snapshot Approach
Base Study

Outcome	DOR/3TC/TDF QD ISG at Study Week 48 (N=447) n (%)	Baseline Regimen DSG at Study Week 24 (N=223) n (%)	DOR/3TC/TDF QD ISG at Study Week 24 (N=447) n (%)	DOR/3TC/TDF QD DSG at Study Week 48 (N=209[§§]) n (%)
HIV-1 RNA <50 copies/mL	406 (90.8)	211 (94.6)	419 (93.7)	198 (94.7)
HIV-1 RNA ≥50 copies/mL[†]	7 (1.6)	4 (1.8)	8 (1.8)	6 (2.9)
No Virologic Data Within the Time Window	34 (7.6)	8 (3.6)	20 (4.5)	5 (2.4)
Reasons				
Discontinued study due to AE or Death[‡]	14 (3.1)	0	6 (1.3)	2 (1.0)
Discontinued study for Other Reasons[§]	20 (4.5)	8 (3.6)	12 (2.7)	3 (1.4)
On study but missing data in window	0	0	2 (0.4)	0

[†] Includes subjects who changed (a) any component of background therapy to a new drug class or (b) background components that were not permitted per protocol or (c) any background drug in the regimen because of lack of efficacy (perceived or documented) before Study Week 24, and subjects who discontinued study drug or study before Study Week 48 for lack or loss of efficacy and subjects with HIV-1 RNA ≥50 copies/mL in the Study Week 48 window (relative day 295 through last day of base study treatment period) and in the Study Week 24 window (relative day for DSG 127 through last day of baseline regimen treatment period and for ISG 127 through reported Study Week 24 visit date for subjects who completed Study Week 24 visit or last day of treatment period for subject discontinued before having Study Week 24 visit).

[‡] Includes subjects who discontinued because of adverse event (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 include: lost to follow-up, non-compliance with study drug, physician decision, protocol deviation, withdrawal by subject.

[§§] Includes only subjects who switched to DOR/3TC/TDF QD at Study Week 24.

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.

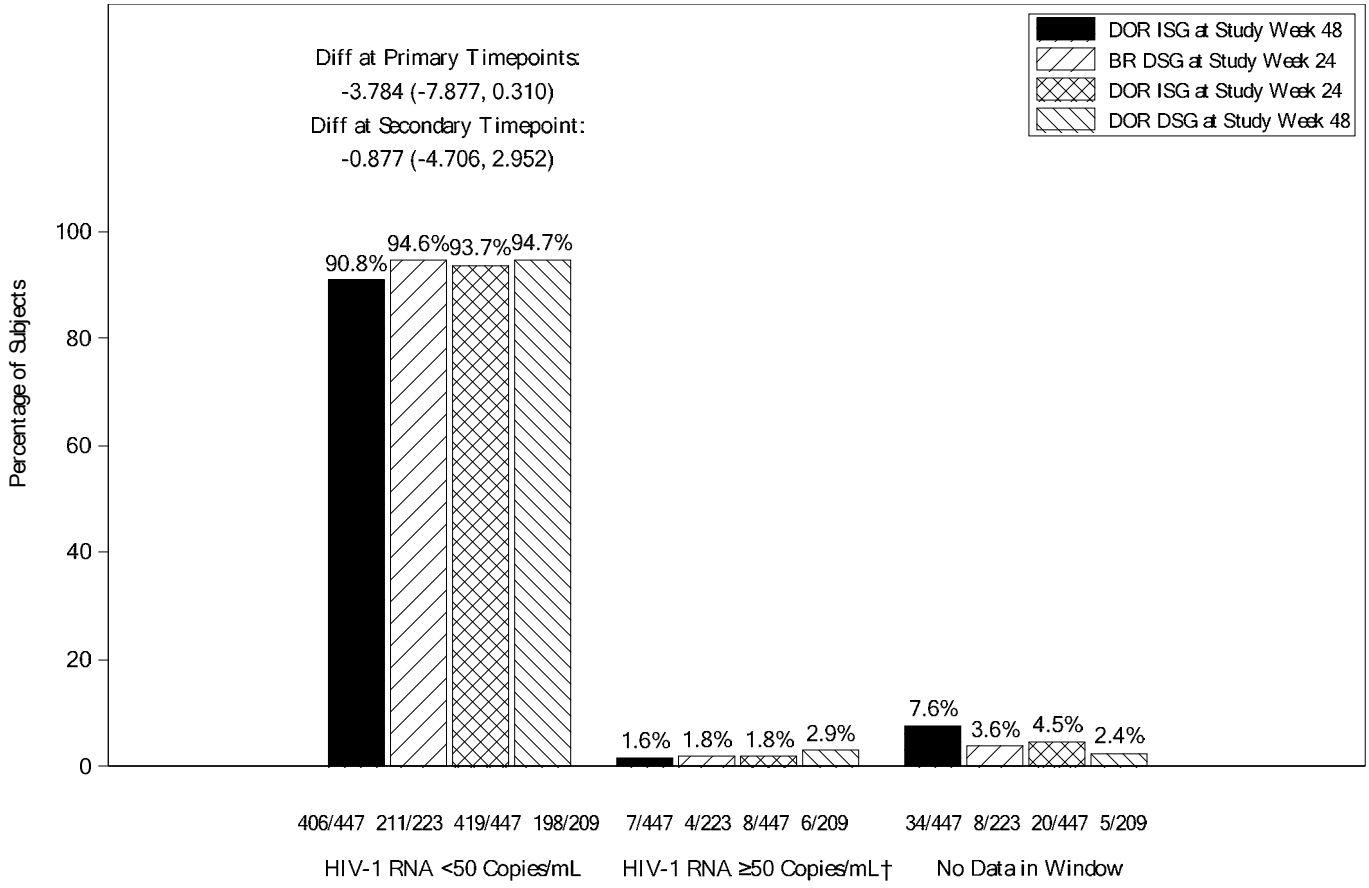
n (%) = Number (Percent) of subjects in each category.

Source: [P024MK1439A: adam-adsl; adeff1]

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Figure 2.7.3-switch48wk: 1

Virologic Outcome
FDA Snapshot Approach
Base Study



DOR=DOR/3TC/TDF QD; BR=Baseline Regimen; ISG= Immediate Switch Group; DSG=Delayed Switch Group

† Includes subjects who changed (a) any component of background therapy to a new drug class or (b) background components that were not permitted per protocol or (c) any background drug in the regimen because of lack of efficacy (perceived or documented) before Study Week 24, and subjects who discontinued study drug or study before Study Week 48 for lack or loss of efficacy and subjects with HIV-1 RNA >=50 copies/mL in the Study Week 48 window (relative day 295 through last day of base study treatment period) and in the Study Week 24 window (relative day for DSG 127 through last day of baseline regimen treatment period and for ISG 127 through reported Study Week 24 visit date for subjects who completed Study Week 24 visit or last day of treatment period for subject discontinued before having Study Week 24 visit).

Source: [P024MK1439A: adam-adsl; adeff1]

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Table 2.7.3-switch48wk: 4

Proportion of Subjects with HIV-1 RNA <50 copies/mL Over Time
FDA Snapshot Approach
Study Weeks 0-48; Base Study

		Response				Treatment Difference (ISG - DSG)[†]	
		ISG		DSG		Difference	95% CI
Endpoint	Study Week	n/N	% (95% CI)	n/N	% (95% CI)		
Proportions with HIV-1 RNA <50 copies/mL	Week 4	439/447	98.2 (96.5, 99.2)	218/223	97.8 (94.8, 99.3)	0.5	(-2.0, 2.9)
	Week 12	430/447	96.2 (94.0, 97.8)	212/223	95.1 (91.3, 97.5)	1.1	(-2.3, 4.6)
	Week 24	419/447	93.7 (91.1, 95.8)	211/223	94.6 (90.8, 97.2)	-0.9	(-4.7, 3.0)
	Week 28[‡]	409/447	91.5 (88.5, 93.9)	203/209	97.1 (93.9, 98.9)		
	Week 36[‡]	412/447	92.2 (89.3, 94.5)	201/209	96.2 (92.6, 98.3)		
	Week 48[‡]	406/447	90.8 (87.8, 93.3)	198/209	94.7 (90.8, 97.3)		

Approach to handling missing values: FDA Snapshot approach under which all missing values were counted as failure.

[†]A positive value means ISG is better than DSG. 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).

[‡]Post-switch visits for DSG: Study Week 28 = post-switch Week 4; Study Week 36 = post-switch Week 12; Study Week 48 = post-switch Week 24.

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]

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Table 2.7.3-switch48wk: 5

Proportion of Subjects with HIV-1 RNA <50 copies/mL Over Time
Observed Failure Approach
Study Weeks 0-48; Base Study

Endpoint	Study Week	Response				Treatment Difference (ISG - DSG)†	
		ISG		DSG		Difference	95% CI
		n/N	% (95% CI)	n/N	% (95% CI)		
Proportions with HIV-1 RNA <50 copies/mL	Week 4	439/443	99.1 (97.7, 99.8)	218/220	99.1 (96.8, 99.9)	0.0	(-1.8, 1.8)
	Week 12	430/435	98.9 (97.3, 99.6)	212/215	98.6 (96.0, 99.7)	0.2	(-1.9, 2.4)
	Week 24	419/427	98.1 (96.3, 99.2)	211/215	98.1 (95.3, 99.5)	0.0	(-2.4, 2.4)
	Week 28‡	409/420	97.4 (95.4, 98.7)	203/207	98.1 (95.1, 99.5)		
	Week 36‡	412/420	98.1 (96.3, 99.2)	201/206	97.6 (94.4, 99.2)		
	Week 48‡	406/413	98.3 (96.5, 99.3)	198/204	97.1 (93.7, 98.9)		

Approach to handling missing values: Observed Failure Approach under which missing values for subjects who discontinued assigned therapy due to lack of efficacy was counted as failure.

†A positive value means ISG is better than DSG. 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).

‡Post-switch visits for DSG: Study Week 28 = post-switch Week 4; Study Week 36 = post-switch Week 12; Study Week 48 = post-switch Week 24.

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]

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Table 2.7.3-switch48wk: 6

Proportion of Subjects with HIV-1 RNA <40 copies/mL Over Time
FDA Snapshot Approach
Study Weeks 0-48; Base Study

Endpoint	Study Week	Response				Treatment Difference (ISG - DSG)†	
		ISG		DSG		Difference	95% CI
		n/N	% (95% CI)	n/N	% (95% CI)		
Proportions with HIV-1 RNA <40 copies/mL	Week 4	437/447	97.8 (95.9, 98.9)	215/223	96.4 (93.1, 98.4)	1.4	(-1.6, 4.3)
	Week 12	427/447	95.5 (93.2, 97.2)	209/223	93.7 (89.7, 96.5)	1.8	(-2.0, 5.6)
	Week 24	415/447	92.8 (90.0, 95.1)	208/223	93.3 (89.1, 96.2)	-0.4	(-4.6, 3.7)
	Week 28‡	406/447	90.8 (87.8, 93.3)	201/209	96.2 (92.6, 98.3)		
	Week 36‡	407/447	91.1 (88.0, 93.5)	200/209	95.7 (92.0, 98.0)		
	Week 48‡	401/447	89.7 (86.5, 92.4)	198/209	94.7 (90.8, 97.3)		

Approach to handling missing values: FDA Snapshot approach under which all missing values were counted as failure.

†A positive value means ISG is better than DSG. 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).

‡Post-switch visits for DSG: Study Week 28 = post-switch Week 4; Study Week 36 = post-switch Week 12; Study Week 48 = post-switch Week 24.

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]

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Table 2.7.3-switch48wk: 7

Proportion of Subjects with HIV-1 RNA <40 copies/mL Over Time
Observed Failure Approach
Study Weeks 0-48; Base Study

Endpoint	Study Week	Response				Treatment Difference (ISG - DSG)†	
		ISG		DSG		Difference	95% CI
		n/N	% (95% CI)	n/N	% (95% CI)		
Proportions with HIV-1 RNA <40 copies/mL	Week 4	437/443	98.6 (97.1, 99.5)	215/220	97.7 (94.8, 99.3)	0.9	(-1.5, 3.4)
	Week 12	427/435	98.2 (96.4, 99.2)	209/215	97.2 (94.0, 99.0)	1.0	(-1.8, 3.7)
	Week 24	415/427	97.2 (95.1, 98.5)	208/215	96.7 (93.4, 98.7)	0.4	(-2.6, 3.5)
	Week 28‡	406/420	96.7 (94.5, 98.2)	201/207	97.1 (93.8, 98.9)		
	Week 36‡	407/420	96.9 (94.8, 98.3)	200/206	97.1 (93.8, 98.9)		
	Week 48‡	401/413	97.1 (95.0, 98.5)	198/204	97.1 (93.7, 98.9)		

Approach to handling missing values: Observed Failure Approach under which missing values for subjects who discontinued assigned therapy due to lack of efficacy was counted as failure.

†A positive value means ISG is better than DSG. 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).

‡Post-switch visits for DSG: Study Week 28 = post-switch Week 4; Study Week 36 = post-switch Week 12; Study Week 48 = post-switch Week 24.

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]

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Table 2.7.3-switch48wk: 8

Proportion of Subjects with HIV-1 RNA ≥50 copies/mL Over Time
FDA Snapshot Approach
Study Weeks 0-48; Base Study

Endpoint	Study Week	Response				Treatment Difference (ISG - DSG)†	
		ISG		DSG		Difference	95% CI
		n/N	% (95% CI)	n/N	% (95% CI)		
Proportions with HIV-1 RNA ≥50 copies/mL	Week 4	4/447	0.9 (0.2, 2.3)	2/223	0.9 (0.1, 3.2)	0.0	(-1.8, 1.8)
	Week 12	5/447	1.1 (0.4, 2.6)	3/223	1.3 (0.3, 3.9)	-0.2	(-2.3, 1.8)
	Week 24	8/447	1.8 (0.8, 3.5)	4/223	1.8 (0.5, 4.5)	0.0	(-2.3, 2.3)
	Week 28‡	11/447	2.5 (1.2, 4.4)	4/209	1.9 (0.5, 4.8)		
	Week 36‡	8/447	1.8 (0.8, 3.5)	5/209	2.4 (0.8, 5.5)		
	Week 48‡	7/447	1.6 (0.6, 3.2)	6/209	2.9 (1.1, 6.1)		

Approach to handling missing values: FDA Snapshot approach under which all missing values were counted as failure.

†A positive value means ISG is better than DSG. 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).

‡Post-switch visits for DSG: Study Week 28 = post-switch Week 4; Study Week 36 = post-switch Week 12; Study Week 48 = post-switch Week 24.

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]

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Table 2.7.3-switch48wk: 9

Proportion of Subjects with HIV-1 RNA ≥50 copies/mL Over Time
Observed Failure Approach
Study Weeks 0-48; Base Study

Endpoint	Study Week	Response				Treatment Difference (ISG - DSG)[†]	
		ISG		DSG		Difference	95% CI
		n/N	% (95% CI)	n/N	% (95% CI)		
Proportions with HIV-1 RNA ≥50 copies/mL	Week 4	4/443	0.9 (0.2, 2.3)	2/220	0.9 (0.1, 3.2)	0.0	(-1.8, 1.8)
	Week 12	5/435	1.1 (0.4, 2.7)	3/215	1.4 (0.3, 4.0)	-0.2	(-2.4, 1.9)
	Week 24	8/427	1.9 (0.8, 3.7)	4/215	1.9 (0.5, 4.7)	0.0	(-2.4, 2.4)
	Week 28[‡]	11/420	2.6 (1.3, 4.6)	4/207	1.9 (0.5, 4.9)		
	Week 36[‡]	8/420	1.9 (0.8, 3.7)	5/206	2.4 (0.8, 5.6)		
	Week 48[‡]	7/413	1.7 (0.7, 3.5)	6/204	2.9 (1.1, 6.3)		

Approach to handling missing values: Observed Failure Approach under which missing values for subjects who discontinued assigned therapy due to lack of efficacy was counted as failure.

[†]A positive value means ISG is better than DSG. 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).

[‡]Post-switch visits for DSG: Study Week 28 = post-switch Week 4; Study Week 36 = post-switch Week 12; Study Week 48 = post-switch Week 24.

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]

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Table 2.7.3-switch48wk: 10

Proportion of Subjects with HIV-1 RNA in Various Categories Over Time
Data as Observed
Weeks 0-48; Base Study

Study Week	Treatment Group	Viral Load Category						
		<40 copies/mL Target Not Detected	<40 copies/mL Target Detected	40 - <50 copies/mL	50 - <100 copies/mL	100 - <200 copies/mL	≥ 200 copies/mL	Missing
		n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)
Week 4	DOR/3TC/TDF QD ISG	349/447 (78.1)	88/447 (19.7)	2/447 (0.4)	4/447 (0.9)	0/447 (0.0)	0/447 (0.0)	4/447 (0.9)
	Baseline Regimen DSG	169/223 (75.8)	46/223 (20.6)	3/223 (1.3)	1/223 (0.4)	0/223 (0.0)	0/223 (0.0)	4/223 (1.8)
Week 12	DOR/3TC/TDF QD ISG	337/447 (75.4)	90/447 (20.1)	3/447 (0.7)	4/447 (0.9)	0/447 (0.0)	1/447 (0.2)	12/447 (2.7)
	Baseline Regimen DSG	164/223 (73.5)	45/223 (20.2)	3/223 (1.3)	1/223 (0.4)	0/223 (0.0)	1/223 (0.4)	9/223 (4.0)
Week 24	DOR/3TC/TDF QD ISG	335/447 (74.9)	80/447 (17.9)	4/447 (0.9)	7/447 (1.6)	1/447 (0.2)	0/447 (0.0)	20/447 (4.5)
	Baseline Regimen DSG	166/223 (74.4)	42/223 (18.8)	3/223 (1.3)	0/223 (0.0)	1/223 (0.4)	2/223 (0.9)	9/223 (4.0)
Week 28‡	DOR/3TC/TDF QD ISG	328/447 (73.4)	78/447 (17.4)	3/447 (0.7)	7/447 (1.6)	2/447 (0.4)	2/447 (0.4)	27/447 (6.0)
	DOR/3TC/TDF QD DSG	167/209 (79.9)	34/209 (16.3)	2/209 (1.0)	2/209 (1.0)	1/209 (0.5)	0/209 (0.0)	3/209 (1.4)
Week 36‡	DOR/3TC/TDF QD ISG	332/447 (74.3)	75/447 (16.8)	5/447 (1.1)	3/447 (0.7)	2/447 (0.4)	1/447 (0.2)	29/447 (6.5)
	DOR/3TC/TDF QD DSG	170/209 (81.3)	30/209 (14.4)	1/209 (0.5)	4/209 (1.9)	0/209 (0.0)	0/209 (0.0)	4/209 (1.9)
Week 48‡	DOR/3TC/TDF QD ISG	318/447 (71.1)	83/447 (18.6)	5/447 (1.1)	1/447 (0.2)	1/447 (0.2)	0/447 (0.0)	39/447 (8.7)
	DOR/3TC/TDF QD DSG	164/209 (78.5)	34/209 (16.3)	0/209 (0.0)	2/209 (1.0)	2/209 (1.0)	0/209 (0.0)	7/209 (3.3)

‡Post-switch visits for DSG: Study Week 28 = post-switch Week 4; Study Week 36 = post-switch Week 12; Study Week 48 = post-switch Week 24.

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]

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Table 2.7.3-switch48wk: 11

Change from Baseline in CD4$^+$ T-Cell Count (cells/mm^3) Over Time
Observed Failure Approach
Weeks 0-48; Base Study

End Point	Study Week	Response						Difference in Mean Changes from Baseline [ISG - DSG]† (95% CI)
		ISG			DSG			
		N	Baseline Mean	Mean Change From Baseline (95% CI)	N	Baseline Mean	Mean Change From Baseline (95% CI)	
Change from baseline in CD4$^+$ T-Cell count (cells/mm^3)	Week 12	424	661.8	16.3 (1.3, 31.4)	211	656.3	24.2 (1.5, 46.9)	-7.9 (-34.5, 18.8)
	Week 24‡	412	664.5	5.1 (-11.8, 22.1)	209	655.6	18.0 (-3.6, 39.5)	-12.8 (-41.1, 15.4)
	Week 36‡	404	663.1	18.0 (1.3, 34.6)	203	677.7	21.5 (0.9, 42.0)	
	Week 48‡	402	660.5	13.9 (-2.6, 30.4)	204	675.5	32.2 (8.7, 55.7)	

Approach to handling missing values: Observed Failure (OF) approach assuming baseline-carry-forward for all failures, exclude other missing values. Baseline CD4$^+$ T-Cell Count (cells/mm^3) was carried forward for subjects who discontinued assigned therapy due to lack of efficacy.

† A positive value favors ISG over DSG. The 95% CIs were calculated based on t-distribution.

‡ Post-switch visits for DSG: Study Week 24 = post-switch baseline; Study Week 36 = post-switch Week 12; Study Week 48 = post-switch Week 24.

At Study Week 24, the post-switch baseline mean for DSG is 675.3.

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 treatment group.

Source: [P024MK1439A: adam-adsl; adeff2]

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Table 2.7.3-switch48wk: 12

Proportion of Subjects with Plasma HIV-1 RNA <50 Copies/mL at Primary Timepoints by Prognostic and Demographic Factors Observed Failure Approach Study Weeks 0-48; Base Study

Prognostic and Demographic Factors	Response				Difference in Percent Response (DOR/3TC/TDF QD ISG - Baseline Regimen DSG)[†]
	DOR/3TC/TDF QD ISG at Study Week 48		Baseline Regimen DSG at Study Week 24		
	n/N	% (95% CI)	n/N	% (95% CI)	% (95% CI)
Total	406/413	98.3 (96.5, 99.3)	211/215	98.1 (95.3, 99.5)	0.2 (-2.2, 2.6)
Baseline CD4$^+$ T-Cell Counts (cells/mm^3)					
<200 cells/mm^3	11/12	91.7 (61.5, 99.8)	3/3	100.0 (29.2, 100.0)	-9.1 (-59.3, 41.1)
≥200 cells/mm^3	388/394	98.5 (96.7, 99.4)	205/209	98.1 (95.2, 99.5)	0.4 (-2.0, 2.8)
Missing	7/7	100.0 (59.0, 100.0)	3/3	100.0 (29.2, 100.0)	0.0 (-57.0, 57.0)
Hepatitis Status[‡]					
Hep B and/or C Positive	11/11	100.0 (71.5, 100.0)	9/9	100.0 (66.4, 100.0)	0.0 (-23.7, 23.7)
Hep B and C Negative	395/402	98.3 (96.4, 99.3)	202/206	98.1 (95.1, 99.5)	0.2 (-2.3, 2.7)
History of Selected NNRTI Mutations in Subjects on PI and InSTI Regimen					
K103N, Y181C, and/or G190A	10/10	100.0 (69.2, 100.0)	13/13	100.0 (75.3, 100.0)	0.0 (-17.2, 17.2)
ART Class in Baseline Regimen					
Ritonavir- or Cobicistat-boosted PI	284/291	97.6 (95.1, 99.0)	148/151	98.0 (94.3, 99.6)	-0.4 (-3.4, 2.6)
Cobicistat-boosted elvitegravir or an NNRTI	122/122	100.0 (97.0, 100.0)	63/64	98.4 (91.6, 100.0)	1.6 (-2.3, 5.4)
Duration of ART Regimen Prior to Enrollment					
<1 year	23/24	95.8 (78.9, 99.9)	12/12	100.0 (73.5, 100.0)	-4.5 (-25.5, 16.4)
≥1 year	383/389	98.5 (96.7, 99.4)	199/203	98.0 (95.0, 99.5)	0.4 (-2.1, 2.9)
Age (years)					
18 to 64	398/405	98.3 (96.5, 99.3)	202/206	98.1 (95.1, 99.5)	0.2 (-2.3, 2.7)
≥65	8/8	100.0 (63.1, 100.0)	9/9	100.0 (66.4, 100.0)	0.0 (-43.3, 43.3)
Age (years)					
≤Median (43 yrs)	201/208	96.6 (93.2, 98.6)	110/114	96.5 (91.3, 99.0)	0.1 (-4.5, 4.7)
>Median (43 yrs)	205/205	100.0 (98.2, 100.0)	101/101	100.0 (96.4, 100.0)	0.0 (-2.2, 2.2)
Gender					
Male	338/344	98.3 (96.2, 99.4)	182/186	97.8 (94.6, 99.4)	0.4 (-2.4, 3.2)
Female	68/69	98.6 (92.2, 100.0)	29/29	100.0 (88.1, 100.0)	-1.4 (-9.2, 6.3)

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Proportion of Subjects with Plasma HIV-1 RNA <50 Copies/mL at Primary Timepoints by Prognostic and Demographic Factors Observed Failure Approach Study Weeks 0-48; Base Study

Prognostic and Demographic Factors	Response				Difference in Percent Response (DOR/3TC/TDF QD ISG - Baseline Regimen DSG)[†]
	DOR/3TC/TDF QD ISG at Study Week 48		Baseline Regimen DSG at Study Week 24		
	n/N	% (95% CI)	n/N	% (95% CI)	% (95% CI)
Race					
American Indian or Alaska Native	5/5	100.0 (47.8, 100.0)	2/2	100.0 (15.8, 100.0)	0.0 (-103.3, 103.3)
Asian	16/16	100.0 (79.4, 100.0)	7/7	100.0 (59.0, 100.0)	0.0 (-30.1, 30.1)
Black or African American	51/52	98.1 (89.7, 100.0)	31/31	100.0 (88.8, 100.0)	-1.8 (-9.9, 6.2)
Multiple	23/24	95.8 (78.9, 99.9)	11/11	100.0 (71.5, 100.0)	-4.7 (-27.2, 17.9)
Native Hawaiian or Other Pacific Islander	1/1	100.0 (2.5, 100.0)	0/0	N/A	N/A
White	310/315	98.4 (96.3, 99.5)	160/164	97.6 (93.9, 99.3)	0.8 (-2.2, 3.9)
Ethnicity					
Hispanic or Latino	87/90	96.7 (90.6, 99.3)	41/43	95.3 (84.2, 99.4)	1.5 (-7.2, 10.1)
Not Hispanic or Latino	312/316	98.7 (96.8, 99.7)	167/169	98.8 (95.8, 99.9)	-0.1 (-2.5, 2.3)
Unknown	7/7	100.0 (59.0, 100.0)	3/3	100.0 (29.2, 100.0)	N/A
Region					
Asia/Pacific	17/17	100.0 (80.5, 100.0)	12/12	100.0 (73.5, 100.0)	0.0 (-20.7, 20.7)
Europe	245/250	98.0 (95.4, 99.3)	130/131	99.2 (95.8, 100.0)	-1.2 (-4.1, 1.6)
Latin America	44/46	95.7 (85.2, 99.5)	23/24	95.8 (78.9, 99.9)	-0.2 (-12.6, 12.2)
North America	100/100	100.0 (96.4, 100.0)	46/48	95.8 (85.7, 99.5)	4.1 (-2.9, 11.1)

[†] 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).

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

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]

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Table 2.7.3-switch48wk: 13

Proportion of Subjects with Plasma HIV-1 RNA <40 Copies/mL at Primary Timepoints by Prognostic and Demographic Factors
Observed Failure Approach
Study Weeks 0-48; Base Study

Prognostic and Demographic Factors	Response				Difference in Percent Response (DOR/3TC/TDF QD ISG - Baseline Regimen DSG)[†]
	DOR/3TC/TDF QD ISG at Study Week 48		Baseline Regimen DSG at Study Week 24		
	n/N	% (95% CI)	n/N	% (95% CI)	% (95% CI)
Total	401/413	97.1 (95.0, 98.5)	208/215	96.7 (93.4, 98.7)	0.4 (-2.7, 3.4)
Baseline CD4$^+$ T-Cell Counts (cells/mm^3)					
<200 cells/mm^3	10/12	83.3 (51.6, 97.9)	3/3	100.0 (29.2, 100.0)	-18.2 (-70.5, 34.1)
≥200 cells/mm^3	384/394	97.5 (95.4, 98.8)	202/209	96.7 (93.2, 98.6)	0.8 (-2.2, 3.9)
Missing	7/7	100.0 (59.0, 100.0)	3/3	100.0 (29.2, 100.0)	0.0 (-57.0, 57.0)
Hepatitis Status[‡]					
Hep B and/or C Positive	11/11	100.0 (71.5, 100.0)	9/9	100.0 (66.4, 100.0)	0.0 (-23.7, 23.7)
Hep B and C Negative	390/402	97.0 (94.8, 98.4)	199/206	96.6 (93.1, 98.6)	0.4 (-2.7, 3.6)
History of Selected NNRTI Mutations in Subjects on PI and InSTI Regimen					
K103N, Y181C, and/or G190A	10/10	100.0 (69.2, 100.0)	13/13	100.0 (75.3, 100.0)	0.0 (-17.2, 17.2)
ART Class in Baseline Regimen					
Ritonavir- or Cobicistat-boosted PI	280/291	96.2 (93.3, 98.1)	146/151	96.7 (92.4, 98.9)	-0.5 (-4.2, 3.3)
Cobicistat-boosted elvitegravir or an NNRTI	121/122	99.2 (95.5, 100.0)	62/64	96.9 (89.2, 99.6)	2.3 (-2.8, 7.4)
Duration of ART Regimen Prior to Enrollment					
<1 year	23/24	95.8 (78.9, 99.9)	12/12	100.0 (73.5, 100.0)	-4.5 (-25.5, 16.4)
≥1 year	378/389	97.2 (95.0, 98.6)	196/203	96.6 (93.0, 98.6)	0.6 (-2.5, 3.8)
Age (years)					
18 to 64	393/405	97.0 (94.9, 98.5)	199/206	96.6 (93.1, 98.6)	0.4 (-2.8, 3.6)
≥65	8/8	100.0 (63.1, 100.0)	9/9	100.0 (66.4, 100.0)	0.0 (-43.3, 43.3)
Age (years)					
≤Median (43 yrs)	199/208	95.7 (91.9, 98.0)	109/114	95.6 (90.1, 98.6)	-0.0 (-5.1, 5.1)
>Median (43 yrs)	202/205	98.5 (95.8, 99.7)	99/101	98.0 (93.0, 99.8)	0.6 (-3.3, 4.4)
Gender					
Male	333/344	96.8 (94.4, 98.4)	179/186	96.2 (92.4, 98.5)	0.6 (-2.9, 4.1)
Female	68/69	98.6 (92.2, 100.0)	29/29	100.0 (88.1, 100.0)	-1.4 (-9.2, 6.3)

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Proportion of Subjects with Plasma HIV-1 RNA <40 Copies/mL at Primary Timepoints by Prognostic and Demographic Factors Observed Failure Approach Study Weeks 0-48; Base Study

Prognostic and Demographic Factors	Response				Difference in Percent Response (DOR/3TC/TDF QD ISG - Baseline Regimen DSG)[†]
	DOR/3TC/TDF QD ISG at Study Week 48		Baseline Regimen DSG at Study Week 24		
	n/N	% (95% CI)	n/N	% (95% CI)	% (95% CI)
Race					
American Indian or Alaska Native	5/5	100.0 (47.8, 100.0)	2/2	100.0 (15.8, 100.0)	0.0 (-103.3, 103.3)
Asian	16/16	100.0 (79.4, 100.0)	7/7	100.0 (59.0, 100.0)	0.0 (-30.1, 30.1)
Black or African American	51/52	98.1 (89.7, 100.0)	31/31	100.0 (88.8, 100.0)	-1.8 (-9.9, 6.2)
Multiple	21/24	87.5 (67.6, 97.3)	11/11	100.0 (71.5, 100.0)	-14.0 (-39.0, 11.1)
Native Hawaiian or Other Pacific Islander	1/1	100.0 (2.5, 100.0)	0/0	N/A	N/A
White	307/315	97.5 (95.1, 98.9)	157/164	95.7 (91.4, 98.3)	1.7 (-2.1, 5.5)
Ethnicity					
Hispanic or Latino	85/90	94.4 (87.5, 98.2)	41/43	95.3 (84.2, 99.4)	-0.8 (-9.9, 8.3)
Not Hispanic or Latino	309/316	97.8 (95.5, 99.1)	164/169	97.0 (93.2, 99.0)	0.7 (-2.6, 4.0)
Unknown	7/7	100.0 (59.0, 100.0)	3/3	100.0 (29.2, 100.0)	N/A
Region					
Asia/Pacific	17/17	100.0 (80.5, 100.0)	12/12	100.0 (73.5, 100.0)	0.0 (-20.7, 20.7)
Europe	243/250	97.2 (94.3, 98.9)	127/131	96.9 (92.4, 99.2)	0.3 (-3.7, 4.2)
Latin America	43/46	93.5 (82.1, 98.6)	23/24	95.8 (78.9, 99.9)	-2.1 (-15.0, 10.7)
North America	98/100	98.0 (93.0, 99.8)	46/48	95.8 (85.7, 99.5)	2.1 (-5.4, 9.6)

[†] 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).

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

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]

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Table 2.7.3-switch48wk: 14

Proportion of Subjects with Plasma HIV-1 RNA ≥50 Copies/mL at Primary Timepoints by Prognostic and Demographic Factors Observed Failure Approach Study Weeks 0-48; Base Study

Prognostic and Demographic Factors	Response				Difference in Percent Response (DOR/3TC/TDF QD ISG - Baseline Regimen DSG)[†]
	DOR/3TC/TDF QD ISG at Study Week 48		Baseline Regimen DSG at Study Week 24		
	n/N	% (95% CI)	n/N	% (95% CI)	% (95% CI)
Total	7/413	1.7 (0.7, 3.5)	4/215	1.9 (0.5, 4.7)	-0.2 (-2.6, 2.2)
Baseline CD4$^+$ T-Cell Counts (cells/mm^3)					
<200 cells/mm^3	1/12	8.3 (0.2, 38.5)	0/3	0.0 (0.0, 70.8)	9.1 (-41.1, 59.3)
≥200 cells/mm^3	6/394	1.5 (0.6, 3.3)	4/209	1.9 (0.5, 4.8)	-0.4 (-2.8, 2.0)
Missing	0/7	0.0 (0.0, 41.0)	0/3	0.0 (0.0, 70.8)	0.0 (-57.0, 57.0)
Hepatitis Status[‡]					
Hep B and/or C Positive	0/11	0.0 (0.0, 28.5)	0/9	0.0 (0.0, 33.6)	0.0 (-23.7, 23.7)
Hep B and C Negative	7/402	1.7 (0.7, 3.6)	4/206	1.9 (0.5, 4.9)	-0.2 (-2.7, 2.3)
History of Selected NNRTI Mutations in Subjects on PI and InSTI Regimen					
K103N, Y181C, and/or G190A	0/10	0.0 (0.0, 30.8)	0/13	0.0 (0.0, 24.7)	0.0 (-17.2, 17.2)
ART Class in Baseline Regimen					
Ritonavir- or Cobicistat-boosted PI	7/291	2.4 (1.0, 4.9)	3/151	2.0 (0.4, 5.7)	0.4 (-2.6, 3.4)
Cobicistat-boosted elvitegravir or an NNRTI	0/122	0.0 (0.0, 3.0)	1/64	1.6 (0.0, 8.4)	-1.6 (-5.4, 2.3)
Duration of ART Regimen Prior to Enrollment					
<1 year	1/24	4.2 (0.1, 21.1)	0/12	0.0 (0.0, 26.5)	4.5 (-16.4, 25.5)
≥1 year	6/389	1.5 (0.6, 3.3)	4/203	2.0 (0.5, 5.0)	-0.4 (-2.9, 2.1)
Age (years)					
18 to 64	7/405	1.7 (0.7, 3.5)	4/206	1.9 (0.5, 4.9)	-0.2 (-2.7, 2.3)
≥65	0/8	0.0 (0.0, 36.9)	0/9	0.0 (0.0, 33.6)	0.0 (-43.3, 43.3)
Age (years)					
≤Median (43 yrs)	7/208	3.4 (1.4, 6.8)	4/114	3.5 (1.0, 8.7)	-0.1 (-4.7, 4.5)
>Median (43 yrs)	0/205	0.0 (0.0, 1.8)	0/101	0.0 (0.0, 3.6)	0.0 (-2.2, 2.2)
Gender					
Male	6/344	1.7 (0.6, 3.8)	4/186	2.2 (0.6, 5.4)	-0.4 (-3.2, 2.4)
Female	1/69	1.4 (0.0, 7.8)	0/29	0.0 (0.0, 11.9)	1.4 (-6.3, 9.2)

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Proportion of Subjects with Plasma HIV-1 RNA ≥50 Copies/mL at Primary Timepoints by Prognostic and Demographic Factors Observed Failure Approach Study Weeks 0-48; Base Study

Prognostic and Demographic Factors	Response				Difference in Percent Response (DOR/3TC/TDF QD ISG - Baseline Regimen DSG)[†]
	DOR/3TC/TDF QD ISG at Study Week 48		Baseline Regimen DSG at Study Week 24		
	n/N	% (95% CI)	n/N	% (95% CI)	% (95% CI)
Race					
American Indian or Alaska Native	0/5	0.0 (0.0, 52.2)	0/2	0.0 (0.0, 84.2)	0.0 (-103.3, 103.3)
Asian	0/16	0.0 (0.0, 20.6)	0/7	0.0 (0.0, 41.0)	0.0 (-30.1, 30.1)
Black or African American	1/52	1.9 (0.0, 10.3)	0/31	0.0 (0.0, 11.2)	1.8 (-6.2, 9.9)
Multiple	1/24	4.2 (0.1, 21.1)	0/11	0.0 (0.0, 28.5)	4.7 (-17.9, 27.2)
Native Hawaiian or Other Pacific Islander	0/1	0.0 (0.0, 97.5)	0/0	N/A	N/A
White	5/315	1.6 (0.5, 3.7)	4/164	2.4 (0.7, 6.1)	-0.8 (-3.9, 2.2)
Ethnicity					
Hispanic or Latino	3/90	3.3 (0.7, 9.4)	2/43	4.7 (0.6, 15.8)	-1.5 (-10.1, 7.2)
Not Hispanic or Latino	4/316	1.3 (0.3, 3.2)	2/169	1.2 (0.1, 4.2)	0.1 (-2.3, 2.5)
Unknown	0/7	0.0 (0.0, 41.0)	0/3	0.0 (0.0, 70.8)	N/A
Region					
Asia/Pacific	0/17	0.0 (0.0, 19.5)	0/12	0.0 (0.0, 26.5)	0.0 (-20.7, 20.7)
Europe	5/250	2.0 (0.7, 4.6)	1/131	0.8 (0.0, 4.2)	1.2 (-1.6, 4.1)
Latin America	2/46	4.3 (0.5, 14.8)	1/24	4.2 (0.1, 21.1)	0.2 (-12.2, 12.6)
North America	0/100	0.0 (0.0, 3.6)	2/48	4.2 (0.5, 14.3)	-4.1 (-11.1, 2.9)

[†] 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).

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

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]

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Table 2.7.3-switch48wk: 15

Proportion of Subjects with Plasma HIV-1 RNA <50 Copies/mL at Secondary Timepoint by Prognostic and Demographic Factors
Observed Failure Approach
Study Weeks 0-24; Base Study

Prognostic and Demographic Factors	Response				Difference in Percent Response (DOR/3TC/TDF QD ISG - Baseline Regimen DSG)[†]
	DOR/3TC/TDF QD ISG at Study Week 24		Baseline Regimen DSG at Study Week 24		
	n/N	% (95% CI)	n/N	% (95% CI)	% (95% CI)
Total	419/427	98.1 (96.3, 99.2)	211/215	98.1 (95.3, 99.5)	-0.0 (-2.4, 2.4)
Baseline CD4$^+$ T-Cell Counts (cells/mm^3)					
<200 cells/mm^3	12/13	92.3 (64.0, 99.8)	3/3	100.0 (29.2, 100.0)	-8.3 (-57.9, 41.2)
≥200 cells/mm^3	400/407	98.3 (96.5, 99.3)	205/209	98.1 (95.2, 99.5)	0.2 (-2.3, 2.7)
Missing	7/7	100.0 (59.0, 100.0)	3/3	100.0 (29.2, 100.0)	0.0 (-57.0, 57.0)
Hepatitis Status[‡]					
Hep B and/or C Positive	12/12	100.0 (73.5, 100.0)	9/9	100.0 (66.4, 100.0)	0.0 (-23.0, 23.0)
Hep B and C Negative	407/415	98.1 (96.2, 99.2)	202/206	98.1 (95.1, 99.5)	0.0 (-2.5, 2.5)
History of Selected NNRTI Mutations in Subjects on PI and InSTI Regimen					
K103N, Y181C, and/or G190A	10/10	100.0 (69.2, 100.0)	13/13	100.0 (75.3, 100.0)	0.0 (-17.2, 17.2)
ART Class in Baseline Regimen					
Ritonavir- or Cobicistat-boosted PI	294/299	98.3 (96.1, 99.5)	148/151	98.0 (94.3, 99.6)	0.3 (-2.5, 3.2)
Cobicistat-boosted elvitegravir or an NNRTI	125/128	97.7 (93.3, 99.5)	63/64	98.4 (91.6, 100.0)	-0.8 (-5.4, 3.9)
Duration of ART Regimen Prior to Enrollment					
<1 year	23/24	95.8 (78.9, 99.9)	12/12	100.0 (73.5, 100.0)	-4.5 (-25.5, 16.4)
≥1 year	396/403	98.3 (96.5, 99.3)	199/203	98.0 (95.0, 99.5)	0.2 (-2.3, 2.8)
Age (years)					
18 to 64	410/418	98.1 (96.3, 99.2)	202/206	98.1 (95.1, 99.5)	0.0 (-2.5, 2.6)
≥65	9/9	100.0 (66.4, 100.0)	9/9	100.0 (66.4, 100.0)	0.0 (-43.1, 43.1)
Age (years)					
≤Median (43 yrs)	210/215	97.7 (94.7, 99.2)	110/114	96.5 (91.3, 99.0)	1.2 (-3.2, 5.5)
>Median (43 yrs)	209/212	98.6 (95.9, 99.7)	101/101	100.0 (96.4, 100.0)	-1.5 (-4.2, 1.2)
Gender					
Male	348/355	98.0 (96.0, 99.2)	182/186	97.8 (94.6, 99.4)	0.2 (-2.6, 3.0)
Female	71/72	98.6 (92.5, 100.0)	29/29	100.0 (88.1, 100.0)	-1.4 (-9.1, 6.3)

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Proportion of Subjects with Plasma HIV-1 RNA <50 Copies/mL at Secondary Timepoint by Prognostic and Demographic Factors Observed Failure Approach Study Weeks 0-24; Base Study

Prognostic and Demographic Factors	Response				Difference in Percent Response (DOR/3TC/TDF QD ISG - Baseline Regimen DSG)[†]
	DOR/3TC/TDF QD ISG at Study Week 24		Baseline Regimen DSG at Study Week 24		
	n/N	% (95% CI)	n/N	% (95% CI)	% (95% CI)
Race					
American Indian or Alaska Native	5/5	100.0 (47.8, 100.0)	2/2	100.0 (15.8, 100.0)	0.0 (-103.3, 103.3)
Asian	16/16	100.0 (79.4, 100.0)	7/7	100.0 (59.0, 100.0)	0.0 (-30.1, 30.1)
Black or African American	51/52	98.1 (89.7, 100.0)	31/31	100.0 (88.8, 100.0)	-1.8 (-9.9, 6.2)
Multiple	23/24	95.8 (78.9, 99.9)	11/11	100.0 (71.5, 100.0)	-4.7 (-27.2, 17.9)
Native Hawaiian or Other Pacific Islander	1/1	100.0 (2.5, 100.0)	0/0	N/A	N/A
White	323/329	98.2 (96.1, 99.3)	160/164	97.6 (93.9, 99.3)	0.6 (-2.4, 3.7)
Ethnicity					
Hispanic or Latino	92/95	96.8 (91.0, 99.3)	41/43	95.3 (84.2, 99.4)	1.6 (-6.9, 10.1)
Not Hispanic or Latino	320/325	98.5 (96.4, 99.5)	167/169	98.8 (95.8, 99.9)	-0.3 (-2.8, 2.1)
Unknown	7/7	100.0 (59.0, 100.0)	3/3	100.0 (29.2, 100.0)	N/A
Region					
Asia/Pacific	18/18	100.0 (81.5, 100.0)	12/12	100.0 (73.5, 100.0)	0.0 (-20.5, 20.5)
Europe	253/258	98.1 (95.5, 99.4)	130/131	99.2 (95.8, 100.0)	-1.2 (-4.0, 1.6)
Latin America	45/47	95.7 (85.5, 99.5)	23/24	95.8 (78.9, 99.9)	-0.1 (-12.4, 12.2)
North America	103/104	99.0 (94.8, 100.0)	46/48	95.8 (85.7, 99.5)	3.1 (-4.2, 10.3)

[†] 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).

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

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]

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Table 2.7.3-switch48wk: 16

Proportion of Subjects with Plasma HIV-1 RNA <40 Copies/mL at Secondary Timepoint by Prognostic and Demographic Factors
Observed Failure Approach
Study Weeks 0-24; Base Study

Prognostic and Demographic Factors	Response				Difference in Percent Response (DOR/3TC/TDF QD ISG - Baseline Regimen DSG)[†]
	DOR/3TC/TDF QD ISG at Study Week 24		Baseline Regimen DSG at Study Week 24		
	n/N	% (95% CI)	n/N	% (95% CI)	% (95% CI)
Total	415/427	97.2 (95.1, 98.5)	208/215	96.7 (93.4, 98.7)	0.4 (-2.6, 3.5)
Baseline $CD4^+$ T-Cell Counts (cells/mm^3)					
<200 cells/mm^3	12/13	92.3 (64.0, 99.8)	3/3	100.0 (29.2, 100.0)	-8.3 (-57.9, 41.2)
≥200 cells/mm^3	396/407	97.3 (95.2, 98.6)	202/209	96.7 (93.2, 98.6)	0.6 (-2.4, 3.7)
Missing	7/7	100.0 (59.0, 100.0)	3/3	100.0 (29.2, 100.0)	0.0 (-57.0, 57.0)
Hepatitis Status[‡]					
Hep B and/or C Positive	12/12	100.0 (73.5, 100.0)	9/9	100.0 (66.4, 100.0)	0.0 (-23.0, 23.0)
Hep B and C Negative	403/415	97.1 (95.0, 98.5)	199/206	96.6 (93.1, 98.6)	0.5 (-2.6, 3.6)
History of Selected NNRTI Mutations in Subjects on PI and InSTI Regimen					
K103N, Y181C, and/or G190A	10/10	100.0 (69.2, 100.0)	13/13	100.0 (75.3, 100.0)	0.0 (-17.2, 17.2)
ART Class in Baseline Regimen					
Ritonavir- or Cobicistat-boosted PI	291/299	97.3 (94.8, 98.8)	146/151	96.7 (92.4, 98.9)	0.6 (-2.9, 4.2)
Cobicistat-boosted elvitegravir or an NNRTI	124/128	96.9 (92.2, 99.1)	62/64	96.9 (89.2, 99.6)	0.0 (-5.7, 5.7)
Duration of ART Regimen Prior to Enrollment					
<1 year	23/24	95.8 (78.9, 99.9)	12/12	100.0 (73.5, 100.0)	-4.5 (-25.5, 16.4)
≥1 year	392/403	97.3 (95.2, 98.6)	196/203	96.6 (93.0, 98.6)	0.7 (-2.4, 3.9)
Age (years)					
18 to 64	406/418	97.1 (95.0, 98.5)	199/206	96.6 (93.1, 98.6)	0.5 (-2.6, 3.7)
≥65	9/9	100.0 (66.4, 100.0)	9/9	100.0 (66.4, 100.0)	0.0 (-43.1, 43.1)
Age (years)					
≤Median (43 yrs)	206/215	95.8 (92.2, 98.1)	109/114	95.6 (90.1, 98.6)	0.2 (-4.8, 5.2)
>Median (43 yrs)	209/212	98.6 (95.9, 99.7)	99/101	98.0 (93.0, 99.8)	0.6 (-3.3, 4.4)
Gender					
Male	345/355	97.2 (94.9, 98.6)	179/186	96.2 (92.4, 98.5)	0.9 (-2.5, 4.4)
Female	70/72	97.2 (90.3, 99.7)	29/29	100.0 (88.1, 100.0)	-2.8 (-10.9, 5.3)

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Proportion of Subjects with Plasma HIV-1 RNA <40 Copies/mL at Secondary Timepoint by Prognostic and Demographic Factors Observed Failure Approach Study Weeks 0-24; Base Study

Prognostic and Demographic Factors	Response				Difference in Percent Response (DOR/3TC/TDF QD ISG - Baseline Regimen DSG)[†]
	DOR/3TC/TDF QD ISG at Study Week 24		Baseline Regimen DSG at Study Week 24		
	n/N	% (95% CI)	n/N	% (95% CI)	% (95% CI)
Race					
American Indian or Alaska Native	5/5	100.0 (47.8, 100.0)	2/2	100.0 (15.8, 100.0)	0.0 (-103.3, 103.3)
Asian	16/16	100.0 (79.4, 100.0)	7/7	100.0 (59.0, 100.0)	0.0 (-30.1, 30.1)
Black or African American	51/52	98.1 (89.7, 100.0)	31/31	100.0 (88.8, 100.0)	-1.8 (-9.9, 6.2)
Multiple	22/24	91.7 (73.0, 99.0)	11/11	100.0 (71.5, 100.0)	-7.6 (-30.7, 15.5)
Native Hawaiian or Other Pacific Islander	1/1	100.0 (2.5, 100.0)	0/0	N/A	N/A
White	320/329	97.3 (94.9, 98.7)	157/164	95.7 (91.4, 98.3)	1.5 (-2.2, 5.3)
Ethnicity					
Hispanic or Latino	89/95	93.7 (86.8, 97.6)	41/43	95.3 (84.2, 99.4)	-1.6 (-10.7, 7.6)
Not Hispanic or Latino	319/325	98.2 (96.0, 99.3)	164/169	97.0 (93.2, 99.0)	1.1 (-2.1, 4.3)
Unknown	7/7	100.0 (59.0, 100.0)	3/3	100.0 (29.2, 100.0)	N/A
Region					
Asia/Pacific	18/18	100.0 (81.5, 100.0)	12/12	100.0 (73.5, 100.0)	0.0 (-20.5, 20.5)
Europe	251/258	97.3 (94.5, 98.9)	127/131	96.9 (92.4, 99.2)	0.3 (-3.6, 4.2)
Latin America	43/47	91.5 (79.6, 97.6)	23/24	95.8 (78.9, 99.9)	-4.8 (-18.5, 8.9)
North America	103/104	99.0 (94.8, 100.0)	46/48	95.8 (85.7, 99.5)	3.1 (-4.2, 10.3)

[†] 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).

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

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]

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Table 2.7.3-switch48wk: 17

Proportion of Subjects with Plasma HIV-1 RNA ≥50 Copies/mL at Secondary Timepoint by Prognostic and Demographic Factors
Observed Failure Approach
Study Weeks 0-24; Base Study

Prognostic and Demographic Factors	Response				Difference in Percent Response (DOR/3TC/TDF QD ISG - Baseline Regimen DSG)[†]
	DOR/3TC/TDF QD ISG at Study Week 24		Baseline Regimen DSG at Study Week 24		
	n/N	% (95% CI)	n/N	% (95% CI)	% (95% CI)
Total	8/427	1.9 (0.8, 3.7)	4/215	1.9 (0.5, 4.7)	0.0 (-2.4, 2.4)
Baseline CD4$^+$ T-Cell Counts (cells/mm^3)					
<200 cells/mm^3	1/13	7.7 (0.2, 36.0)	0/3	0.0 (0.0, 70.8)	8.3 (-41.2, 57.9)
≥200 cells/mm^3	7/407	1.7 (0.7, 3.5)	4/209	1.9 (0.5, 4.8)	-0.2 (-2.7, 2.3)
Missing	0/7	0.0 (0.0, 41.0)	0/3	0.0 (0.0, 70.8)	0.0 (-57.0, 57.0)
Hepatitis Status[‡]					
Hep B and/or C Positive	0/12	0.0 (0.0, 26.5)	0/9	0.0 (0.0, 33.6)	0.0 (-23.0, 23.0)
Hep B and C Negative	8/415	1.9 (0.8, 3.8)	4/206	1.9 (0.5, 4.9)	-0.0 (-2.5, 2.5)
History of Selected NNRTI Mutations in Subjects on PI and InSTI Regimen					
K103N, Y181C, and/or G190A	0/10	0.0 (0.0, 30.8)	0/13	0.0 (0.0, 24.7)	0.0 (-17.2, 17.2)
ART Class in Baseline Regimen					
Ritonavir- or Cobicistat-boosted PI	5/299	1.7 (0.5, 3.9)	3/151	2.0 (0.4, 5.7)	-0.3 (-3.2, 2.5)
Cobicistat-boosted elvitegravir or an NNRTI	3/128	2.3 (0.5, 6.7)	1/64	1.6 (0.0, 8.4)	0.8 (-3.9, 5.4)
Duration of ART Regimen Prior to Enrollment					
<1 year	1/24	4.2 (0.1, 21.1)	0/12	0.0 (0.0, 26.5)	4.5 (-16.4, 25.5)
≥1 year	7/403	1.7 (0.7, 3.5)	4/203	2.0 (0.5, 5.0)	-0.2 (-2.8, 2.3)
Age (years)					
18 to 64	8/418	1.9 (0.8, 3.7)	4/206	1.9 (0.5, 4.9)	-0.0 (-2.6, 2.5)
≥65	0/9	0.0 (0.0, 33.6)	0/9	0.0 (0.0, 33.6)	0.0 (-43.1, 43.1)
Age (years)					
≤Median (43 yrs)	5/215	2.3 (0.8, 5.3)	4/114	3.5 (1.0, 8.7)	-1.2 (-5.5, 3.2)
>Median (43 yrs)	3/212	1.4 (0.3, 4.1)	0/101	0.0 (0.0, 3.6)	1.5 (-1.2, 4.2)
Gender					
Male	7/355	2.0 (0.8, 4.0)	4/186	2.2 (0.6, 5.4)	-0.2 (-3.0, 2.6)
Female	1/72	1.4 (0.0, 7.5)	0/29	0.0 (0.0, 11.9)	1.4 (-6.3, 9.1)

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Proportion of Subjects with Plasma HIV-1 RNA ≥50 Copies/mL at Secondary Timepoint by Prognostic and Demographic Factors Observed Failure Approach Study Weeks 0-24; Base Study

Prognostic and Demographic Factors	Response				Difference in Percent Response (DOR/3TC/TDF QD ISG - Baseline Regimen DSG)[†]
	DOR/3TC/TDF QD ISG at Study Week 24		Baseline Regimen DSG at Study Week 24		
	n/N	% (95% CI)	n/N	% (95% CI)	% (95% CI)
Race					
American Indian or Alaska Native	0/5	0.0 (0.0, 52.2)	0/2	0.0 (0.0, 84.2)	0.0 (-103.3, 103.3)
Asian	0/16	0.0 (0.0, 20.6)	0/7	0.0 (0.0, 41.0)	0.0 (-30.1, 30.1)
Black or African American	1/52	1.9 (0.0, 10.3)	0/31	0.0 (0.0, 11.2)	1.8 (-6.2, 9.9)
Multiple	1/24	4.2 (0.1, 21.1)	0/11	0.0 (0.0, 28.5)	4.7 (-17.9, 27.2)
Native Hawaiian or Other Pacific Islander	0/1	0.0 (0.0, 97.5)	0/0	N/A	N/A
White	6/329	1.8 (0.7, 3.9)	4/164	2.4 (0.7, 6.1)	-0.6 (-3.7, 2.4)
Ethnicity					
Hispanic or Latino	3/95	3.2 (0.7, 9.0)	2/43	4.7 (0.6, 15.8)	-1.6 (-10.1, 6.9)
Not Hispanic or Latino	5/325	1.5 (0.5, 3.6)	2/169	1.2 (0.1, 4.2)	0.3 (-2.1, 2.8)
Unknown	0/7	0.0 (0.0, 41.0)	0/3	0.0 (0.0, 70.8)	N/A
Region					
Asia/Pacific	0/18	0.0 (0.0, 18.5)	0/12	0.0 (0.0, 26.5)	0.0 (-20.5, 20.5)
Europe	5/258	1.9 (0.6, 4.5)	1/131	0.8 (0.0, 4.2)	1.2 (-1.6, 4.0)
Latin America	2/47	4.3 (0.5, 14.5)	1/24	4.2 (0.1, 21.1)	0.1 (-12.2, 12.4)
North America	1/104	1.0 (0.0, 5.2)	2/48	4.2 (0.5, 14.3)	-3.1 (-10.3, 4.2)

[†] 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).

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

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]

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Table 2.7.3-switch48wk: 18

Change from Baseline in CD4+ T-Cell Count (cells/mm3) at Primary Timepoints
by Prognostic and Demographic Factors
Observed Failure Approach
Base Study

Prognostic and Demographic Factors	Response						Difference in Mean Changes from Baseline [DOR/3TC/TDF QD ISG - Baseline Regimen DSG][†] (95% CI)
	DOR/3TC/TDF QD ISG at Study Week 48			Baseline Regimen DSG at Study Week 24			
	N	Baseline Mean	Mean Change from Baseline (95% CI)	N	Baseline Mean	Mean Change from Baseline (95% CI)	
Total	402	660.5	13.9 (-2.6, 30.4)	209	655.6	18.0 (-3.6, 39.5)	-4.0 (-31.6, 23.5)
Baseline CD4$^+$ T-Cell Counts (cells/mm^3)							
<200 cells/mm^3	12	146.7	123.9 (42.6, 205.2)	3	167.3	66.0 (-0.2, 132.2)	57.9 (-106.9, 222.7)
≥200 cells/mm^3	390	676.4	10.5 (-6.2, 27.3)	206	662.7	17.3 (-4.5, 39.1)	-6.7 (-34.6, 21.2)
Hepatitis Status[‡]							
Hepatitis B and C Negative	392	664.7	13.7 (-3.1, 30.6)	200	663.4	20.5 (-1.8, 42.8)	-6.8 (-35.2, 21.7)
Hepatitis B and/or C Positive	10	499.7	21.2 (-28.5, 70.9)	9	481.9	-38.3 (-105.3, 28.7)	59.5 (-16.3, 135.4)
Duration of ART Regimen Prior to Enrollment							
<1 year	24	541.4	74.8 (-0.9, 150.5)	12	570.1	65.0 (-63.3, 193.3)	9.8 (-124.6, 144.1)
≥1 year	378	668.1	10.1 (-6.8, 26.9)	197	660.8	15.1 (-6.7, 36.8)	-5.0 (-33.1, 23.1)
History of Selected NNRTI Mutations in Subjects on PI and InSTI Regimen							
K103N, Y181C, and/or G190A	10	640.7	4.5 (-96.3, 105.3)	13	845.5	59.4 (-46.5, 165.3)	-54.9 (-196.1, 86.3)
ART Class in Baseline Regimen							
Ritonavir- or Cobicistat-boosted PI	284	652.0	7.8 (-12.5, 28.1)	147	645.3	9.8 (-16.3, 35.9)	-2.0 (-35.8, 31.8)
Cobicistat-boosted elvitegravir or an NNRTI	118	681.0	28.7 (0.9, 56.5)	62	679.9	37.3 (-1.1, 75.8)	-8.6 (-55.7, 38.5)
Age (years)							
18 to 64	394	665.7	12.2 (-4.5, 28.9)	200	653.1	18.1 (-4.0, 40.3)	-5.9 (-34.2, 22.3)
≥65	8	407.4	98.9 (9.6, 188.1)	9	710.1	13.9 (-98.0, 125.8)	85.0 (-48.5, 218.5)
Age (years)							

Change from Baseline in CD4+ T-Cell Count (cells/mm3) at Primary Timepoints by Prognostic and Demographic Factors Observed Failure Approach Base Study

Prognostic and Demographic Factors	Response						Difference in Mean Changes from Baseline [DOR/3TC/TDF QD ISG - Baseline Regimen DSG][†] (95% CI)
	DOR/3TC/TDF QD ISG at Study Week 48			Baseline Regimen DSG at Study Week 24			
	N	Baseline Mean	Mean Change from Baseline (95% CI)	N	Baseline Mean	Mean Change from Baseline (95% CI)	
≤Median (43 Yrs)	202	650.6	16.2 (-7.0, 39.5)	110	690.6	19.7 (-14.0, 53.3)	-3.4 (-43.4, 36.5)
>Median (43 Yrs)	200	670.6	11.6 (-12.0, 35.2)	99	616.7	16.1 (-10.3, 42.5)	-4.5 (-42.7, 33.7)
Gender							
Male	334	657.4	17.0 (-0.9, 34.9)	181	651.7	10.6 (-12.5, 33.6)	6.5 (-23.1, 36.1)
Female	68	676.2	-1.4 (-44.2, 41.4)	28	680.8	65.7 (5.1, 126.3)	-67.1 (-143.5, 9.3)
Race							
American Indian or Alaska Native	5	554.4	37.8 (-229.7, 305.3)	2	461.5	-49.0 (-913.0, 815.0)	86.8 (-337.8, 511.4)
Asian	16	635.4	-24.7 (-76.4, 27.0)	7	668.4	12.0 (-108.8, 132.8)	-36.7 (-138.2, 64.8)
Black or African American	49	621.5	55.7 (14.0, 97.3)	29	702.7	62.1 (1.8, 122.4)	-6.4 (-76.5, 63.6)
Multiple	22	484.0	80.3 (23.2, 137.3)	11	648.7	45.5 (-65.5, 156.4)	34.8 (-71.7, 141.4)
Native Hawaiian or Other Pacific Islander	1	877.0	-136.0 (N/A)	0	N/A	N/A	N/A
White	309	681.6	4.7 (-14.9, 24.2)	160	649.4	9.2 (-15.6, 33.9)	-4.5 (-36.9, 27.9)
Ethnicity							
Hispanic or Latino	87	634.0	5.6 (-28.4, 39.7)	42	676.9	16.3 (-37.2, 69.8)	-10.6 (-71.5, 50.2)
Not Hispanic or Latino	308	668.5	17.1 (-2.1, 36.3)	164	644.5	18.4 (-5.5, 42.4)	-1.3 (-32.8, 30.2)
Unknown	7	639.4	-23.1 (-171.7, 125.4)	3	962.3	16.3 (-296.8, 329.5)	-39.5 (-282.5, 203.6)
Region							
Asia/Pacific	17	773.9	-34.0 (-89.8, 21.8)	12	674.5	-15.0 (-115.2, 85.2)	-19.0 (-120.2, 82.2)
Europe	245	651.9	14.3 (-7.8, 36.4)	127	638.1	16.1 (-11.8, 44.1)	-1.8 (-38.4, 34.8)
Latin America	44	595.0	17.8 (-28.3, 63.8)	23	659.4	18.3 (-42.7, 79.3)	-0.6 (-76.6, 75.5)

Change from Baseline in CD4+ T-Cell Count (cells/mm3) at Primary Timepoints by Prognostic and Demographic Factors
Observed Failure Approach
Base Study

Prognostic and Demographic Factors	Response						Difference in Mean Changes from Baseline [DOR/3TC/TDF QD ISG - Baseline Regimen DSG][†] (95% CI)
	DOR/3TC/TDF QD ISG at Study Week 48			Baseline Regimen DSG at Study Week 24			
	N	Baseline Mean	Mean Change from Baseline (95% CI)	N	Baseline Mean	Mean Change from Baseline (95% CI)	
North America	96	692.7	19.7 (-13.6, 53.1)	47	695.9	31.2 (-17.2, 79.6)	-11.5 (-69.4, 46.5)

[†] The 95% CIs were based on t-distribution.

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

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 treatment group.

Source: [P024MK1439A: adam-adsl; adeff2]

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Table 2.7.3-switch48wk: 19

Change from Baseline in CD4+ T-Cell Count (cells/mm3) at Secondary Timepoint
by Prognostic and Demographic Factors
Observed Failure Approach
Base Study

Prognostic and Demographic Factors	Response						Difference in Mean Changes from Baseline [DOR/3TC/TDF QD ISG - Baseline Regimen DSG][†] (95% CI)
	DOR/3TC/TDF QD ISG at Study Week 24			Baseline Regimen DSG at Study Week 24			
	N	Baseline Mean	Mean Change from Baseline (95% CI)	N	Baseline Mean	Mean Change from Baseline (95% CI)	
Total	412	664.5	5.1 (-11.8, 22.1)	209	655.6	18.0 (-3.6, 39.5)	-12.8 (-41.1, 15.4)
Baseline CD4$^+$ T-Cell Counts (cells/mm^3)							
<200 cells/mm^3	13	145.2	149.5 (68.3, 230.7)	3	167.3	66.0 (-0.2, 132.2)	83.5 (-87.9, 255.0)
≥200 cells/mm^3	399	681.4	0.4 (-16.7, 17.6)	206	662.7	17.3 (-4.5, 39.1)	-16.8 (-45.3, 11.7)
Hepatitis Status[‡]							
Hepatitis B and C Negative	401	665.9	7.0 (-9.7, 23.6)	200	663.4	20.5 (-1.8, 42.8)	-13.5 (-41.8, 14.8)
Hepatitis B and/or C Positive	11	615.1	-61.7 (-275.1, 151.7)	9	481.9	-38.3 (-105.3, 28.7)	-23.4 (-253.6, 206.8)
Duration of ART Regimen Prior to Enrollment							
<1 year	24	541.4	63.8 (-6.0, 133.6)	12	570.1	65.0 (-63.3, 193.3)	-1.2 (-129.0, 126.7)
≥1 year	388	672.1	1.5 (-16.0, 19.0)	197	660.8	15.1 (-6.7, 36.8)	-13.6 (-42.5, 15.4)
History of Selected NNRTI Mutations in Subjects on PI and InSTI Regimen							
K103N, Y181C, and/or G190A	10	640.7	14.8 (-101.7, 131.3)	13	845.5	59.4 (-46.5, 165.3)	-44.6 (-193.3, 104.2)
ART Class in Baseline Regimen							
Ritonavir- or Cobicistat-boosted PI	290	654.6	-6.1 (-27.5, 15.3)	147	645.3	9.8 (-16.3, 35.9)	-15.9 (-51.1, 19.4)
Cobicistat-boosted elvitegravir or an NNRTI	122	688.2	31.8 (5.7, 57.8)	62	679.9	37.3 (-1.1, 75.8)	-5.6 (-50.9, 39.8)
Age (years)							
18 to 64	403	671.0	4.5 (-12.8, 21.8)	200	653.1	18.1 (-4.0, 40.3)	-13.7 (-42.7, 15.3)
≥65	9	376.2	34.4 (-30.5, 99.4)	9	710.1	13.9 (-98.0, 125.8)	20.6 (-98.4, 139.5)
Age (years)							

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Change from Baseline in CD4+ T-Cell Count (cells/mm3) at Secondary Timepoint by Prognostic and Demographic Factors Observed Failure Approach Base Study

Prognostic and Demographic Factors	Response						Difference in Mean Changes from Baseline [DOR/3TC/TDF QD ISG - Baseline Regimen DSG][†] (95% CI)
	DOR/3TC/TDF QD ISG at Study Week 24			Baseline Regimen DSG at Study Week 24			
	N	Baseline Mean	Mean Change from Baseline (95% CI)	N	Baseline Mean	Mean Change from Baseline (95% CI)	
≤Median (43 Yrs)	208	657.0	7.4 (-17.9, 32.6)	110	690.6	19.7 (-14.0, 53.3)	-12.3 (-54.7, 30.1)
>Median (43 Yrs)	204	672.2	2.9 (-19.8, 25.6)	99	616.7	16.1 (-10.3, 42.5)	-13.2 (-50.5, 24.1)
Gender							
Male	343	658.8	9.7 (-7.8, 27.3)	181	651.7	10.6 (-12.5, 33.6)	-0.8 (-30.2, 28.5)
Female	69	692.8	-17.7 (-69.9, 34.5)	28	680.8	65.7 (5.1, 126.3)	-83.4 (-173.2, 6.3)
Race							
American Indian or Alaska Native	5	554.4	31.0 (-245.9, 307.9)	2	461.5	-49.0 (-913.0, 815.0)	80.0 (-358.9, 518.9)
Asian	16	635.4	-26.1 (-78.1, 26.0)	7	668.4	12.0 (-108.8, 132.8)	-38.1 (-139.9, 63.8)
Black or African American	49	620.3	29.1 (-19.0, 77.3)	29	702.7	62.1 (1.8, 122.4)	-33.0 (-109.6, 43.7)
Multiple	22	484.0	60.4 (-1.5, 122.3)	11	648.7	45.5 (-65.5, 156.4)	15.0 (-96.8, 126.7)
Native Hawaiian or Other Pacific Islander	1	877.0	-283.0 (N/A)	0	N/A	N/A	N/A
White	319	686.3	-0.3 (-20.1, 19.5)	160	649.4	9.2 (-15.6, 33.9)	-9.5 (-42.4, 23.5)
Ethnicity							
Hispanic or Latino	91	635.6	28.5 (-4.6, 61.6)	42	676.9	16.3 (-37.2, 69.8)	12.2 (-47.9, 72.4)
Not Hispanic or Latino	315	673.6	-2.8 (-22.6, 16.9)	164	644.5	18.4 (-5.5, 42.4)	-21.2 (-53.5, 11.1)
Unknown	6	626.7	68.2 (-164.0, 300.4)	3	962.3	16.3 (-296.8, 329.5)	51.8 (-280.5, 384.2)
Region							
Asia/Pacific	17	757.5	-48.8 (-104.3, 6.7)	12	674.5	-15.0 (-115.2, 85.2)	-33.8 (-134.8, 67.1)
Europe	253	663.6	1.4 (-21.7, 24.6)	127	638.1	16.1 (-11.8, 44.1)	-14.7 (-52.8, 23.4)
Latin America	45	596.8	55.6 (11.8, 99.4)	23	659.4	18.3 (-42.7, 79.3)	37.3 (-36.5, 111.1)

Change from Baseline in CD4+ T-Cell Count (cells/mm3) at Secondary Timepoint by Prognostic and Demographic Factors Observed Failure Approach Base Study

Prognostic and Demographic Factors	Response						Difference in Mean Changes from Baseline [DOR/3TC/TDF QD ISG - Baseline Regimen DSG][†] (95% CI)
	DOR/3TC/TDF QD ISG at Study Week 24			Baseline Regimen DSG at Study Week 24			
	N	Baseline Mean	Mean Change from Baseline (95% CI)	N	Baseline Mean	Mean Change from Baseline (95% CI)	
North America	97	682.0	0.9 (-31.6, 33.3)	47	695.9	31.2 (-17.2, 79.6)	-30.3 (-87.3, 26.7)

[†] The 95% CIs were based on t-distribution.

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

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 treatment group.

Source: [P024MK1439A: adam-adsl; adeff2]

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Table 2.7.3-switch48wk: 20

Proportion of Subjects with Plasma HIV-1 RNA <50 Copies/mL at Primary Timepoints by Prognostic and Demographic Factors FDA Snapshot Approach Study Weeks 0-48; Base Study

Prognostic and Demographic Factors	Response				Difference in Percent Response (DOR/3TC/TDF QD ISG - Baseline Regimen DSG)[†]
	DOR/3TC/TDF QD ISG at Study Week 48		Baseline Regimen DSG at Study Week 24		
	n/N	% (95% CI)	n/N	% (95% CI)	% (95% CI)
Total	406/447	90.8 (87.8, 93.3)	211/223	94.6 (90.8, 97.2)	-3.8 (-7.9, 0.3)
Baseline CD4$^+$ T-Cell Counts (cells/mm^3)					
<200 cells/mm^3	11/13	84.6 (54.6, 98.1)	3/4	75.0 (19.4, 99.4)	8.3 (-48.5, 65.2)
≥200 cells/mm^3	388/426	91.1 (88.0, 93.6)	205/216	94.9 (91.1, 97.4)	-3.8 (-7.9, 0.3)
Missing	7/8	87.5 (47.3, 99.7)	3/3	100.0 (29.2, 100.0)	-20.0 (-82.5, 42.5)
Hepatitis Status[‡]					
Hep B and/or C Positive	11/14	78.6 (49.2, 95.3)	9/9	100.0 (66.4, 100.0)	-23.1 (-54.3, 8.2)
Hep B and C Negative	395/433	91.2 (88.2, 93.7)	202/214	94.4 (90.4, 97.1)	-3.2 (-7.4, 1.0)
History of Selected NNRTI Mutations in Subjects on PI and InSTI Regimen					
K103N, Y181C, and/or G190A	10/11	90.9 (58.7, 99.8)	13/13	100.0 (75.3, 100.0)	-9.1 (-32.1, 13.9)
ART Class in Baseline Regimen					
Ritonavir- or Cobicistat-boosted PI	284/316	89.9 (86.0, 93.0)	148/157	94.3 (89.4, 97.3)	-4.4 (-9.4, 0.6)
Cobicistat-boosted elvitegravir or an NNRTI	122/131	93.1 (87.4, 96.8)	63/66	95.5 (87.3, 99.1)	-2.3 (-9.3, 4.7)
Duration of ART Regimen Prior to Enrollment					
<1 year	23/26	88.5 (69.8, 97.6)	12/12	100.0 (73.5, 100.0)	-11.2 (-33.7, 11.2)
≥1 year	383/421	91.0 (87.8, 93.5)	199/211	94.3 (90.3, 97.0)	-3.3 (-7.6, 0.9)
Age (years)					
18 to 64	398/438	90.9 (87.8, 93.4)	202/214	94.4 (90.4, 97.1)	-3.6 (-7.8, 0.6)
≥65	8/9	88.9 (51.8, 99.7)	9/9	100.0 (66.4, 100.0)	-6.9 (-51.6, 37.7)
Age (years)					
≤Median (43 yrs)	201/230	87.4 (82.4, 91.4)	110/118	93.2 (87.1, 97.0)	-5.9 (-12.4, 0.6)
>Median (43 yrs)	205/217	94.5 (90.5, 97.1)	101/105	96.2 (90.5, 99.0)	-1.6 (-6.8, 3.5)
Gender					
Male	338/372	90.9 (87.5, 93.6)	182/194	93.8 (89.4, 96.8)	-3.0 (-7.6, 1.6)
Female	68/75	90.7 (81.7, 96.2)	29/29	100.0 (88.1, 100.0)	-9.3 (-18.9, 0.3)

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Proportion of Subjects with Plasma HIV-1 RNA <50 Copies/mL at Primary Timepoints by Prognostic and Demographic Factors FDA Snapshot Approach Study Weeks 0-48; Base Study

Prognostic and Demographic Factors	Response				Difference in Percent Response (DOR/3TC/TDF QD ISG - Baseline Regimen DSG)[†]
	DOR/3TC/TDF QD ISG at Study Week 48		Baseline Regimen DSG at Study Week 24		
	n/N	% (95% CI)	n/N	% (95% CI)	% (95% CI)
Race					
American Indian or Alaska Native	5/5	100.0 (47.8, 100.0)	2/2	100.0 (15.8, 100.0)	0.0 (-103.3, 103.3)
Asian	16/17	94.1 (71.3, 99.9)	7/8	87.5 (47.3, 99.7)	6.1 (-29.0, 41.3)
Black or African American	51/56	91.1 (80.4, 97.0)	31/34	91.2 (76.3, 98.1)	-0.2 (-13.4, 13.0)
Multiple	23/24	95.8 (78.9, 99.9)	11/11	100.0 (71.5, 100.0)	-4.7 (-27.2, 17.9)
Native Hawaiian or Other Pacific Islander	1/1	100.0 (2.5, 100.0)	0/0	N/A	N/A
White	310/344	90.1 (86.5, 93.1)	160/168	95.2 (90.8, 97.9)	-5.2 (-9.8, -0.5)
Ethnicity					
Hispanic or Latino	87/99	87.9 (79.8, 93.6)	41/45	91.1 (78.8, 97.5)	-3.2 (-14.6, 8.2)
Not Hispanic or Latino	312/341	91.5 (88.0, 94.2)	167/175	95.4 (91.2, 98.0)	-4.0 (-8.4, 0.5)
Unknown	7/7	100.0 (59.0, 100.0)	3/3	100.0 (29.2, 100.0)	N/A
Region					
Asia/Pacific	17/19	89.5 (66.9, 98.7)	12/12	100.0 (73.5, 100.0)	-11.5 (-35.8, 12.9)
Europe	245/268	91.4 (87.4, 94.5)	130/137	94.9 (89.8, 97.9)	-3.5 (-8.7, 1.7)
Latin America	44/49	89.8 (77.8, 96.6)	23/24	95.8 (78.9, 99.9)	-6.2 (-20.0, 7.7)
North America	100/111	90.1 (83.0, 94.9)	46/50	92.0 (80.8, 97.8)	-2.0 (-12.1, 8.1)

[†] 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).

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

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]

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Table 2.7.3-switch48wk: 21

Proportion of Subjects with Plasma HIV-1 RNA <40 Copies/mL at Primary Timepoints by Prognostic and Demographic Factors
FDA Snapshot Approach
Study Weeks 0-48; Base Study

Prognostic and Demographic Factors	Response				Difference in Percent Response (DOR/3TC/TDF QD ISG - Baseline Regimen DSG)[†]
	DOR/3TC/TDF QD ISG at Study Week 48		Baseline Regimen DSG at Study Week 24		
	n/N	% (95% CI)	n/N	% (95% CI)	% (95% CI)
Total	401/447	89.7 (86.5, 92.4)	208/223	93.3 (89.1, 96.2)	-3.6 (-8.0, 0.9)
Baseline CD4$^+$ T-Cell Counts (cells/mm^3)					
<200 cells/mm^3	10/13	76.9 (46.2, 95.0)	3/4	75.0 (19.4, 99.4)	0.0 (-58.1, 58.1)
≥200 cells/mm^3	384/426	90.1 (86.9, 92.8)	202/216	93.5 (89.4, 96.4)	-3.4 (-7.8, 1.1)
Missing	7/8	87.5 (47.3, 99.7)	3/3	100.0 (29.2, 100.0)	-20.0 (-82.5, 42.5)
Hepatitis Status[‡]					
Hep B and/or C Positive	11/14	78.6 (49.2, 95.3)	9/9	100.0 (66.4, 100.0)	-23.1 (-54.3, 8.2)
Hep B and C Negative	390/433	90.1 (86.9, 92.7)	199/214	93.0 (88.7, 96.0)	-2.9 (-7.5, 1.6)
History of Selected NNRTI Mutations in Subjects on PI and InSTI Regimen					
K103N, Y181C, and/or G190A	10/11	90.9 (58.7, 99.8)	13/13	100.0 (75.3, 100.0)	-9.1 (-32.1, 13.9)
ART Class in Baseline Regimen					
Ritonavir- or Cobicistat-boosted PI	280/316	88.6 (84.6, 91.9)	146/157	93.0 (87.8, 96.5)	-4.4 (-9.8, 1.0)
Cobicistat-boosted elvitegravir or an NNRTI	121/131	92.4 (86.4, 96.3)	62/66	93.9 (85.2, 98.3)	-1.6 (-9.2, 6.1)
Duration of ART Regimen Prior to Enrollment					
<1 year	23/26	88.5 (69.8, 97.6)	12/12	100.0 (73.5, 100.0)	-11.2 (-33.7, 11.2)
≥1 year	378/421	89.8 (86.5, 92.5)	196/211	92.9 (88.5, 96.0)	-3.1 (-7.7, 1.5)
Age (years)					
18 to 64	393/438	89.7 (86.5, 92.4)	199/214	93.0 (88.7, 96.0)	-3.3 (-7.9, 1.2)
≥65	8/9	88.9 (51.8, 99.7)	9/9	100.0 (66.4, 100.0)	-6.9 (-51.6, 37.7)
Age (years)					
≤Median (43 yrs)	199/230	86.5 (81.4, 90.7)	109/118	92.4 (86.0, 96.5)	-5.9 (-12.7, 0.8)
>Median (43 yrs)	202/217	93.1 (88.9, 96.1)	99/105	94.3 (88.0, 97.9)	-1.1 (-7.0, 4.8)
Gender					
Male	333/372	89.5 (85.9, 92.4)	179/194	92.3 (87.6, 95.6)	-2.8 (-7.7, 2.2)
Female	68/75	90.7 (81.7, 96.2)	29/29	100.0 (88.1, 100.0)	-9.3 (-18.9, 0.3)

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Proportion of Subjects with Plasma HIV-1 RNA <40 Copies/mL at Primary Timepoints by Prognostic and Demographic Factors FDA Snapshot Approach Study Weeks 0-48; Base Study

Prognostic and Demographic Factors	Response				Difference in Percent Response (DOR/3TC/TDF QD ISG - Baseline Regimen DSG)[†]
	DOR/3TC/TDF QD ISG at Study Week 48		Baseline Regimen DSG at Study Week 24		
	n/N	% (95% CI)	n/N	% (95% CI)	% (95% CI)
Race					
American Indian or Alaska Native	5/5	100.0 (47.8, 100.0)	2/2	100.0 (15.8, 100.0)	0.0 (-103.3, 103.3)
Asian	16/17	94.1 (71.3, 99.9)	7/8	87.5 (47.3, 99.7)	6.1 (-29.0, 41.3)
Black or African American	51/56	91.1 (80.4, 97.0)	31/34	91.2 (76.3, 98.1)	-0.2 (-13.4, 13.0)
Multiple	21/24	87.5 (67.6, 97.3)	11/11	100.0 (71.5, 100.0)	-14.0 (-39.0, 11.1)
Native Hawaiian or Other Pacific Islander	1/1	100.0 (2.5, 100.0)	0/0	N/A	N/A
White	307/344	89.2 (85.5, 92.3)	157/168	93.5 (88.6, 96.7)	-4.2 (-9.3, 0.9)
Ethnicity					
Hispanic or Latino	85/99	85.9 (77.4, 92.0)	41/45	91.1 (78.8, 97.5)	-5.2 (-16.8, 6.4)
Not Hispanic or Latino	309/341	90.6 (87.0, 93.5)	164/175	93.7 (89.0, 96.8)	-3.2 (-8.1, 1.7)
Unknown	7/7	100.0 (59.0, 100.0)	3/3	100.0 (29.2, 100.0)	N/A
Region					
Asia/Pacific	17/19	89.5 (66.9, 98.7)	12/12	100.0 (73.5, 100.0)	-11.5 (-35.8, 12.9)
Europe	243/268	90.7 (86.5, 93.9)	127/137	92.7 (87.0, 96.4)	-2.0 (-7.8, 3.7)
Latin America	43/49	87.8 (75.2, 95.4)	23/24	95.8 (78.9, 99.9)	-8.0 (-22.1, 6.2)
North America	98/111	88.3 (80.8, 93.6)	46/50	92.0 (80.8, 97.8)	-3.8 (-14.1, 6.6)

[†] 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).

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

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]

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Table 2.7.3-switch48wk: 22

Proportion of Subjects with Plasma HIV-1 RNA ≥50 Copies/mL at Primary Timepoints by Prognostic and Demographic Factors
FDA Snapshot Approach
Study Weeks 0-48; Base Study

Prognostic and Demographic Factors	Response				Difference in Percent Response (DOR/3TC/TDF QD ISG - Baseline Regimen DSG)[†]
	DOR/3TC/TDF QD ISG at Study Week 48		Baseline Regimen DSG at Study Week 24		
	n/N	% (95% CI)	n/N	% (95% CI)	% (95% CI)
Total	7/447	1.6 (0.6, 3.2)	4/223	1.8 (0.5, 4.5)	-0.2 (-2.5, 2.1)
Baseline CD4$^+$ T-Cell Counts (cells/mm^3)					
<200 cells/mm^3	1/13	7.7 (0.2, 36.0)	0/4	0.0 (0.0, 60.2)	8.3 (-30.5, 47.2)
≥200 cells/mm^3	6/426	1.4 (0.5, 3.0)	4/216	1.9 (0.5, 4.7)	-0.5 (-2.8, 1.9)
Missing	0/8	0.0 (0.0, 36.9)	0/3	0.0 (0.0, 70.8)	0.0 (-53.2, 53.2)
Hepatitis Status[‡]					
Hep B and/or C Positive	0/14	0.0 (0.0, 23.2)	0/9	0.0 (0.0, 33.6)	0.0 (-22.0, 22.0)
Hep B and C Negative	7/433	1.6 (0.7, 3.3)	4/214	1.9 (0.5, 4.7)	-0.3 (-2.6, 2.1)
History of Selected NNRTI Mutations in Subjects on PI and InSTI Regimen					
K103N, Y181C, and/or G190A	0/11	0.0 (0.0, 28.5)	0/13	0.0 (0.0, 24.7)	0.0 (-16.2, 16.2)
ART Class in Baseline Regimen					
Ritonavir- or Cobicistat-boosted PI	7/316	2.2 (0.9, 4.5)	3/157	1.9 (0.4, 5.5)	0.3 (-2.6, 3.2)
Cobicistat-boosted elvitegravir or an NNRTI	0/131	0.0 (0.0, 2.8)	1/66	1.5 (0.0, 8.2)	-1.5 (-5.3, 2.2)
Duration of ART Regimen Prior to Enrollment					
<1 year	1/26	3.8 (0.1, 19.6)	0/12	0.0 (0.0, 26.5)	4.3 (-16.4, 24.9)
≥1 year	6/421	1.4 (0.5, 3.1)	4/211	1.9 (0.5, 4.8)	-0.5 (-2.9, 1.9)
Age (years)					
18 to 64	7/438	1.6 (0.6, 3.3)	4/214	1.9 (0.5, 4.7)	-0.2 (-2.6, 2.1)
≥65	0/9	0.0 (0.0, 33.6)	0/9	0.0 (0.0, 33.6)	0.0 (-43.1, 43.1)
Age (years)					
≤Median (43 yrs)	7/230	3.0 (1.2, 6.2)	4/118	3.4 (0.9, 8.5)	-0.3 (-4.6, 4.1)
>Median (43 yrs)	0/217	0.0 (0.0, 1.7)	0/105	0.0 (0.0, 3.5)	0.0 (-2.1, 2.1)
Gender					
Male	6/372	1.6 (0.6, 3.5)	4/194	2.1 (0.6, 5.2)	-0.4 (-3.1, 2.2)
Female	1/75	1.3 (0.0, 7.2)	0/29	0.0 (0.0, 11.9)	1.3 (-6.3, 8.9)

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Proportion of Subjects with Plasma HIV-1 RNA ≥50 Copies/mL at Primary Timepoints by Prognostic and Demographic Factors FDA Snapshot Approach Study Weeks 0-48; Base Study

Prognostic and Demographic Factors	Response				Difference in Percent Response (DOR/3TC/TDF QD ISG - Baseline Regimen DSG)[†]
	DOR/3TC/TDF QD ISG at Study Week 48		Baseline Regimen DSG at Study Week 24		
	n/N	% (95% CI)	n/N	% (95% CI)	% (95% CI)
Race					
American Indian or Alaska Native	0/5	0.0 (0.0, 52.2)	0/2	0.0 (0.0, 84.2)	0.0 (-103.3, 103.3)
Asian	0/17	0.0 (0.0, 19.5)	0/8	0.0 (0.0, 36.9)	0.0 (-26.8, 26.8)
Black or African American	1/56	1.8 (0.0, 9.6)	0/34	0.0 (0.0, 10.3)	1.6 (-5.8, 9.1)
Multiple	1/24	4.2 (0.1, 21.1)	0/11	0.0 (0.0, 28.5)	4.7 (-17.9, 27.2)
Native Hawaiian or Other Pacific Islander	0/1	0.0 (0.0, 97.5)	0/0	N/A	N/A
White	5/344	1.5 (0.5, 3.4)	4/168	2.4 (0.7, 6.0)	-0.9 (-3.8, 2.0)
Ethnicity					
Hispanic or Latino	3/99	3.0 (0.6, 8.6)	2/45	4.4 (0.5, 15.1)	-1.5 (-9.7, 6.7)
Not Hispanic or Latino	4/341	1.2 (0.3, 3.0)	2/175	1.1 (0.1, 4.1)	0.1 (-2.3, 2.4)
Unknown	0/7	0.0 (0.0, 41.0)	0/3	0.0 (0.0, 70.8)	N/A
Region					
Asia/Pacific	0/19	0.0 (0.0, 17.6)	0/12	0.0 (0.0, 26.5)	0.0 (-19.7, 19.7)
Europe	5/268	1.9 (0.6, 4.3)	1/137	0.7 (0.0, 4.0)	1.1 (-1.5, 3.8)
Latin America	2/49	4.1 (0.5, 14.0)	1/24	4.2 (0.1, 21.1)	-0.1 (-12.3, 12.1)
North America	0/111	0.0 (0.0, 3.3)	2/50	4.0 (0.5, 13.7)	-4.0 (-10.7, 2.8)

[†] 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).

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

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]

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Table 2.7.3-switch48wk: 23

Proportion of Subjects with Plasma HIV-1 RNA <50 Copies/mL at Secondary Timepoint by Prognostic and Demographic Factors FDA Snapshot Approach Study Weeks 0-24; Base Study

Prognostic and Demographic Factors	Response				Difference in Percent Response (DOR/3TC/TDF QD ISG - Baseline Regimen DSG)[†]
	DOR/3TC/TDF QD ISG at Study Week 24		Baseline Regimen DSG at Study Week 24		
	n/N	% (95% CI)	n/N	% (95% CI)	% (95% CI)
Total	419/447	93.7 (91.1, 95.8)	211/223	94.6 (90.8, 97.2)	-0.9 (-4.7, 3.0)
Baseline CD4$^+$ T-Cell Counts (cells/mm^3)					
<200 cells/mm^3	12/13	92.3 (64.0, 99.8)	3/4	75.0 (19.4, 99.4)	16.7 (-38.5, 71.9)
≥200 cells/mm^3	400/426	93.9 (91.2, 96.0)	205/216	94.9 (91.1, 97.4)	-1.0 (-4.8, 2.8)
Missing	7/8	87.5 (47.3, 99.7)	3/3	100.0 (29.2, 100.0)	-20.0 (-82.5, 42.5)
Hepatitis Status[‡]					
Hep B and/or C Positive	12/14	85.7 (57.2, 98.2)	9/9	100.0 (66.4, 100.0)	-15.4 (-44.4, 13.7)
Hep B and C Negative	407/433	94.0 (91.3, 96.0)	202/214	94.4 (90.4, 97.1)	-0.4 (-4.3, 3.5)
History of Selected NNRTI Mutations in Subjects on PI and InSTI Regimen					
K103N, Y181C, and/or G190A	10/11	90.9 (58.7, 99.8)	13/13	100.0 (75.3, 100.0)	-9.1 (-32.1, 13.9)
ART Class in Baseline Regimen					
Ritonavir- or Cobicistat-boosted PI	294/316	93.0 (89.6, 95.6)	148/157	94.3 (89.4, 97.3)	-1.2 (-5.9, 3.5)
Cobicistat-boosted elvitegravir or an NNRTI	125/131	95.4 (90.3, 98.3)	63/66	95.5 (87.3, 99.1)	-0.0 (-6.6, 6.5)
Duration of ART Regimen Prior to Enrollment					
<1 year	23/26	88.5 (69.8, 97.6)	12/12	100.0 (73.5, 100.0)	-11.2 (-33.7, 11.2)
≥1 year	396/421	94.1 (91.4, 96.1)	199/211	94.3 (90.3, 97.0)	-0.2 (-4.2, 3.7)
Age (years)					
18 to 64	410/438	93.6 (90.9, 95.7)	202/214	94.4 (90.4, 97.1)	-0.8 (-4.8, 3.1)
≥65	9/9	100.0 (66.4, 100.0)	9/9	100.0 (66.4, 100.0)	0.0 (-43.1, 43.1)
Age (years)					
≤Median (43 yrs)	210/230	91.3 (86.9, 94.6)	110/118	93.2 (87.1, 97.0)	-2.0 (-8.1, 4.1)
>Median (43 yrs)	209/217	96.3 (92.9, 98.4)	101/105	96.2 (90.5, 99.0)	0.2 (-4.7, 5.0)
Gender					
Male	348/372	93.5 (90.6, 95.8)	182/194	93.8 (89.4, 96.8)	-0.3 (-4.6, 4.1)
Female	71/75	94.7 (86.9, 98.5)	29/29	100.0 (88.1, 100.0)	-5.3 (-14.0, 3.4)

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Proportion of Subjects with Plasma HIV-1 RNA <50 Copies/mL at Secondary Timepoint by Prognostic and Demographic Factors FDA Snapshot Approach Study Weeks 0-24; Base Study

Prognostic and Demographic Factors	Response				Difference in Percent Response (DOR/3TC/TDF QD ISG - Baseline Regimen DSG)[†]
	DOR/3TC/TDF QD ISG at Study Week 24		Baseline Regimen DSG at Study Week 24		
	n/N	% (95% CI)	n/N	% (95% CI)	% (95% CI)
Race					
American Indian or Alaska Native	5/5	100.0 (47.8, 100.0)	2/2	100.0 (15.8, 100.0)	0.0 (-103.3, 103.3)
Asian	16/17	94.1 (71.3, 99.9)	7/8	87.5 (47.3, 99.7)	6.1 (-29.0, 41.3)
Black or African American	51/56	91.1 (80.4, 97.0)	31/34	91.2 (76.3, 98.1)	-0.2 (-13.4, 13.0)
Multiple	23/24	95.8 (78.9, 99.9)	11/11	100.0 (71.5, 100.0)	-4.7 (-27.2, 17.9)
Native Hawaiian or Other Pacific Islander	1/1	100.0 (2.5, 100.0)	0/0	N/A	N/A
White	323/344	93.9 (90.8, 96.2)	160/168	95.2 (90.8, 97.9)	-1.4 (-5.6, 2.9)
Ethnicity					
Hispanic or Latino	92/99	92.9 (86.0, 97.1)	41/45	91.1 (78.8, 97.5)	2.0 (-8.7, 12.6)
Not Hispanic or Latino	320/341	93.8 (90.7, 96.1)	167/175	95.4 (91.2, 98.0)	-1.6 (-5.8, 2.6)
Unknown	7/7	100.0 (59.0, 100.0)	3/3	100.0 (29.2, 100.0)	N/A
Region					
Asia/Pacific	18/19	94.7 (74.0, 99.9)	12/12	100.0 (73.5, 100.0)	-7.0 (-30.0, 15.9)
Europe	253/268	94.4 (90.9, 96.8)	130/137	94.9 (89.8, 97.9)	-0.5 (-5.3, 4.4)
Latin America	45/49	91.8 (80.4, 97.7)	23/24	95.8 (78.9, 99.9)	-4.4 (-17.8, 9.1)
North America	103/111	92.8 (86.3, 96.8)	46/50	92.0 (80.8, 97.8)	0.6 (-9.1, 10.4)

[†] 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).

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

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]

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Table 2.7.3-switch48wk: 24

Proportion of Subjects with Plasma HIV-1 RNA <40 Copies/mL at Secondary Timepoint by Prognostic and Demographic Factors FDA Snapshot Approach Study Weeks 0-24; Base Study

Prognostic and Demographic Factors	Response				Difference in Percent Response (DOR/3TC/TDF QD ISG - Baseline Regimen DSG)[†]
	DOR/3TC/TDF QD ISG at Study Week 24		Baseline Regimen DSG at Study Week 24		
	n/N	% (95% CI)	n/N	% (95% CI)	% (95% CI)
Total	415/447	92.8 (90.0, 95.1)	208/223	93.3 (89.1, 96.2)	-0.4 (-4.6, 3.7)
Baseline CD4$^+$ T-Cell Counts (cells/mm^3)					
<200 cells/mm^3	12/13	92.3 (64.0, 99.8)	3/4	75.0 (19.4, 99.4)	16.7 (-38.5, 71.9)
≥200 cells/mm^3	396/426	93.0 (90.1, 95.2)	202/216	93.5 (89.4, 96.4)	-0.5 (-4.7, 3.6)
Missing	7/8	87.5 (47.3, 99.7)	3/3	100.0 (29.2, 100.0)	-20.0 (-82.5, 42.5)
Hepatitis Status[‡]					
Hep B and/or C Positive	12/14	85.7 (57.2, 98.2)	9/9	100.0 (66.4, 100.0)	-15.4 (-44.4, 13.7)
Hep B and C Negative	403/433	93.1 (90.3, 95.3)	199/214	93.0 (88.7, 96.0)	0.1 (-4.2, 4.4)
History of Selected NNRTI Mutations in Subjects on PI and InSTI Regimen					
K103N, Y181C, and/or G190A	10/11	90.9 (58.7, 99.8)	13/13	100.0 (75.3, 100.0)	-9.1 (-32.1, 13.9)
ART Class in Baseline Regimen					
Ritonavir- or Cobicistat-boosted PI	291/316	92.1 (88.5, 94.8)	146/157	93.0 (87.8, 96.5)	-0.9 (-6.0, 4.2)
Cobicistat-boosted elvitegravir or an NNRTI	124/131	94.7 (89.3, 97.8)	62/66	93.9 (85.2, 98.3)	0.7 (-6.6, 8.0)
Duration of ART Regimen Prior to Enrollment					
<1 year	23/26	88.5 (69.8, 97.6)	12/12	100.0 (73.5, 100.0)	-11.2 (-33.7, 11.2)
≥1 year	392/421	93.1 (90.3, 95.3)	196/211	92.9 (88.5, 96.0)	0.2 (-4.1, 4.6)
Age (years)					
18 to 64	406/438	92.7 (89.8, 94.9)	199/214	93.0 (88.7, 96.0)	-0.3 (-4.6, 4.0)
≥65	9/9	100.0 (66.4, 100.0)	9/9	100.0 (66.4, 100.0)	0.0 (-43.1, 43.1)
Age (years)					
≤Median (43 yrs)	206/230	89.6 (84.9, 93.2)	109/118	92.4 (86.0, 96.5)	-2.8 (-9.3, 3.6)
>Median (43 yrs)	209/217	96.3 (92.9, 98.4)	99/105	94.3 (88.0, 97.9)	2.1 (-3.4, 7.6)
Gender					
Male	345/372	92.7 (89.6, 95.2)	179/194	92.3 (87.6, 95.6)	0.5 (-4.2, 5.2)
Female	70/75	93.3 (85.1, 97.8)	29/29	100.0 (88.1, 100.0)	-6.6 (-15.6, 2.4)

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Proportion of Subjects with Plasma HIV-1 RNA <40 Copies/mL at Secondary Timepoint by Prognostic and Demographic Factors FDA Snapshot Approach Study Weeks 0-24; Base Study

Prognostic and Demographic Factors	Response				Difference in Percent Response (DOR/3TC/TDF QD ISG - Baseline Regimen DSG)[†]
	DOR/3TC/TDF QD ISG at Study Week 24		Baseline Regimen DSG at Study Week 24		
	n/N	% (95% CI)	n/N	% (95% CI)	% (95% CI)
Race					
American Indian or Alaska Native	5/5	100.0 (47.8, 100.0)	2/2	100.0 (15.8, 100.0)	0.0 (-103.3, 103.3)
Asian	16/17	94.1 (71.3, 99.9)	7/8	87.5 (47.3, 99.7)	6.1 (-29.0, 41.3)
Black or African American	51/56	91.1 (80.4, 97.0)	31/34	91.2 (76.3, 98.1)	-0.2 (-13.4, 13.0)
Multiple	22/24	91.7 (73.0, 99.0)	11/11	100.0 (71.5, 100.0)	-7.6 (-30.7, 15.5)
Native Hawaiian or Other Pacific Islander	1/1	100.0 (2.5, 100.0)	0/0	N/A	N/A
White	320/344	93.0 (89.8, 95.5)	157/168	93.5 (88.6, 96.7)	-0.5 (-5.2, 4.3)
Ethnicity					
Hispanic or Latino	89/99	89.9 (82.2, 95.0)	41/45	91.1 (78.8, 97.5)	-1.1 (-12.1, 10.0)
Not Hispanic or Latino	319/341	93.5 (90.4, 95.9)	164/175	93.7 (89.0, 96.8)	-0.2 (-4.8, 4.4)
Unknown	7/7	100.0 (59.0, 100.0)	3/3	100.0 (29.2, 100.0)	N/A
Region					
Asia/Pacific	18/19	94.7 (74.0, 99.9)	12/12	100.0 (73.5, 100.0)	-7.0 (-30.0, 15.9)
Europe	251/268	93.7 (90.0, 96.3)	127/137	92.7 (87.0, 96.4)	1.0 (-4.5, 6.4)
Latin America	43/49	87.8 (75.2, 95.4)	23/24	95.8 (78.9, 99.9)	-8.8 (-23.3, 5.7)
North America	103/111	92.8 (86.3, 96.8)	46/50	92.0 (80.8, 97.8)	0.6 (-9.1, 10.4)

[†] 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).

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

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]

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Table 2.7.3-switch48wk: 25

Proportion of Subjects with Plasma HIV-1 RNA ≥50 Copies/mL at Secondary Timepoint by Prognostic and Demographic Factors
FDA Snapshot Approach
Study Weeks 0-24; Base Study

Prognostic and Demographic Factors	Response				Difference in Percent Response (DOR/3TC/TDF QD ISG - Baseline Regimen DSG)[†]
	DOR/3TC/TDF QD ISG at Study Week 24		Baseline Regimen DSG at Study Week 24		
	n/N	% (95% CI)	n/N	% (95% CI)	% (95% CI)
Total	8/447	1.8 (0.8, 3.5)	4/223	1.8 (0.5, 4.5)	-0.0 (-2.3, 2.3)
Baseline CD4$^+$ T-Cell Counts (cells/mm^3)					
<200 cells/mm^3	1/13	7.7 (0.2, 36.0)	0/4	0.0 (0.0, 60.2)	8.3 (-30.5, 47.2)
≥200 cells/mm^3	7/426	1.6 (0.7, 3.4)	4/216	1.9 (0.5, 4.7)	-0.2 (-2.6, 2.2)
Missing	0/8	0.0 (0.0, 36.9)	0/3	0.0 (0.0, 70.8)	0.0 (-53.2, 53.2)
Hepatitis Status[‡]					
Hep B and/or C Positive	0/14	0.0 (0.0, 23.2)	0/9	0.0 (0.0, 33.6)	0.0 (-22.0, 22.0)
Hep B and C Negative	8/433	1.8 (0.8, 3.6)	4/214	1.9 (0.5, 4.7)	-0.0 (-2.5, 2.4)
History of Selected NNRTI Mutations in Subjects on PI and InSTI Regimen					
K103N, Y181C, and/or G190A	0/11	0.0 (0.0, 28.5)	0/13	0.0 (0.0, 24.7)	0.0 (-16.2, 16.2)
ART Class in Baseline Regimen					
Ritonavir- or Cobicistat-boosted PI	5/316	1.6 (0.5, 3.7)	3/157	1.9 (0.4, 5.5)	-0.3 (-3.1, 2.4)
Cobicistat-boosted elvitegravir or an NNRTI	3/131	2.3 (0.5, 6.5)	1/66	1.5 (0.0, 8.2)	0.8 (-3.8, 5.3)
Duration of ART Regimen Prior to Enrollment					
<1 year	1/26	3.8 (0.1, 19.6)	0/12	0.0 (0.0, 26.5)	4.3 (-16.4, 24.9)
≥1 year	7/421	1.7 (0.7, 3.4)	4/211	1.9 (0.5, 4.8)	-0.2 (-2.7, 2.2)
Age (years)					
18 to 64	8/438	1.8 (0.8, 3.6)	4/214	1.9 (0.5, 4.7)	-0.0 (-2.5, 2.4)
≥65	0/9	0.0 (0.0, 33.6)	0/9	0.0 (0.0, 33.6)	0.0 (-43.1, 43.1)
Age (years)					
≤Median (43 yrs)	5/230	2.2 (0.7, 5.0)	4/118	3.4 (0.9, 8.5)	-1.2 (-5.4, 3.0)
>Median (43 yrs)	3/217	1.4 (0.3, 4.0)	0/105	0.0 (0.0, 3.5)	1.4 (-1.2, 4.1)
Gender					
Male	7/372	1.9 (0.8, 3.8)	4/194	2.1 (0.6, 5.2)	-0.2 (-2.9, 2.5)
Female	1/75	1.3 (0.0, 7.2)	0/29	0.0 (0.0, 11.9)	1.3 (-6.3, 8.9)

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Proportion of Subjects with Plasma HIV-1 RNA ≥50 Copies/mL at Secondary Timepoint by Prognostic and Demographic Factors FDA Snapshot Approach Study Weeks 0-24; Base Study

Prognostic and Demographic Factors	Response				Difference in Percent Response (DOR/3TC/TDF QD ISG - Baseline Regimen DSG)[†]
	DOR/3TC/TDF QD ISG at Study Week 24		Baseline Regimen DSG at Study Week 24		
	n/N	% (95% CI)	n/N	% (95% CI)	% (95% CI)
Race					
American Indian or Alaska Native	0/5	0.0 (0.0, 52.2)	0/2	0.0 (0.0, 84.2)	0.0 (-103.3, 103.3)
Asian	0/17	0.0 (0.0, 19.5)	0/8	0.0 (0.0, 36.9)	0.0 (-26.8, 26.8)
Black or African American	1/56	1.8 (0.0, 9.6)	0/34	0.0 (0.0, 10.3)	1.6 (-5.8, 9.1)
Multiple	1/24	4.2 (0.1, 21.1)	0/11	0.0 (0.0, 28.5)	4.7 (-17.9, 27.2)
Native Hawaiian or Other Pacific Islander	0/1	0.0 (0.0, 97.5)	0/0	N/A	N/A
White	6/344	1.7 (0.6, 3.8)	4/168	2.4 (0.7, 6.0)	-0.7 (-3.6, 2.3)
Ethnicity					
Hispanic or Latino	3/99	3.0 (0.6, 8.6)	2/45	4.4 (0.5, 15.1)	-1.5 (-9.7, 6.7)
Not Hispanic or Latino	5/341	1.5 (0.5, 3.4)	2/175	1.1 (0.1, 4.1)	0.3 (-2.0, 2.7)
Unknown	0/7	0.0 (0.0, 41.0)	0/3	0.0 (0.0, 70.8)	N/A
Region					
Asia/Pacific	0/19	0.0 (0.0, 17.6)	0/12	0.0 (0.0, 26.5)	0.0 (-19.7, 19.7)
Europe	5/268	1.9 (0.6, 4.3)	1/137	0.7 (0.0, 4.0)	1.1 (-1.5, 3.8)
Latin America	2/49	4.1 (0.5, 14.0)	1/24	4.2 (0.1, 21.1)	-0.1 (-12.3, 12.1)
North America	1/111	0.9 (0.0, 4.9)	2/50	4.0 (0.5, 13.7)	-3.1 (-10.0, 3.9)

[†] 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).

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

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]

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Table 2.7.3-switch48wk: 26

Proportion of Subjects with Plasma HIV-1 RNA <50 Copies/mL at Primary Timepoints by ART Class in Baseline Regimen Received Observed Failure Approach Study Weeks 0-48; Base Study

Prognostic and Demographic Factors	Response				Difference in Percent Response (DOR/3TC/TDF QD ISG - Baseline Regimen DSG)[†]
	DOR/3TC/TDF QD ISG at Study Week 48		Baseline Regimen DSG at Study Week 24		
	n/N	% (95% CI)	n/N	% (95% CI)	% (95% CI)
Total	406/413	98.3 (96.5, 99.3)	211/215	98.1 (95.3, 99.5)	0.2 (-2.3, 2.7)
ART Class in Baseline Regimen Received					
Ritonavir- or Cobicistat- boosted PI	284/291	97.6 (95.1, 99.0)	147/150	98.0 (94.3, 99.6)	-0.4 (-3.4, 2.6)
Cobicistat-boosted elvitegravir	23/23	100.0 (85.2, 100.0)	11/11	100.0 (71.5, 100.0)	0.0 (-13.7, 13.7)
NNRTI	99/99	100.0 (96.3, 100.0)	53/54	98.1 (90.1, 100.0)	1.9 (-2.8, 6.5)

[†] 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 (actual ART class included in baseline regimen: ritonavir- or cobicistat-boosted PI vs. cobicistat-boosted elvitegravir vs. NNRTI).

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; adbase; adeff1]

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Table 2.7.3-switch48wk: 27

Proportion of Subjects with Plasma HIV-1 RNA <40 Copies/mL at Primary Timepoints by ART Class in Baseline Regimen Received Observed Failure Approach Study Weeks 0-48; Base Study

Prognostic and Demographic Factors	Response				Difference in Percent Response (DOR/3TC/TDF QD ISG - Baseline Regimen DSG)[†]
	DOR/3TC/TDF QD ISG at Study Week 48		Baseline Regimen DSG at Study Week 24		
	n/N	% (95% CI)	n/N	% (95% CI)	% (95% CI)
Total	401/413	97.1 (95.0, 98.5)	208/215	96.7 (93.4, 98.7)	0.4 (-2.8, 3.5)
ART Class in Baseline Regimen Received					
Ritonavir- or Cobicistat- boosted PI	280/291	96.2 (93.3, 98.1)	145/150	96.7 (92.4, 98.9)	-0.4 (-4.2, 3.3)
Cobicistat-boosted elvitegravir	23/23	100.0 (85.2, 100.0)	11/11	100.0 (71.5, 100.0)	0.0 (-13.7, 13.7)
NNRTI	98/99	99.0 (94.5, 100.0)	52/54	96.3 (87.3, 99.5)	2.7 (-3.4, 8.8)

[†] 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 (actual ART class included in baseline regimen: ritonavir- or cobicistat-boosted PI vs. cobicistat-boosted elvitegravir vs. NNRTI).

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; adbase; adeff1]

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Table 2.7.3-switch48wk: 28

Proportion of Subjects with Plasma HIV-1 RNA ≥50 Copies/mL at Primary Timepoints by ART Class in Baseline Regimen Received Observed Failure Approach Study Weeks 0-48; Base Study

Prognostic and Demographic Factors	Response				Difference in Percent Response (DOR/3TC/TDF QD ISG - Baseline Regimen DSG)[†]
	DOR/3TC/TDF QD ISG at Study Week 48		Baseline Regimen DSG at Study Week 24		
	n/N	% (95% CI)	n/N	% (95% CI)	% (95% CI)
Total	7/413	1.7 (0.7, 3.5)	4/215	1.9 (0.5, 4.7)	-0.2 (-2.7, 2.3)
ART Class in Baseline Regimen Received					
Ritonavir- or Cobicistat- boosted PI	7/291	2.4 (1.0, 4.9)	3/150	2.0 (0.4, 5.7)	0.4 (-2.6, 3.4)
Cobicistat-boosted elvitegravir	0/23	0.0 (0.0, 14.8)	0/11	0.0 (0.0, 28.5)	0.0 (-13.7, 13.7)
NNRTI	0/99	0.0 (0.0, 3.7)	1/54	1.9 (0.0, 9.9)	-1.9 (-6.5, 2.8)

[†] 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 (actual ART class included in baseline regimen: ritonavir- or cobicistat-boosted PI vs. cobicistat-boosted elvitegravir vs. NNRTI).

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; adbase; adeff1]

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Table 2.7.3-switch48wk: 29

Proportion of Subjects with Plasma HIV-1 RNA <50 Copies/mL at Secondary Timepoint by ART Class in Baseline Regimen Received Observed Failure Approach Study Weeks 0-24; Base Study

Prognostic and Demographic Factors	Response				Difference in Percent Response (DOR/3TC/TDF QD ISG - Baseline Regimen DSG)[†]
	DOR/3TC/TDF QD ISG at Study Week 24		Baseline Regimen DSG at Study Week 24		
	n/N	% (95% CI)	n/N	% (95% CI)	% (95% CI)
Total	419/427	98.1 (96.3, 99.2)	211/215	98.1 (95.3, 99.5)	-0.0 (-2.6, 2.5)
ART Class in Baseline Regimen Received					
Ritonavir- or Cobicistat- boosted PI	294/299	98.3 (96.1, 99.5)	147/150	98.0 (94.3, 99.6)	0.3 (-2.5, 3.2)
Cobicistat-boosted elvitegravir	25/25	100.0 (86.3, 100.0)	11/11	100.0 (71.5, 100.0)	0.0 (-13.5, 13.5)
NNRTI	100/103	97.1 (91.7, 99.4)	53/54	98.1 (90.1, 100.0)	-1.1 (-6.7, 4.5)

[†] 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 (actual ART class included in baseline regimen: ritonavir- or cobicistat-boosted PI vs. cobicistat-boosted elvitegravir vs. NNRTI).

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; adbase; adeff1]

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Table 2.7.3-switch48wk: 30

Proportion of Subjects with Plasma HIV-1 RNA <40 Copies/mL at Secondary Timepoint by ART Class in Baseline Regimen Received Observed Failure Approach Study Weeks 0-24; Base Study

Prognostic and Demographic Factors	Response				Difference in Percent Response (DOR/3TC/TDF QD ISG - Baseline Regimen DSG)[†]
	DOR/3TC/TDF QD ISG at Study Week 24		Baseline Regimen DSG at Study Week 24		
	n/N	% (95% CI)	n/N	% (95% CI)	% (95% CI)
Total	415/427	97.2 (95.1, 98.5)	208/215	96.7 (93.4, 98.7)	0.4 (-2.7, 3.5)
ART Class in Baseline Regimen Received					
Ritonavir- or Cobicistat- boosted PI	291/299	97.3 (94.8, 98.8)	145/150	96.7 (92.4, 98.9)	0.7 (-2.9, 4.2)
Cobicistat-boosted elvitegravir	25/25	100.0 (86.3, 100.0)	11/11	100.0 (71.5, 100.0)	0.0 (-13.5, 13.5)
NNRTI	99/103	96.1 (90.4, 98.9)	52/54	96.3 (87.3, 99.5)	-0.2 (-7.0, 6.7)

[†] 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 (actual ART class included in baseline regimen: ritonavir- or cobicistat-boosted PI vs. cobicistat-boosted elvitegravir vs. NNRTI).

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; adbase; adeff1]

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Table 2.7.3-switch48wk: 31

Proportion of Subjects with Plasma HIV-1 RNA ≥50 Copies/mL at Secondary Timepoint by ART Class in Baseline Regimen Received Observed Failure Approach Study Weeks 0-24; Base Study

Prognostic and Demographic Factors	Response				Difference in Percent Response (DOR/3TC/TDF QD ISG - Baseline Regimen DSG)[†]
	DOR/3TC/TDF QD ISG at Study Week 24		Baseline Regimen DSG at Study Week 24		
	n/N	% (95% CI)	n/N	% (95% CI)	% (95% CI)
Total	8/427	1.9 (0.8, 3.7)	4/215	1.9 (0.5, 4.7)	0.0 (-2.5, 2.6)
ART Class in Baseline Regimen Received					
Ritonavir- or Cobicistat- boosted PI	5/299	1.7 (0.5, 3.9)	3/150	2.0 (0.4, 5.7)	-0.3 (-3.2, 2.5)
Cobicistat-boosted elvitegravir	0/25	0.0 (0.0, 13.7)	0/11	0.0 (0.0, 28.5)	0.0 (-13.5, 13.5)
NNRTI	3/103	2.9 (0.6, 8.3)	1/54	1.9 (0.0, 9.9)	1.1 (-4.5, 6.7)

[†] 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 (actual ART class included in baseline regimen: ritonavir- or cobicistat-boosted PI vs. cobicistat-boosted elvitegravir vs. NNRTI).

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; adbase; adeff1]

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Table 2.7.3-switch48wk: 32

Change from Baseline in CD4+ T-Cell Count (cells/mm3) at Primary Timepoints by ART Class in Baseline Regimen Received Observed Failure Approach Base Study

Prognostic and Demographic Factors	Response: DOR/3TC/TDF QD ISG at Study Week 48 N	Baseline Mean	Mean Change from Baseline (95% CI)	Response: Baseline Regimen DSG at Study Week 24 N	Baseline Mean	Mean Change from Baseline (95% CI)	Difference in Mean Changes from Baseline [DOR/3TC/TDF QD ISG - Baseline Regimen DSG][†] (95% CI)
Total	402	660.5	13.9 (-2.6, 30.4)	209	655.6	18.0 (-3.6, 39.5)	-4.0 (-31.6, 23.5)
ART Class in Baseline Regimen Received							
Ritonavir– or Cobicistat- boosted PI	284	653.1	7.1 (-13.2, 27.5)	146	645.3	8.1 (-18.0, 34.1)	-0.9 (-34.8, 32.9)
Cobicistat-boosted elvitegravir	22	689.0	19.6 (-22.3, 61.5)	11	710.0	48.9 (-100.9, 198.7)	-29.3 (-141.2, 82.6)
NNRTI	96	676.1	32.7 (-0.3, 65.8)	52	672.9	39.2 (1.2, 77.1)	-6.4 (-58.9, 46.0)

[†] The 95% CIs were 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).

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 treatment group.

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

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Table 2.7.3-switch48wk: 33

Change from Baseline in CD4+ T-Cell Count (cells/mm3) at Secondary Timepoint by ART Class in Baseline Regimen Received Observed Failure Approach Base Study

Prognostic and Demographic Factors	Response: DOR/3TC/TDF QD ISG at Study Week 24 N	Baseline Mean	Mean Change from Baseline (95% CI)	Response: Baseline Regimen DSG at Study Week 24 N	Baseline Mean	Mean Change from Baseline (95% CI)	Difference in Mean Changes from Baseline [DOR/3TC/TDF QD ISG - Baseline Regimen DSG][†] (95% CI)
Total	412	664.5	5.1 (-11.8, 22.1)	209	655.6	18.0 (-3.6, 39.5)	-12.8 (-41.1, 15.4)
ART Class in Baseline Regimen Received							
Ritonavir– or Cobicistat- boosted PI	290	655.6	-6.5 (-27.9, 14.9)	146	645.3	8.1 (-18.0, 34.1)	-14.6 (-49.8, 20.7)
Cobicistat-boosted elvitegravir	24	701.4	67.6 (3.0, 132.3)	11	710.0	48.9 (-100.9, 198.7)	18.7 (-112.5, 150.0)
NNRTI	98	681.9	24.3 (-4.4, 53.0)	52	672.9	39.2 (1.2, 77.1)	-14.9 (-62.6, 32.9)

[†] The 95% CIs were 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).

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 treatment group.

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

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Table 2.7.3-switch48wk: 34

Proportion of Subjects with Plasma HIV-1 RNA <50 Copies/mL at Primary Timepoints by ART Class in Baseline Regimen Received FDA Snapshot Approach Study Weeks 0-48; Base Study

Prognostic and Demographic Factors	Response				Difference in Percent Response (DOR/3TC/TDF QD ISG - Baseline Regimen DSG)[†]
	DOR/3TC/TDF QD ISG at Study Week 48		Baseline Regimen DSG at Study Week 24		
	n/N	% (95% CI)	n/N	% (95% CI)	% (95% CI)
Total	406/447	90.8 (87.8, 93.3)	211/223	94.6 (90.8, 97.2)	-3.8 (-7.9, 0.4)
ART Class in Baseline Regimen Received					
Ritonavir- or Cobicistat- boosted PI	284/316	89.9 (86.0, 93.0)	147/156	94.2 (89.3, 97.3)	-4.4 (-9.4, 0.7)
Cobicistat-boosted elvitegravir	23/25	92.0 (74.0, 99.0)	11/12	91.7 (61.5, 99.8)	0.3 (-21.9, 22.6)
NNRTI	99/106	93.4 (86.9, 97.3)	53/55	96.4 (87.5, 99.6)	-3.0 (-10.3, 4.4)

[†] 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 (actual ART class included in baseline regimen: ritonavir- or cobicistat-boosted PI vs. cobicistat-boosted elvitegravir vs. NNRTI).

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; adbase; adeff1]

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Table 2.7.3-switch48wk: 35

Proportion of Subjects with Plasma HIV-1 RNA <50 Copies/mL at Secondary Timepoint by ART Class in Baseline Regimen Received FDA Snapshot Approach Study Weeks 0-24; Base Study

Prognostic and Demographic Factors	Response				Difference in Percent Response (DOR/3TC/TDF QD ISG - Baseline Regimen DSG)[†]
	DOR/3TC/TDF QD ISG at Study Week 24		Baseline Regimen DSG at Study Week 24		
	n/N	% (95% CI)	n/N	% (95% CI)	% (95% CI)
Total	419/447	93.7 (91.1, 95.8)	211/223	94.6 (90.8, 97.2)	-0.9 (-4.8, 3.0)
ART Class in Baseline Regimen Received					
Ritonavir- or Cobicistat- boosted PI	294/316	93.0 (89.6, 95.6)	147/156	94.2 (89.3, 97.3)	-1.2 (-5.9, 3.5)
Cobicistat-boosted elvitegravir	25/25	100.0 (86.3, 100.0)	11/12	91.7 (61.5, 99.8)	8.3 (-11.3, 28.0)
NNRTI	100/106	94.3 (88.1, 97.9)	53/55	96.4 (87.5, 99.6)	-2.0 (-9.2, 5.1)

[†] 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 (actual ART class included in baseline regimen: ritonavir- or cobicistat-boosted PI vs. cobicistat-boosted elvitegravir vs. NNRTI).

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; adbase; adeff1]

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Table 2.7.3-switch48wk: 36

Proportion of Subjects with Plasma HIV-1 RNA <40 Copies/mL at Primary Timepoints by ART Class in Baseline Regimen Received FDA Snapshot Approach Study Weeks 0-48; Base Study

Prognostic and Demographic Factors	Response				Difference in Percent Response (DOR/3TC/TDF QD ISG - Baseline Regimen DSG)[†]
	DOR/3TC/TDF QD ISG at Study Week 48		Baseline Regimen DSG at Study Week 24		
	n/N	% (95% CI)	n/N	% (95% CI)	% (95% CI)
Total	401/447	89.7 (86.5, 92.4)	208/223	93.3 (89.1, 96.2)	-3.5 (-8.0, 0.9)
ART Class in Baseline Regimen Received					
Ritonavir- or Cobicistat- boosted PI	280/316	88.6 (84.6, 91.9)	145/156	92.9 (87.7, 96.4)	-4.3 (-9.7, 1.1)
Cobicistat-boosted elvitegravir	23/25	92.0 (74.0, 99.0)	11/12	91.7 (61.5, 99.8)	0.3 (-21.9, 22.6)
NNRTI	98/106	92.5 (85.7, 96.7)	52/55	94.5 (84.9, 98.9)	-2.1 (-10.4, 6.2)

[†] 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 (actual ART class included in baseline regimen: ritonavir- or cobicistat-boosted PI vs. cobicistat-boosted elvitegravir vs. NNRTI).

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; adbase; adeff1]

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Table 2.7.3-switch48wk: 37

Proportion of Subjects with Plasma HIV-1 RNA <40 Copies/mL at Secondary Timepoint by ART Class in Baseline Regimen Received
FDA Snapshot Approach
Study Weeks 0-24; Base Study

Prognostic and Demographic Factors	Response				Difference in Percent Response (DOR/3TC/TDF QD ISG - Baseline Regimen DSG)[†]
	DOR/3TC/TDF QD ISG at Study Week 24		Baseline Regimen DSG at Study Week 24		
	n/N	% (95% CI)	n/N	% (95% CI)	% (95% CI)
Total	415/447	92.8 (90.0, 95.1)	208/223	93.3 (89.1, 96.2)	-0.4 (-4.6, 3.8)
ART Class in Baseline Regimen Received					
Ritonavir- or Cobicistat- boosted PI	291/316	92.1 (88.5, 94.8)	145/156	92.9 (87.7, 96.4)	-0.9 (-5.9, 4.2)
Cobicistat-boosted elvitegravir	25/25	100.0 (86.3, 100.0)	11/12	91.7 (61.5, 99.8)	8.3 (-11.3, 28.0)
NNRTI	99/106	93.4 (86.9, 97.3)	52/55	94.5 (84.9, 98.9)	-1.1 (-9.2, 6.9)

[†] 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 (actual ART class included in baseline regimen: ritonavir- or cobicistat-boosted PI vs. cobicistat-boosted elvitegravir vs. NNRTI).

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; adbase; adeff1]

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Table 2.7.3-switch48wk: 38

Proportion of Subjects with Plasma HIV-1 RNA ≥50 Copies/mL at Primary Timepoints by ART Class in Baseline Regimen Received FDA Snapshot Approach Study Weeks 0-48; Base Study

Prognostic and Demographic Factors	Response				Difference in Percent Response (DOR/3TC/TDF QD ISG - Baseline Regimen DSG)[†]
	DOR/3TC/TDF QD ISG at Study Week 48		Baseline Regimen DSG at Study Week 24		
	n/N	% (95% CI)	n/N	% (95% CI)	% (95% CI)
Total	7/447	1.6 (0.6, 3.2)	4/223	1.8 (0.5, 4.5)	-0.2 (-2.6, 2.2)
ART Class in Baseline Regimen Received					
Ritonavir- or Cobicistat- boosted PI	7/316	2.2 (0.9, 4.5)	3/156	1.9 (0.4, 5.5)	0.3 (-2.6, 3.2)
Cobicistat-boosted elvitegravir	0/25	0.0 (0.0, 13.7)	0/12	0.0 (0.0, 26.5)	0.0 (-12.6, 12.6)
NNRTI	0/106	0.0 (0.0, 3.4)	1/55	1.8 (0.0, 9.7)	-1.8 (-6.3, 2.7)

[†] 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 (actual ART class included in baseline regimen: ritonavir- or cobicistat-boosted PI vs. cobicistat-boosted elvitegravir vs. NNRTI).

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; adbase; adeff1]

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Table 2.7.3-switch48wk: 39

Proportion of Subjects with Plasma HIV-1 RNA ≥50 Copies/mL at Secondary Timepoint by ART Class in Baseline Regimen Received
FDA Snapshot Approach
Study Weeks 0-24; Base Study

Prognostic and Demographic Factors	Response				Difference in Percent Response (DOR/3TC/TDF QD ISG - Baseline Regimen DSG)[†]
	DOR/3TC/TDF QD ISG at Study Week 24		Baseline Regimen DSG at Study Week 24		
	n/N	% (95% CI)	n/N	% (95% CI)	% (95% CI)
Total	8/447	1.8 (0.8, 3.5)	4/223	1.8 (0.5, 4.5)	0.0 (-2.4, 2.4)
ART Class in Baseline Regimen Received					
Ritonavir- or Cobicistat- boosted PI	5/316	1.6 (0.5, 3.7)	3/156	1.9 (0.4, 5.5)	-0.3 (-3.1, 2.4)
Cobicistat-boosted elvitegravir	0/25	0.0 (0.0, 13.7)	0/12	0.0 (0.0, 26.5)	0.0 (-12.6, 12.6)
NNRTI	3/106	2.8 (0.6, 8.0)	1/55	1.8 (0.0, 9.7)	1.0 (-4.5, 6.5)

[†] 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 (actual ART class included in baseline regimen: ritonavir- or cobicistat-boosted PI vs. cobicistat-boosted elvitegravir vs. NNRTI).

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; adbase; adeff1]

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Table 2.7.3-switch48wk: 40

Number of Subjects with Protocol Defined Virologic Failure
Study Weeks 0-48; Base Study

	DOR/3TC/TDF QD ISG Study Weeks 0-48 N=(447) n (%)	Baseline Regimen DSG Study Weeks 0-24 N=(223) n (%)	DOR/3TC/TDF QD DSG Study Weeks 24-48 N=(209) n (%)
Virologic Failure (confirmed)† by Study Week 24	0 (0.0)	1 (0.4)	
Virologic Failure (confirmed)† by Study Week 36	6 (1.3)		1 (0.5)
Virologic Failure (confirmed)† by Study Week 48	6 (1.3)		1 (0.5)

† Protocol defined virologic failure (PDVF) for this study is defined as: subjects who have two consecutive measurements of HIV-1 RNA ≥50 copies/mL at least one week apart.

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; advf]

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Figure 2.7.3-switch48wk: 2
Viral Drug Resistance in Participants With PDVF

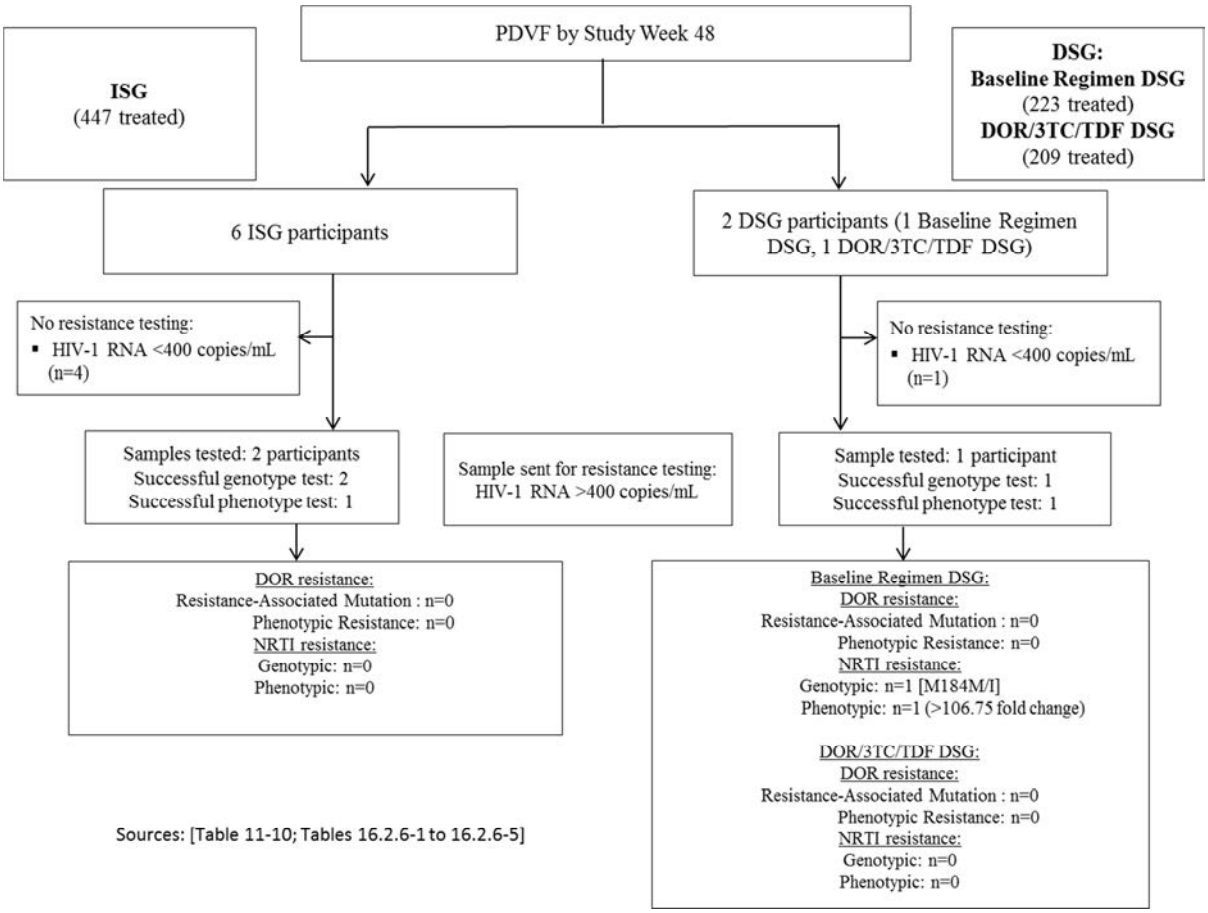
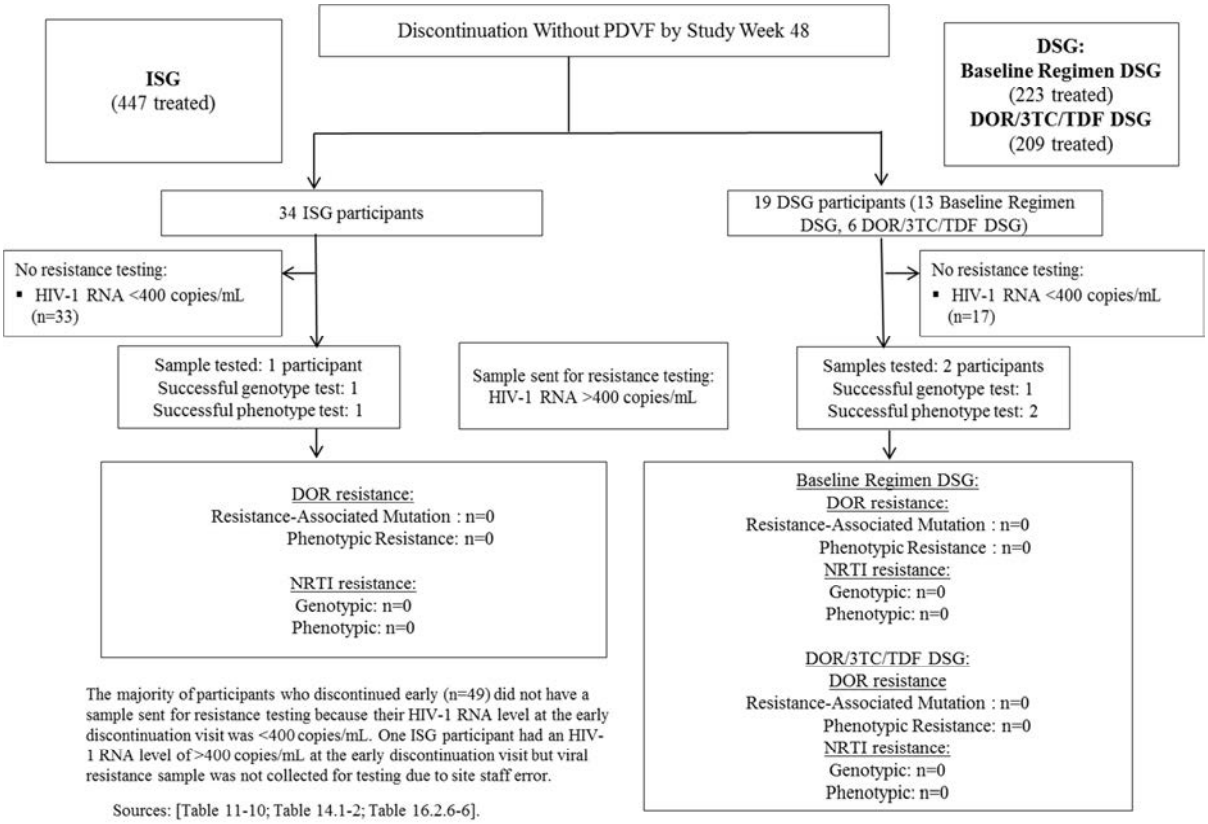


Figure 2.7.3-switch48wk: 3
Viral Drug Resistance in Participants Who Discontinued Without PDVF



The majority of participants who discontinued early (n=49) did not have a sample sent for resistance testing because their HIV-1 RNA level at the early discontinuation visit was <400 copies/mL. One ISG participant had an HIV-1 RNA level of >400 copies/mL at the early discontinuation visit but viral resistance sample was not collected for testing due to site staff error.

Sources: [Table 11-10; Table 14.1-2; Table 16.2.6-6].

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Table 2.7.3-switch48wk: 41

Descriptive Statistics for DOR Plasma Concentrations by Nominal Time and Group

Doravirine Plasma Concentration (nM)							
Immediate Switch Group	Week						
	0	4	12	24		48	
	Time (hr)	Time (hr)	Time (hr)	Time (hr)		Time (hr)	
	0.00	0.00	0.00	0.00	2.00	0.00	2.00
N	443	438	435	389	378	394	385
AM	0.858	1460	1820	1450	2510	1440	2520
SD	18.1	903	1060	772	1220	813	1340
CV%	2104.8	61.6	58.2	53.3	48.8	56.3	53.0
Min	0.00	38.5	0.00	0.00	319	25.1	203
Median	0.00	1270	1630	1320	2460	1300	2310
Max	380	9720	9370	4180	7540	5000	8410
GM	NC	1230	NC	NC	2200	1220	2150
GCV	NC	70.8	NC	NC	59.5	69.1	65.5
IQR	0	1092	1310	1140	1630	1065	1790

AM = Arithmetic mean, CV = coefficient of variation, Max = Maximum, Med = Median, Min = Minimum, GCV = Geometric coefficient of variation, GM = Geometric Mean, IQR = Interquartile Range, NC = Not Calculated, SD= Standard Deviation.
GCV is calculated in the natural log-scale with the equation: 100 x sqrt(exp(s2) - 1), where s2 is the observed variance on the natural log-scale.

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Descriptive Statistics for DOR Plasma Concentrations by Nominal Time and Group

Doravirine Plasma Concentration (nM)			
Delayed Switch Group	Week		
	0	48	
	Time (hr)	Time (hr)	
	0.00	0.00	2.00
N	195	181	187
AM	0.00	1540	2490
SD	0.00	992	1370
CV%	NC	64.5	54.9
Min	0.00	45.3	44.9
Median	0.00	1320	2330
Max	0.00	4790	6810
GM	NC	1230	2080
GCV	NC	84.4	76.5
IQR	0	1142	1970

AM = Arithmetic mean, CV = coefficient of variation, Max = Maximum, Med = Median, Min = Minimum, GCV = Geometric coefficient of variation, GM = Geometric Mean, IQR = Interquartile Range, NC = Not Calculated, SD= Standard Deviation.
GCV is calculated in the natural log-scale with the equation: 100 x sqrt(exp(s2) - 1), where s2 is the observed variance on the natural log-scale.

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Table 2.7.3-switch48wk: 42

Number of Subjects Included in Each PRO Analysis
All Randomized Subjects, Study Weeks 0 - 48

	ISG		DSG		Total	
IBS-QoL						
Number of Randomized Subjects	450		223		673	
Number of Subjects Included in PRO FAS[†]	444	(98.7)	223	(100.0)	667	(99.1)
Baseline Assessment Only	9	(2.0)	5	(2.2)	14	(2.1)
Baseline and at least one post-baseline assessment	414	(92.0)	206	(92.4)	620	(92.1)
Post-baseline Assessment(s) Only	21	(4.7)	12	(5.4)	33	(4.9)
Number of Subjects Excluded from PRO FAS	6	(1.3)	0	(0.0)	6	(0.9)
Subjects Randomized But Not Treated	3	(0.7)	0	(0.0)	3	(0.4)
Missing all PRO Assessments	3	(0.7)	0	(0.0)	3	(0.4)
HIV-SI						
Number of Randomized Subjects	450		223		673	
Number of Subjects Included in PRO FAS[†]	443	(98.4)	223	(100.0)	666	(99.0)
Baseline Assessment Only	8	(1.8)	5	(2.2)	13	(1.9)
Baseline and at least one post-baseline assessment	413	(91.8)	206	(92.4)	619	(92.0)
Post-baseline Assessment(s) Only	22	(4.9)	12	(5.4)	34	(5.1)
Number of Subjects Excluded from PRO FAS	7	(1.6)	0	(0.0)	7	(1.0)
Subjects Randomized But Not Treated	3	(0.7)	0	(0.0)	3	(0.4)
Missing all PRO Assessments	4	(0.9)	0	(0.0)	4	(0.6)
WPAI:GH						
Number of Randomized Subjects	450		223		673	
Number of Subjects Included in PRO FAS[†]	443	(98.4)	223	(100.0)	666	(99.0)
Baseline Assessment Only	8	(1.8)	5	(2.2)	13	(1.9)
Baseline and at least one post-baseline assessment	413	(91.8)	206	(92.4)	619	(92.0)
Post-baseline Assessment(s) Only	22	(4.9)	12	(5.4)	34	(5.1)
Number of Subjects Excluded from PRO FAS	7	(1.6)	0	(0.0)	7	(1.0)
Subjects Randomized But Not Treated	3	(0.7)	0	(0.0)	3	(0.4)
Missing all PRO Assessments	4	(0.9)	0	(0.0)	4	(0.6)
EQ-5D-5L						
Number of Randomized Subjects	450		223		673	
Number of Subjects Included in PRO FAS[†]	443	(98.4)	223	(100.0)	666	(99.0)
Baseline Assessment Only	8	(1.8)	5	(2.2)	13	(1.9)
Baseline and at least one post-baseline assessment	413	(91.8)	206	(92.4)	619	(92.0)
Post-baseline Assessment(s) Only	22	(4.9)	12	(5.4)	34	(5.1)
Number of Subjects Excluded from PRO FAS	7	(1.6)	0	(0.0)	7	(1.0)
Subjects Randomized But Not Treated	3	(0.7)	0	(0.0)	3	(0.4)
Missing all PRO Assessments	4	(0.9)	0	(0.0)	4	(0.6)

[†] PRO Full analysis set (FAS) includes subjects who took at least one dose of study medication and with at least one non-missing PRO assessment at baseline or post-baseline. The number of Subjects in the PRO FAS is specific to each questionnaire.

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; adpro]

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Table 2.7.3-switch48wk: 43

Completion and Compliance Rates for Each PRO Questionnaire
All Randomized and Treated Subjects, Study Weeks 0 – 48

	ISG N=446				DSG N=221				Total N=667			
	Number of Subjects With PRO Assessment[1]	Completion Rate[2] (%)	Compliance Rate[3]		Number of Subjects With PRO Assessment[1]	Completion Rate[2] (%)	Compliance Rate[3]		Number of Subjects With PRO Assessment[1]	Completion Rate[2] (%)	Compliance Rate[3]	
Study Week			N†	%			N†	%			N†	%
IBS-QoL												
Baseline	423	(94.8)	446	(94.8)	211	(95.5)	221	(95.5)	634	(95.1)	667	(95.1)
Week 24	386	(86.5)	427	(90.4)	201	(91.0)	209	(96.2)	587	(88.0)	636	(92.3)
Week 48	369	(82.7)	407	(90.7)	188	(85.1)	202	(93.1)	557	(83.5)	609	(91.5)
HIV-SI												
Baseline	421	(94.4)	446	(94.4)	211	(95.5)	221	(95.5)	632	(94.8)	667	(94.8)
Week 24	383	(85.9)	427	(89.7)	200	(90.5)	209	(95.7)	583	(87.4)	636	(91.7)
Week 48	368	(82.5)	407	(90.4)	188	(85.1)	202	(93.1)	556	(83.4)	609	(91.3)
WPAI:GH												
Baseline	421	(94.4)	446	(94.4)	211	(95.5)	221	(95.5)	632	(94.8)	667	(94.8)
Week 24	383	(85.9)	427	(89.7)	200	(90.5)	209	(95.7)	583	(87.4)	636	(91.7)
Week 48	368	(82.5)	407	(90.4)	188	(85.1)	202	(93.1)	556	(83.4)	609	(91.3)
EQ-5D-5L												
Baseline	421	(94.4)	446	(94.4)	211	(95.5)	221	(95.5)	632	(94.8)	667	(94.8)
Week 24	383	(85.9)	427	(89.7)	200	(90.5)	209	(95.7)	583	(87.4)	636	(91.7)
Week 48	368	(82.5)	407	(90.4)	188	(85.1)	202	(93.1)	556	(83.4)	609	(91.3)

[1]Subjects who complete at least one item of the instrument at each time point.
[2]Completion rate is defined as the number of subjects who complete at least one item over number of randomized and treated subjects.
[3]Compliance rate is defined as the number of subjects who complete at least one item over the number of eligible subjects who are expected to complete the instrument (excluding discontinued subjects).
N†=number of eligible subjects who are expected to complete the instrument at each visit
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; adpro]

Table 2.7.3-switch48wk: 44

Summary of Mean Change from Baseline Score for WPAI
WPAI PRO FAS, Study Weeks 0-48
Data as Observed

		Baseline		Value		Change from Baseline[†]		Treatment Difference ISG - DSG	
Study Week	Treatment	N	Mean (SD)	N	Mean (SD)	Mean (SD)	95% CI	Mean (SD)	95% CI[‡]
Percent Work Time Missed Due To Health									
Week 24	ISG	227	2.63 (10.27)	255	4.47 (15.91)	1.88 (18.22)	(-0.506, 4.260)	-0.53 (18.34)	(-4.710, 3.649)
	DSG	111	2.00 (9.05)	131	3.83 (14.76)	2.41 (18.59)	(-1.090, 5.905)		
Week 48	ISG	221	2.75 (10.56)	248	5.73 (17.04)	2.22 (18.21)	(-0.197, 4.631)		
	DSG	102	1.36 (6.22)	117	7.13 (16.79)	6.28 (18.72)	(2.603, 9.955)		
Percent Impairment while Working Due To Health									
Week 24	ISG	222	5.95 (12.47)	251	8.73 (17.95)	2.66 (16.50)	(0.476, 4.839)	2.66 (17.00)	(-1.241, 6.556)
	DSG	110	7.64 (14.20)	130	7.69 (15.87)	0.00 (17.97)	(-3.396, 3.396)		
Week 48	ISG	218	6.93 (13.48)	244	10.00 (19.07)	2.57 (17.59)	(0.220, 4.917)		
	DSG	102	6.18 (11.26)	117	7.35 (15.28)	1.57 (17.28)	(-1.825, 4.962)		
Percent Overall Work Impairment Due To Health									
Week 24	ISG	222	7.80 (14.76)	251	10.72 (20.49)	2.66 (19.88)	(0.030, 5.289)	1.12 (21.28)	(-3.763, 5.996)
	DSG	110	9.10 (16.82)	130	10.32 (19.29)	1.54 (23.85)	(-2.965, 6.051)		
Week 48	ISG	218	8.93 (15.84)	244	12.81 (21.73)	3.37 (21.30)	(0.525, 6.211)		
	DSG	102	7.38 (13.05)	117	13.95 (21.26)	7.40 (24.77)	(2.533, 12.264)		

Summary of Mean Change from Baseline Score for WPAI
WPAI PRO FAS, Study Weeks 0-48
Data as Observed

Study Week	Treatment	Baseline		Value		Change from Baseline[†]		Treatment Difference ISG - DSG	
		N	Mean (SD)	N	Mean (SD)	Mean (SD)	95% CI	Mean (SD)	95% CI[‡]
Percent Activity Impairment Due To Health									
Week 24	ISG	364	11.24 (20.62)	364	12.80 (22.29)	1.57 (20.92)	(-0.590, 3.722)	2.09 (20.55)	(-1.514, 5.687)
	DSG	192	10.16 (19.54)	192	9.64 (17.68)	-0.52 (19.84)	(-3.344, 2.303)		
Week 48	ISG	348	11.29 (20.88)	348	13.65 (23.94)	2.36 (21.93)	(0.044, 4.668)		
	DSG	177	9.60 (17.94)	177	9.60 (18.60)	0.00 (20.75)	(-3.078, 3.078)		

This analysis includes subjects with non-missing PRO assessment at baseline and at least one non-missing PRO assessments at post-baseline.
‡ The 95% CIs were based on t-distribution
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; adpro]

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Table 2.7.3-switch48wk: 45

Summary of Mean Scores for IBS-QoL Subscales
IBS-QoL PRO FAS, Study Weeks 0 - 48
Data as Observed

IBS-QoL Subscales[†]	Strata I-III (Baseline PI-Based Regimens)[‡]						All Patients					
	ISG			DSG			ISG			DSG		
	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD
Baseline												
Dysphoria Score	300	4.92	10.75	152	4.44	10.24	423	4.85	11.20	211	3.92	9.63
Interference with Activity Score	300	6.06	11.95	152	6.09	12.57	423	5.73	12.01	211	5.42	11.76
Body Image Score	300	6.19	12.58	152	5.63	11.44	423	6.41	13.29	211	4.98	10.96
Health Worry Score	300	6.31	11.80	152	6.03	12.44	423	6.38	12.50	211	5.17	11.64
Food Avoidance Score	300	8.69	15.84	152	7.68	16.01	423	8.33	16.03	211	6.95	15.03
Social Reaction Score	300	4.56	10.63	152	4.65	10.71	423	4.93	11.72	211	4.12	10.04
Sexual Score	300	5.63	14.57	152	5.18	13.38	423	6.24	16.64	211	4.44	12.75
Relationships Score	300	4.33	10.44	152	4.82	13.24	423	4.45	11.32	211	4.07	11.82
Study Week 24												
Dysphoria Score	267	4.00	10.88	144	5.25	12.41	386	4.32	11.64	201	4.28	11.02
Interference with Activity Score	267	5.02	11.59	144	6.18	13.73	386	5.19	12.04	201	5.17	12.28
Body Image Score	267	6.02	12.38	144	5.99	13.38	386	6.44	13.22	201	5.13	11.99
Health Worry Score	267	4.53	10.47	144	5.32	11.52	386	4.90	11.46	201	4.60	10.50
Food Avoidance Score	267	7.27	15.05	144	8.28	16.80	386	7.64	16.16	201	7.13	15.26
Social Reaction Score	267	3.98	10.04	144	4.95	12.10	386	4.55	11.17	201	4.29	11.21
Sexual Score	267	6.60	16.09	144	7.29	17.02	386	7.09	17.34	201	6.09	15.47
Relationships Score	267	4.03	10.55	144	5.21	14.71	386	4.34	11.37	201	4.27	13.05

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Summary of Mean Scores for IBS-QoL Subscales
IBS-QoL PRO FAS, Study Weeks 0 - 48
Data as Observed

	Strata I-III (Baseline PI-Based Regimens)‡						All Patients					
	ISG			DSG			ISG			DSG		
IBS-QoL Subscales†	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD
Study Week 48												
Dysphoria Score	258	3.77	10.18	137	4.01	10.63	369	4.01	11.25	188	3.61	9.48
Interference with Activity Score	258	4.49	10.66	137	5.16	13.83	369	4.78	11.70	188	4.58	12.33
Body Image Score	258	6.20	14.18	137	5.57	11.98	369	6.67	14.66	188	5.09	11.11
Health Worry Score	258	4.59	10.88	137	5.11	13.72	369	4.81	11.39	188	4.79	12.55
Food Avoidance Score	258	6.91	15.99	137	6.57	14.76	369	7.18	16.90	188	6.07	14.10
Social Reaction Score	258	4.36	11.44	137	4.79	12.71	369	4.86	12.92	188	4.12	11.40
Sexual Score	258	5.67	15.08	137	6.66	19.30	369	6.17	16.72	188	5.59	17.16
Relationships Score	258	3.71	10.29	137	4.81	15.05	369	4.20	11.71	188	3.95	13.22

† IBS-QoL Subscales: range from 0 (poor quality of life) to 100 (maximum quality of life).

‡ Strata I-III have been combined and analyzed separately as the IBS-QOL was specifically included in the trial to measure the impact of GI complications of treatment on patient QoL as related to the effects of boosted PI-based antiretroviral regimens.

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; adpro]

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Table 2.7.3-switch48wk: 46

Completion and Compliance Rates for Each PRO Questionnaire
All Randomized and Treated Subjects, Study Weeks 0 – 48

	ISG N=446				DSG N=221				Total N=667			
	Number of Subjects With PRO Assessment[1]	Completion Rate[2] (%)	Compliance Rate[3]		Number of Subjects With PRO Assessment[1]	Completion Rate[2] (%)	Compliance Rate[3]		Number of Subjects With PRO Assessment[1]	Completion Rate[2] (%)	Compliance Rate[3]	
Study Week			N†	%			N†	%			N†	%
IBS-QoL												
Baseline	423	(94.8)	446	(94.8)	211	(95.5)	221	(95.5)	634	(95.1)	667	(95.1)
Week 24	386	(86.5)	427	(90.4)	201	(91.0)	209	(96.2)	587	(88.0)	636	(92.3)
Week 48	369	(82.7)	407	(90.7)	188	(85.1)	202	(93.1)	557	(83.5)	609	(91.5)
HIV-SI												
Baseline	421	(94.4)	446	(94.4)	211	(95.5)	221	(95.5)	632	(94.8)	667	(94.8)
Week 24	383	(85.9)	427	(89.7)	200	(90.5)	209	(95.7)	583	(87.4)	636	(91.7)
Week 48	368	(82.5)	407	(90.4)	188	(85.1)	202	(93.1)	556	(83.4)	609	(91.3)
WPAI:GH												
Baseline	421	(94.4)	446	(94.4)	211	(95.5)	221	(95.5)	632	(94.8)	667	(94.8)
Week 24	383	(85.9)	427	(89.7)	200	(90.5)	209	(95.7)	583	(87.4)	636	(91.7)
Week 48	368	(82.5)	407	(90.4)	188	(85.1)	202	(93.1)	556	(83.4)	609	(91.3)
EQ-5D-5L												
Baseline	421	(94.4)	446	(94.4)	211	(95.5)	221	(95.5)	632	(94.8)	667	(94.8)
Week 24	383	(85.9)	427	(89.7)	200	(90.5)	209	(95.7)	583	(87.4)	636	(91.7)
Week 48	368	(82.5)	407	(90.4)	188	(85.1)	202	(93.1)	556	(83.4)	609	(91.3)

[1]Subjects who complete at least one item of the instrument at each time point.
[2]Completion rate is defined as the number of subjects who complete at least one item over number of randomized and treated subjects.
[3]Compliance rate is defined as the number of subjects who complete at least one item over the number of eligible subjects who are expected to complete the instrument (excluding discontinued subjects).
N†=number of eligible subjects who are expected to complete the instrument at each visit
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; adpro]

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Table 2.7.3-switch48wk: 47

Summary of Mean Change from Baseline Score for IBS-QoL for PI-Based Regimens
IBS-QoL PRO FAS, Study Weeks 0-48
Data as Observed, Strata I-III

		Baseline		Value		Change from Baseline[†]		Treatment Difference ISG - DSG	
Study Week	Treatment	N	Mean (SD)	N	Mean (SD)	Mean (SD)	95% CI	Mean (SD)	95% CI[‡]
Overall IBS-QoL Score									
Week 24	ISG	254	5.35 (9.18)	254	5.04 (10.51)	-0.32 (7.96)	(-1.299, 0.668)	-0.64 (8.00)	(-2.298, 1.015)
	DSG	140	5.55 (10.53)	140	5.88 (12.40)	0.33 (8.09)	(-1.026, 1.677)		
Week 48	ISG	244	5.06 (8.87)	244	4.87 (10.72)	-0.19 (8.01)	(-1.200, 0.821)		
	DSG	132	5.50 (10.69)	132	5.24 (12.26)	-0.26 (10.13)	(-2.005, 1.482)		

This analysis includes subjects with non-missing PRO assessment at baseline and at least one non-missing PRO assessments at post-baseline.

Strata I-III have been combined and analyzed separately as the IBS-QoL was specifically included in the trial to measure the impact of GI complications of treatment on patient QoL as related to the effects of boosted PI-based antiretroviral regimens.

‡ The 95% CIs were based on t-distribution

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; adpro]

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Table 2.7.3-switch48wk: 48

Proportion of Subjects With HIV-SI Bothersome Symptoms
HIV-SI PRO FAS, Study Weeks 0 - 48
Data as Observed

	ISG			DSG			Treatment Difference ISG - DSG	
HIV-SI Bothersome Symptoms[†]	N	n	n/N(%)	N	n	n/N(%)	Difference in Percentage	95% CI[‡]
Day 1 (Baseline)								
Fatigue or Loss of Energy	421	161	(38.2)	211	79	(37.4)	0.80	-7.30 to 8.68
Fevers, Chills or Sweats	421	64	(15.2)	211	25	(11.8)	3.35	-2.57 to 8.67
Feeling Dizzy or Lightheaded	421	79	(18.8)	211	33	(15.6)	3.13	-3.37 to 9.04
Pain, Numbness or Tingling	421	89	(21.1)	211	44	(20.9)	0.29	-6.72 to 6.78
Trouble Remembering	421	107	(25.4)	211	45	(21.3)	4.09	-3.09 to 10.78
Nausea or Vomiting	421	33	(7.8)	211	19	(9.0)	-1.17	-6.30 to 3.20
Diarrhea or Loose Bowel Movements	421	101	(24.0)	211	43	(20.4)	3.61	-3.46 to 10.17
Felt Sad, Down or Depressed	421	128	(30.4)	211	57	(27.0)	3.39	-4.24 to 10.61
Felt Nervous or Anxious	421	121	(28.7)	211	54	(25.6)	3.15	-4.37 to 10.24
Difficulty Falling/Staying Asleep	421	143	(34.0)	211	77	(36.5)	-2.53	-10.54 to 5.25
Skin Problems	421	100	(23.8)	211	46	(21.8)	1.95	-5.21 to 8.62
Cough, Trouble Catching Breath	421	67	(15.9)	211	29	(13.7)	2.17	-4.01 to 7.74
Headache	421	84	(20.0)	211	43	(20.4)	-0.43	-7.36 to 5.97
Loss of Appetite, Change in Taste	421	32	(7.6)	211	17	(8.1)	-0.46	-5.42 to 3.75
Bloating, Pain or Gas in Stomach	421	104	(24.7)	211	54	(25.6)	-0.89	-8.30 to 6.08
Muscle Aches or Joint Pain	421	120	(28.5)	211	62	(29.4)	-0.88	-8.56 to 6.44
Problems With Having Sex	421	91	(21.6)	211	36	(17.1)	4.55	-2.18 to 10.74
Changes in Body, Weight Gain	421	92	(21.9)	211	41	(19.4)	2.42	-4.51 to 8.82
Problems With Weight Loss, Wasting	421	46	(10.9)	211	28	(13.3)	-2.34	-8.23 to 2.83
Hair Loss, Changes in Look of Hair	421	58	(13.8)	211	24	(11.4)	2.40	-3.39 to 7.57

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Proportion of Subjects With HIV-SI Bothersome Symptoms
HIV-SI PRO FAS, Study Weeks 0 - 48
Data as Observed

HIV-SI Bothersome Symptoms[†]	ISG			DSG			Treatment Difference ISG - DSG	
	N	n	n/N(%)	N	n	n/N(%)	Difference in Percentage	95% CI[‡]
Week 24								
Fatigue or Loss of Energy	383	145	(37.9)	200	67	(33.5)	4.36	-3.93 to 12.33
Fevers, Chills or Sweats	383	50	(13.1)	200	28	(14.0)	-0.95	-7.22 to 4.67
Feeling Dizzy or Lightheaded	383	56	(14.6)	200	29	(14.5)	0.12	-6.29 to 5.90
Pain, Numbness or Tingling	383	80	(20.9)	200	41	(20.5)	0.39	-6.82 to 7.07
Trouble Remembering	383	103	(26.9)	200	45	(22.5)	4.39	-3.16 to 11.46
Nausea or Vomiting	383	29	(7.6)	200	19	(9.5)	-1.93	-7.30 to 2.64
Diarrhea or Loose Bowel Movements	383	61	(15.9)	200	40	(20.0)	-4.07	-11.04 to 2.32
Felt Sad, Down or Depressed	383	97	(25.3)	200	51	(25.5)	-0.17	-7.84 to 7.06
Felt Nervous or Anxious	383	103	(26.9)	200	50	(25.0)	1.89	-5.80 to 9.14
Difficulty Falling/Staying Asleep	383	113	(29.5)	200	64	(32.0)	-2.50	-10.56 to 5.25
Skin Problems	383	79	(20.6)	200	36	(18.0)	2.63	-4.38 to 9.08
Cough, Trouble Catching Breath	383	49	(12.8)	200	30	(15.0)	-2.21	-8.57 to 3.49
Headache	383	71	(18.5)	200	44	(22.0)	-3.46	-10.68 to 3.23
Loss of Appetite, Change in Taste	383	29	(7.6)	200	25	(12.5)	-4.93	-10.72 to 0.03
Bloating, Pain or Gas in Stomach	383	90	(23.5)	200	47	(23.5)	-0.00	-7.50 to 7.02
Muscle Aches or Joint Pain	383	93	(24.3)	200	54	(27.0)	-2.72	-10.43 to 4.58
Problems With Having Sex	383	68	(17.8)	200	35	(17.5)	0.25	-6.59 to 6.52
Changes in Body, Weight Gain	383	85	(22.2)	200	40	(20.0)	2.19	-5.03 to 8.89
Problems With Weight Loss, Wasting	383	31	(8.1)	200	27	(13.5)	-5.41	-11.35 to -0.27
Hair Loss, Changes in Look of Hair	383	30	(7.8)	200	27	(13.5)	-5.67	-11.60 to -0.56

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Proportion of Subjects With HIV-SI Bothersome Symptoms
HIV-SI PRO FAS, Study Weeks 0 - 48
Data as Observed

HIV-SI Bothersome Symptoms[†]	ISG			DSG			Treatment Difference ISG - DSG	
	N	n	n/N(%)	N	n	n/N(%)	Difference in Percentage	95% CI[‡]
Week 48								
Fatigue or Loss of Energy	368	127	(34.5)	188	58	(30.9)		
Fevers, Chills or Sweats	368	41	(11.1)	188	19	(10.1)		
Feeling Dizzy or Lightheaded	368	48	(13.0)	188	22	(11.7)		
Pain, Numbness or Tingling	368	86	(23.4)	188	27	(14.4)		
Trouble Remembering	368	89	(24.2)	188	38	(20.2)		
Nausea or Vomiting	368	26	(7.1)	188	10	(5.3)		
Diarrhea or Loose Bowel Movements	368	50	(13.6)	188	22	(11.7)		
Felt Sad, Down or Depressed	368	90	(24.5)	188	42	(22.3)		
Felt Nervous or Anxious	368	83	(22.6)	188	39	(20.7)		
Difficulty Falling/Staying Asleep	368	101	(27.4)	188	52	(27.7)		
Skin Problems	368	75	(20.4)	188	38	(20.2)		
Cough, Trouble Catching Breath	368	49	(13.3)	188	22	(11.7)		
Headache	368	53	(14.4)	188	27	(14.4)		
Loss of Appetite, Change in Taste	368	32	(8.7)	188	14	(7.4)		
Bloating, Pain or Gas in Stomach	368	80	(21.7)	188	37	(19.7)		
Muscle Aches or Joint Pain	368	90	(24.5)	188	40	(21.3)		
Problems With Having Sex	368	52	(14.1)	188	30	(16.0)		
Changes in Body, Weight Gain	368	67	(18.2)	188	40	(21.3)		
Problems With Weight Loss, Wasting	368	32	(8.7)	188	23	(12.2)		

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Proportion of Subjects With HIV-SI Bothersome Symptoms
HIV-SI PRO FAS, Study Weeks 0 - 48
Data as Observed

HIV-SI Bothersome Symptoms[†]	ISG			DSG			Treatment Difference ISG - DSG	
	N	n	n/N(%)	N	n	n/N(%)	Difference in Percentage	95% CI[‡]
Hair Loss, Changes in Look of Hair	368	43	(11.7)	188	17	(9.0)		

[†] Responses for each symptom at each time point were dichotomized into a 0 (not present or symptom present with no bother) or 1 (symptom present and bothers me a little, bothers me, or bothers me a lot)

ISG = Immediate Switch Group; DSG = Delayed Switch Group; N = number of subjects completed that particular item from HIV-SI questionnaire; n = number of subjects having presence of bothersome symptoms

[‡] The 95% CIs were based on M&N method.

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; adpro]

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Table 2.7.3-switch48wk: 49

Summary of Mean Change from Baseline Score for HIV-SI Bothersome Symptom Count
HIV-SI PRO FAS, Study Weeks 0-48
Data as Observed

Study Week	Treatment	Baseline		Value		Change from Baseline†		Treatment Difference ISG - DSG	
		N	Mean (SD)	N	Mean (SD)	Mean (SD)	95% CI	Mean (SD)	95% CI‡
HIV-SI Bothersome Symptom Count									
Week 24	ISG	364	4.19 (4.44)	364	3.91 (4.43)	-0.28 (3.80)	(-0.675, 0.109)	-0.31 (3.59)	(-0.939, 0.321)
	DSG	192	3.97 (4.29)	192	4.00 (4.69)	0.03 (3.16)	(-0.424, 0.476)		
Week 48	ISG	348	4.16 (4.46)	348	3.64 (4.52)	-0.52 (3.74)	(-0.911, -0.123)		
	DSG	177	3.93 (4.22)	177	3.29 (4.41)	-0.64 (3.71)	(-1.189, -0.088)		

This analysis includes subjects with non-missing PRO assessment at baseline and at least one non-missing PRO assessments at post-baseline.

† Responses for each symptom at each time point were dichotomized into a 0 (not present or symptom present with no bother) or 1 (symptom present and bothers me a little, bothers me, or bothers me a lot). HIV-SI bothersome symptom count is a summation of the presence of the individual HIV-SI items and ranges from 0 to 20, with higher counts indicating more bothersome symptoms.

‡ The 95% CIs were based on t-distribution

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; adpro]

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Table 2.7.3-switch48wk: 50

Summary of EQ-5D-5L at Baseline
EQ-5D-5L PRO FAS, Study Weeks 0 – 48
Data as Observed

	ISG			DSG		
	N	n	n/N (%)	N	n	n/N (%)
Mobility						
I am unable to walk	421	1	(0.2)	211	1	(0.5)
I have moderate problems in walking about	421	12	(2.9)	211	8	(3.8)
I have no problems in walking about	421	366	(86.9)	211	190	(90.0)
I have severe problems in walking about	421	2	(0.5)	211	0	(0.0)
I have slight problems in walking about	421	40	(9.5)	211	12	(5.7)
Self-Care						
I have moderate problems washing or dressing myself	421	1	(0.2)	211	0	(0.0)
I have no problems washing or dressing myself	421	407	(96.7)	211	205	(97.2)
I have severe problems washing or dressing myself	421	1	(0.2)	211	0	(0.0)
I have slight problems washing or dressing myself	421	12	(2.9)	211	6	(2.8)
Usual Activities						
I have moderate problems doing my usual activities	421	12	(2.9)	211	7	(3.3)
I have no problems doing my usual activities	421	359	(85.3)	211	184	(87.2)
I have severe problems doing my usual activities	421	3	(0.7)	211	0	(0.0)
I have slight problems doing my usual activities	421	47	(11.2)	211	20	(9.5)
Pain/Discomfort						
I have extreme pain or discomfort	421	2	(0.5)	211	0	(0.0)
I have moderate pain or discomfort	421	26	(6.2)	211	17	(8.1)
I have no pain or discomfort	421	287	(68.2)	211	153	(72.5)
I have severe pain or discomfort	421	5	(1.2)	211	1	(0.5)
I have slight pain or discomfort	421	101	(24.0)	211	40	(19.0)
Anxiety/Depression						
I am extremely anxious or depressed	421	2	(0.5)	211	2	(0.9)
I am moderately anxious or depressed	421	19	(4.5)	211	12	(5.7)
I am not anxious or depressed	421	289	(68.6)	211	135	(64.0)
I am severely anxious or depressed	421	9	(2.1)	211	3	(1.4)
I am slightly anxious or depressed	421	102	(24.2)	211	59	(28.0)

ISG= Immediate Switch Group; DSG=Delayed Switch Group; N=number of subjects completed a particular health state; n=number of subjects in each level from a health state

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; adpro]

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Table 2.7.3-switch48wk: 51

Summary of Mean Change from Baseline Score for EQ VAS
EQ-5D-5L PRO FAS, Study Weeks 0-48
Data as Observed

Study Week	Treatment	Baseline		Value		Change from Baseline[†]		Treatment Difference ISG - DSG	
		N	Mean (SD)	N	Mean (SD)	Mean (SD)	95% CI	Mean (SD)	95% CI[‡]
EQ VAS Score[*]									
Week 24	ISG	364	85.67 (14.22)	364	84.44 (15.96)	-1.23 (15.62)	(-2.844, 0.377)	-0.54 (14.45)	(-3.067, 1.996)
	DSG	192	87.15 (11.77)	192	86.45 (12.26)	-0.70 (11.92)	(-2.394, 0.998)		
Week 48	ISG	348	85.45 (14.70)	348	84.69 (16.43)	-0.76 (16.69)	(-2.524, 0.996)		
	DSG	177	87.27 (11.36)	177	86.40 (14.55)	-0.86 (15.22)	(-3.122, 1.393)		

This analysis includes subjects with non-missing PRO assessment at baseline and at least one non-missing PRO assessments at post-baseline.
[*] EQ VAS: range from 0 (worst imaginable health state) to 100 (best imaginable health state).
[†] Mean Change from Baseline in EQ VAS Score: <0: worst health status, ≥ 0: same or better health status.
[‡] The 95% CIs were based on t-distribution
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; adpro]

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3 COMPARISON AND ANALYSES OF RESULTS ACROSS STUDIES

Not applicable for current application.

4 ANALYSIS OF CLINICAL INFORMATION RELEVANT TO DOSING RECOMMENDATIONS

Dosing recommendations for DOR/3TC/TDF are unchanged from currently marketed products; therefore, no additional data are presented here.

5 PERSISTENCE OF EFFICACY AND/OR TOLERANCE EFFECTS

DOR/3TC/TDF demonstrated robust antiretroviral and immunologic responses that were non-inferior to continuation of a ritonavir- or cobicistat-boosted PI-based or cobicistat-boosted EVG-based or NNRTI-based regimen for 24 weeks. DOR/3TC/TDF demonstrated sustained antiretroviral and immunologic responses through 48 weeks of treatment.

6 CONCLUSIONS

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.

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In follow-up to the EU Committee for Medicinal Products for Human Use (CHMP) [redacted] obtained on [redacted]-20[redacted] (as also summarized in the original marketing application), the CHMP did not agree with the Applicant's proposal [redacted]

To support the review of the current Switch Application by the CHMP, and in support of proposed labeling in the EU SmPC, an ad-hoc analysis was performed to provide virologic outcomes based on the HIV-1 RNA 40 copies/mL endpoint (FDA Snapshot Approach) [Table 1].

The primary objective 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. Secondary objectives compared efficacy of the ISG at Study Week 24 to the DSG at Study Week 24 to avoid these associated potential biases. As such, both Study Week 24 and Study Week 48 for the ISG and DSG groups are provided in the summary table.

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Table 1

Virologic Outcome (40 copies/mL Endpoint)
FDA Snapshot Approach
Base Study

Outcome	DOR/3TC/TDF QD ISG at Study Week 48 (N=447) n (%)	Baseline Regimen DSG at Study Week 24 (N=223) n (%)	DOR/3TC/TDF QD ISG at Study Week 24 (N=447) n (%)	DOR/3TC/TDF QD DSG at Study Week 48 (N=209[§§]) n (%)
HIV-1 RNA <40 copies/mL	401 (89.7)	208 (93.3)	415 (92.8)	198 (94.7)
HIV-1 RNA ≥40 copies/mL[†]	12 (2.7)	8 (3.6)	12 (2.7)	6 (2.9)
No Virologic Data Within the Time Window	34 (7.6)	7 (3.1)	20 (4.5)	5 (2.4)
Reasons				
Discontinued study due to AE or Death[‡]	14 (3.1)	0	6 (1.3)	2 (1.0)
Discontinued study for Other Reasons[§]	20 (4.5)	7 (3.1)	12 (2.7)	3 (1.4)
On study but missing data in window	0	0	2 (0.4)	0

[†] Includes subjects who changed (a) any component of background therapy to a new drug class or (b) background components that were not permitted per protocol or (c) any background drug in the regimen because of lack of efficacy (perceived or documented) before Study Week 24, and subjects who discontinued study drug or study before Study Week 48 for lack or loss of efficacy and subjects with HIV-1 RNA ≥40 copies/mL in the Study Week 48 window (relative day 295 through last day of base study treatment period) and in the Study Week 24 window (relative day for DSG 127 through last day of baseline regimen treatment period and for ISG 127 through reported Study Week 24 visit date for subjects who completed Study Week 24 visit or last day of treatment period for subject discontinued before having Study Week 24 visit).

[‡] Includes subjects who discontinued because of adverse event (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 include: lost to follow-up, non-compliance with study drug, physician decision, protocol deviation, withdrawal by subject.

[§§] Includes only subjects who switched to DOR/3TC/TDF QD at Study Week 24.

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 (Percent) of subjects in each category.

Source: [P024MK1439A: adam-adsl; adeff1eu]

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation/Term	Definition
3TC	lamivudine
ABC	abacavir
ABC/3TC	abacavir (ABC) plus lamivudine (3TC)
AE	adverse event or adverse experience
AIDS	acquired immune deficiency syndrome
CI	confidence interval
CNS	central nervous system
CSR	clinical study report
D/C	discontinued
DOR	doravirine (MK-1439, PIFELTRO™)
DOR/3TC/TDF	fixed-dose combination of doravirine, lamivudine and tenofovir disoproxil fumarate (MK-1439A, DELSTRIGO™)
DRV	darunavir
DRV+r	darunavir boosted with ritonavir
EFV	efavirenz
EPZICOM / KIVEXA	alternative brand names for fixed dose combination of abacavir (ABC) plus lamivudine (3TC)
FAS	full analysis set (analysis population)
FDA	Food and Drug Administration
FDC	fixed-dose combination
FTC	emtricitabine
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV-1	human immunodeficiency virus type 1
IC50	50% inhibitory concentration
MK-1439	doravirine
MK-1439A	fixed-dose combination of DOR, 3TC, and TDF
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleos(t)ide reverse transcriptase inhibitors
OF	observed failure
PDVF	protocol-defined virologic failure

Abbreviation/Term	Definition
PI	protease inhibitor
QD	once a day
RPV	rilpivirine
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)
US	United States

1 BACKGROUND AND OVERVIEW OF CLINICAL EFFICACY

1.1 Background and Rationale

Doravirine (DOR, also known MK-1439) is an NNRTI active against HIV-1 infection.

DOR is available as a single agent (PIFELTRO™) and as a FDC with the 2 NRTIs, 3TC and TDF, (DELSTRIGO™) (DOR/3TC/TDF; also known as MK-1439A).

The original marketing application was based on the demonstration of safety and efficacy through Week 48 in the pivotal Phase 3 trials of DOR and DOR/3TC/TDF. The complete 96-week data from P018 and P021, demonstrating comparable efficacy of DOR or DOR/3TC/TDF with the respective comparators and supporting the demonstration of noninferiority at Week 48, are provided in this application.

1.2 Overview of the Clinical Development Program for Doravirine

The clinical development program for DOR and DOR/3TC/TDF includes 36 completed Phase 1 trials, 1 completed Phase 2b trial (P007), 2 ongoing Phase 2 trials (P028 and P030), and 3 Phase 3 trials (P018, P021, and P024). Complete 96-week data from two Phase 3 trials, P018 and P021, are the primary focus of this supplemental application [Table 2.7.3-trtmtnve96wk: 1].

The clinical development program for DOR and DOR/3TC/TDF proceeded as follows:

1. Demonstration of in vivo HIV-1 antiretroviral activity in the Phase 1 trial, P005.

2. Selection of the clinical dose in the Phase 2b trial, P007.

   P007 is a dose-ranging trial in HIV-1-infected, treatment-naïve participants, which provided evidence to support dose selection for subsequent Phase 2 and Phase 3 trials and demonstrated long-term (through 96 weeks) efficacy and safety data for the selected dose.

3. Demonstration of efficacy and safety in the pivotal Phase 3 trials, P018 and P021.

   Results of these Phase 3 trials in HIV-1-infected treatment-naïve adults demonstrated the efficacy of DOR 100 mg, after 48 weeks of treatment, was non-inferior when compared with that of 2 commonly prescribed anti-retroviral therapies: the protease inhibitor (PI) darunavir (DRV) boosted with ritonavir (DRV+r) in P018, and EFV/FTC/TDF in P021. In P018, DOR was evaluated as a single agent in combination with either FTC/TDF or abacavir (ABC) plus 3TC (ABC/3TC), as chosen by the investigator. In P021, DOR was evaluated as the fixed-dose combination DOR/3TC/TDF.

   The complete 96-week data from P018 and P021 are provided in this application. Following Week 96, participants in each of these trials may continue in an extension with open-label DOR-regimen.

4. Demonstration of safety and efficacy in a Switch population (P024).

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

5. Additional characterization of the clinical profile of DOR is expected from 2 ongoing Phase 2 trials: P028, and P030.

   - P028 is a Phase 2 trial in which HIV-1-infected participants, virologically suppressed on EFV/FTC/TDF and experiencing EFV-associated CNS toxicity, are switched to DOR/3TC/TDF to assess whether CNS toxicities resolve or improve. Enrollment had been completed as of the data cutoff date.
   - P030 is a Phase 2 trial in which treatment-naïve, HIV-1-infected 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.

Exposure to DOR and DOR/3TC/TDF in Clinical Development Program

As of the data cutoff date for the integrated analysis, DOR (as a single agent or as DOR/3TC/TDF) has been administered to a total of 2406 participants in the clinical development program: 678 participants in the Phase 1 trials and 1728 participants in the Phase 2 and 3 trials, as described below.

- Phase 1: 678 participants in the trials received at least 1 dose of DOR or DOR/3TC/TDF: 650 healthy participants, 12 HIV-1-infected participants, 8 participants with moderate hepatic impairment, and 8 participants with severe renal impairment. DOR was administered as a single dose up to 1200 mg and as multiple doses up to 750 mg QD for 10 days in the Phase 1 trials.

- Phases 2 and 3 (completed and ongoing): 1728 HIV-1-infected participants received DOR or DOR/3TC/TDF in 6 trials: 232 in the completed P007 trial, 747 in the pivotal Phase 3 trials (P018, P021), and 749 in the 3 other ongoing trials (P024, P028 [completely enrolled; blinded as of cut-off date], P030). The characterization of the efficacy of DOR and DOR/3TC/TDF in this application is primarily based on data from the 747 HIV-1-infected, treatment-naïve participants who received DOR or the FDC DOR/3TC/TDF in trials P018 and P021.

Efficacy Data in This Supplemental Application

The Phase 3 trials that provide data for this supplemental application (P018 and P021) are summarized in [Table 2.7.3-trtmtnve96wk: 1]; efficacy findings from these trials are found in [Table 2.7.3-trtmtnve96wk: 2].

1.3 Overview of the Data Presented in This Summary of Clinical Efficacy

This integrated efficacy summary provides data through 96 weeks of treatment in the ongoing Phase 3 trials (P018 and P021). Efficacy data from these trials demonstrate the potent and durable antiretroviral efficacy of DOR, when used in combination with other antiretroviral drugs, and DOR/3TC/TDF.

Complete results and analyses from the individual trials are found in the respective study reports [Ref. 5.3.5.1: P018MK1439] and [Ref. 5.3.5.1: P021MK1439A]; additional results for pooled data are found in the Integrated Summary of Efficacy [Sec. 5.3.5.3.2-trtmtnve96wk].

1.4 Clinical Efficacy Analyses

1.4.1 Efficacy Endpoints Presented in This Summary of Clinical Efficacy

Consistent with guidelines for the clinical development of HIV drugs [Ref. 5.4: 04KB08, 04DT6Q], the continued efficacy of DOR 100 mg, as the single entity in combination with other antiretroviral drugs or as DOR/3TC/TDF, was assessed by the following parameters, measured at Week 96 in the pivotal Phase 3 trials:

- Proportion of participants achieving HIV-1 RNA <50 copies/mL;
- Proportion of participants achieving HIV-1 RNA <40 copies/mL;
- Proportion of participants achieving HIV-1 RNA <200 copies/mL;
- Time to loss of virologic response (TLVOR);
- Change from baseline in $CD4^+$ T-cell count;
- Protocol-defined virologic failure (PDVF) and viral drug resistance.

The efficacy endpoints for the analysis of pooled data for the Week 96 analysis and summaries follow the same approach as the Week 48 analysis provided in the original application (Integrated Statistical Analysis Plan [Ref. 5.3.5.3: 04LVBJ]). Efficacy endpoints from the individual trials included in this application are summarized in [Table 2.7.3-trtmtnve96wk: 2].

1.4.1.1 Antiretroviral Efficacy

Proportion of Participants with Virologic Response

Three HIV-1 RNA thresholds were used in evaluating antiretroviral efficacy: <50, <40, and <200 copies/mL. The threshold of <50 copies/mL, commonly used in clinical trials of HIV therapies, was used for the primary analyses in the Phase 3 trials. The threshold of <40 copies/mL reflects the lower limit of quantification of the assay used in the Phase 3 trials that support this application. The threshold of <200 copies/mL has also been frequently used in clinical trials as well as in clinical practice, particularly in defining virologic failure.

In both P018 and P021, the primary endpoint was the proportion of participants with HIV-1 RNA <50 copies/mL at Week 48. Secondary and exploratory endpoints included proportions of participants with HIV-1 RNA <50, <40 and <200 copies/mL at Week 96.

Time to Loss of Virologic Response

In P018 and P021, TLOVR was defined, for participants who had achieved HIV-1 RNA <50 copies/mL and subsequently had 2 consecutive measurements (≥1 week apart) of HIV-1 RNA ≥50 copies/mL, as the time between Day 1 and the first of the 2 consecutive values of ≥50 copies/mL. For participants who achieved and sustained HIV-1 RNA levels of <50 copies/mL, TLOVR was censored at the time of the last available measurement. For participants who did not achieve HIV-1 RNA <50 copies/mL, TLOVR was defined as 0 weeks.

1.4.1.2 Immunologic Efficacy

In P018 and P021, immunologic efficacy was assessed, as a secondary efficacy endpoint, by the change in $CD4^+$ T-cell count from baseline at Weeks 48 and 96.

1.4.1.3 Protocol-Defined Virologic Failure

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

- Non-responder: A participant 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 96

  OR

- Rebounder: A participant 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.

1.4.1.4 Evaluation of Viral Drug Resistance

Genotypic and phenotypic data for viral drug resistance to DOR, and to each comparator and each background nucleos(t)ide reverse transcriptase inhibitor (NRTI), were assessed in P018

and P021 for participants with PDVF and for participants who discontinued study treatment for other reasons (and had HIV-1 RNA >400 copies/mL at the PDVF confirmation or discontinuation visit).

Post-baseline genotypic resistance to DOR was defined, for the purpose of the Phase 3 trials, as any of the following mutations, based on in vitro testing performed by the Sponsor: RT A98G, L100I, K101E, V106A, V106I, V106M, V108I, E138K, Y188L, G190A, G190S, H221Y, P225H, F227C, F227L, F227V, M230I, M230L, L234I, P236L, and Y318F. While no threshold for phenotypic resistance to DOR has yet been clinically defined, the central laboratory used a 2.5-fold change in IC50 versus wild-type virus as a broad assay-reproducibility cut-off for potential phenotypic resistance to DOR (commonly done for other antiretrovirals in development before sufficient data are available to define a clinically relevant cut-off).

1.4.2 Statistical Methodology

1.4.2.1 Definitions of Analysis Populations

Efficacy analyses were based on the Full Analysis Set (FAS) for the individual trials (P018 and P021) and for pooled data from P018 and P021. 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. (The rationale for pooling data is found in [Sec. 2.7.3-trtmtnve96wk: 3.1].)

1.4.2.2 Missing Data Approaches

Two approaches to missing data were used in the individual P018 and P021 trials as well as for the pooled data:

- FDA Snapshot: In this approach, all participants with missing data were considered to be failures, regardless of reason.

- Observed Failure (OF): In this approach, participants with non-intermittent missing data who prematurely discontinued study treatment due to lack of efficacy were considered to be failures.

The FDA snapshot approach was the primary method for analysis of the proportion of participants achieving various levels of virologic suppression (ie, HIV-1 RNA levels <40, <50 and <200 copies/mL), while the OF approach was used as a sensitivity analysis. Each approach provides a frame of reference for efficacy analysis: the FDA snapshot approach considers a study failure endpoint, which depends on the conduct of the trial, while the OF approach focuses on antiretroviral efficacy of the treatment.

Analysis of immunologic response (change in $CD4^+$ T-cell count from baseline) in P018 and P021 and in the pooled analysis of P018 and P021 used the OF approach, as did subgroup analyses of antiretroviral and immunologic efficacy. The OF approach was used for the subgroup analyses because it provides an evaluation that focuses on virologic factors and not

administrative factors such as missing visits or visits outside of pre-specified time windows. The FDA Snapshot approach was used to confirm the analysis using the OF approach.

Approaches used to address missing values are summarized in [Table 2.7.3-trtmtnve96wk: 1].

Table 2.7.3-trtmtnve96wk: 1

Summary of the Approaches to Missing Data

		Non-Intermittent Missing Values† Not Related to Treatment		Non-Intermittent Missing Values Related to Treatment	
Approach	**Intermittent Missing Values**	**Success at Study Therapy Discontinuation**	**Failure at Study Therapy Discontinuation**	**Study Therapy D/C Due to Clinical or Lab AE**	**Study Therapy D/C Due to Lack of Efficacy**
FDA Snapshot	Failure	Failure	Failure	Failure	Failure
OF	Excluded‡	Excluded	Failure	Excluded	Failure

† Values missing due to permanent discontinuation from the trial.
‡ 'Excluded' refers to exclusion of missing data value from a given participant at a given time point.
Abbreviations: D/C: discontinuation; OF: observed failure.
Note: FDA snapshot approach was the primary approach for P018 and P021 analyses.

1.4.2.3 Other Statistical Methods

The statistical methods applied to each efficacy endpoint in the individual trials are found in the respective Clinical Study Reports (CSRs) [Ref. 5.3.5.1: P018MK1439] [Ref. 5.3.5.1: P021MK1439A]. Pooled data in the integrated analysis of P018 and P021 are summarized with descriptive statistics only; analyses of Week 96 data follow the same approach as the Week 48 analysis provided in the original application (Integrated Statistical Analysis Plan [Ref. 5.3.5.3: 04LVBJ]). Inferential statistics presented within this document are not adjusted for multiplicity.

2 SUMMARY OF RESULTS OF INDIVIDUAL STUDIES

Results of the individual Phase 3 (P018, P021) trials are summarized in [Table 2.7.3-trtmtnve96wk: 2] and described in this section. Detailed results from each trial are available in the respective CSRs [Ref. 5.3.5.1: P018MK1439] [Ref. 5.3.5.1: P021MK1439A].

Table 2.7.3-trtmtnve96wk: 2

Summary of DOR and DOR/3TC/TDF Efficacy Data Supporting the Current Application

Trial Number [Link]	Study Design Countries with Participants Status	No. of Participants (Treated) by Treatment Group	No. of Participants by Sex and Median Age (Range)	Efficacy Objectives and Endpoints Evaluated in This Summary	Major Efficacy Findings Regarding DOR or DOR/3TC/TDF
018 [ ]	Multicenter, double-blind, randomized, active-comparator-controlled, trial in HIV-1-infected, treatment-naïve adults Argentina, Australia, Austria, Canada, Chile, Denmark, France, Germany, Italy, Romania, Russian Federation, South Africa, Spain, United Kingdom, United States (including Puerto Rico) Ongoing (open -label DOR extension)	DOR 100 mg QD N=383 DRV+r 800/100 mg N=383	DOR 100 mg 319 M / 64 F 34.8 yrs (18-68) DRV+r, 800/100 mg 326 M / 57 F 35.7 yrs (18-69)	**Secondary** Evaluate the antiretroviral activity of DOR 100 mg QD, compared with DRV+r, each in combination with FTC/TDF or ABC/3TC, as measured by the proportion of participants with HIV-1 RNA <50 copies/mL at Week 96. Evaluate the antiretroviral activity of DOR 100 mg QD, compared with DRV+r, each in combination with FTC/TDF or ABC/3TC, as measured by the proportion of participants with HIV-1 RNA <40 copies/mL at Week 96. Evaluate the immunologic effect of DOR 100 mg QD, compared with DRV+r, each in combination with FTC/TDF or ABC/3TC, as measured by change from baseline in $CD4^+$ T cell count at Week 96. **Exploratory** Evaluate the antiretroviral activity of DOR 100 mg QD, compared with DRV+r, each in combination with FTC/TDF or ABC/3TC, as measured by the proportion of participants with HIV-1 RNA <200 copies/mL at Week 96. Evaluate the antiretroviral activity of DOR 100 mg QD, compared with DRV+r, each in combination with FTC/TDF or ABC/3TC, as measured by TLOVR. Assess the development of resistance to DOR in participants with virologic failure.	▪ DOR showed higher antiretroviral efficacy and comparable immunologic efficacy versus DRV+r at Week 96, supporting the non-inferiority of DOR to DRV+r previously established at Week 48. ▪ Rates of development of viral drug resistance through Week 96 were low, with viral isolates from 2 of 383 (0.5%) DOR-treated participants shown to have primary genotypic and high-level phenotypic resistance to DOR via the RT V106 pathway. No primary genotypic or phenotypic resistance to DRV was observed among 383 DRV+r-treated participants.

Trial Number [Link]	Study Design Countries with Participants Status	No. of Participants (Treated) by Treatment Group	No. of Participants by Sex and Median Age (Range)	Efficacy Objectives and Endpoints Evaluated in This Summary	Major Efficacy Findings Regarding DOR or DOR/3TC/TDF
021 [ ]	Multicenter, double-blind, randomized, active-comparator-controlled, trial in HIV-1-infected, treatment-naïve adults Australia, Belgium, Canada, Chile, Colombia, Denmark, Germany, Guatemala, Honduras, Israel, Mexico, New Zealand, Peru, Portugal, Russian Federation, South Africa, Spain, Switzerland, Taiwan, Thailand, United Kingdom, United States Ongoing (open-label DOR extension)	DOR/3TC/TDF (DOR 100 mg) N=364 EFV/FTC/TDF N=364	DOR/3TC/TDF 305 M / 59 F 33.6 yrs (18-70 yrs) EFV/FTC/TDF 311 M / 53 F 32.7 yrs (18-69 yrs)	**Secondary** Evaluate the antiretroviral activity of DOR/3TC/TDF QD, compared with EFV/FTC/TDF QD, as measured by the proportion of participants with HIV-1 RNA <50 copies/mL at Week 96. Evaluate the antiretroviral activity of DOR/3TC/TDF QD, compared with EFV/FTC/TDF QD, as measured by the proportion of participants with HIV-1 RNA <40 copies/mL at Week 96. Evaluate the immunologic effect of DOR/3TC/TDF QD, compared with EFV/FTC/TDF QD, as measured by change from baseline in $CD4^+$ T-cell count at Week 96. **Exploratory** Evaluate the antiretroviral activity of DOR/3TC/TDF QD, compared with EFV/FTC/TDF QD, as measured by the proportion of participants with HIV-1 RNA <200 copies/mL at Week 96. Evaluate the antiretroviral activity of DOR/3TC/TDF QD, compared with EFV/FTC/TDF QD, as measured by TLOVR. Assess the development of resistance to DOR in participants with virologic failure.	▪ DOR/3TC/TDF showed comparable antiretroviral and immunologic efficacy versus EFV/FTC/TDF at Week 96, supporting the non-inferiority of DOR/3TC/TDF to EFV/FTC/TDF established at Week 48. ▪ Rates of development of viral drug resistance through Week 96 were low, with viral isolates from 6 of 364 (1.6%) DOR/3TC/TDF-treated participants shown to have primary genotypic and phenotypic resistance to DOR, and none occurring after Week 48. Primary genotypic or phenotypic resistance to EFV was observed among 12 of 364 (3.3%) EFV/FTC/TDF-treated participants.

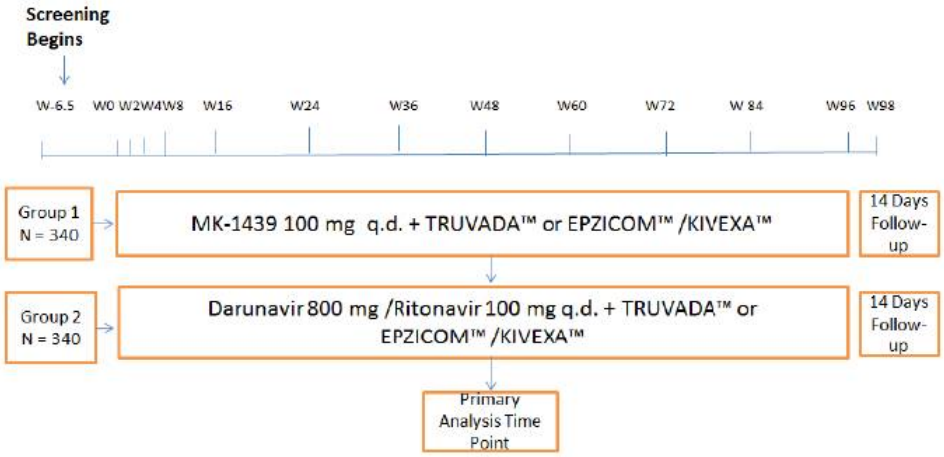
2.1 Protocol 018: Phase 3 Trial – Comparison with Darunavir+Ritonavir

2.1.1 Protocol 018 Study Design

P018 is a Phase 3, multicenter, double-blind, randomized, active-controlled trial in HIV-1-infected, treatment-naïve men and women, 18 years of age or older, with an HIV-1 RNA level of ≥1,000 copies/mL at screening. A total of 769 participants were randomized to receive DOR 100 mg QD or ritonavir-boosted darunavir (DRV+r) 800 mg/100 mg QD, each in combination with NRTI therapy. One of 2 NRTI therapies was chosen by the investigator: FTC/TDF, supplied as TRUVADA™ (TDF 300 mg/FTC 200 mg), or ABC/3TC, supplied as either EPZICOM® or KIVEXA™ (ABC 600 mg/3TC 300 mg). Participants were stratified by HIV-1 RNA level at screening (≤ or >100,000 copies/mL) and investigator-chosen NRTI therapy. Participants received blinded treatment for 96 weeks in the base study, and, if eligible, could have chosen to enter an optional 96-week study extension. All participants had completed the base study at the time of the database lock for the efficacy endpoint analysis for Week 96. The design of the base study is shown in [Figure 2.7.3-trtmtnve96wk: 1], and objectives relevant to the Week 96 time point are listed in [Table 2.7.3-trtmtnve96wk: 2].

Figure 2.7.3-trtmtnve96wk: 1

Protocol 018 Study Design



2.1.2 Protocol 018 Key Efficacy Results

2.1.2.1 Demographic and Prognostic Characteristics at Baseline

The DOR and DRV+r treatment groups were generally well balanced with respect to demographic and prognostic characteristics at baseline [Ref. 5.3.5.1: P018MK1439: 10.4]. Most participants were male and white. The median age was 33 years and 34 years in the DOR and DRV+r groups, respectively; each group had 4 or fewer participants aged 65 years or older. Baseline $CD4^+$ T-cell counts were >200 cells/mm^3 (mean 422 cells/mm^3) in most

(85.8%) participants. Baseline mean plasma HIV-1 RNA was 4.4 $\log_{10}$ copies/mL in each group; the proportions of participants with baseline HIV-1 RNA >100,000 copies/mL were 21.7% and 19.1% in the DOR and DRV+r groups, respectively. The background NRTI regimen for the majority (87.2%) of participants in both groups was FTC/TDF.

2.1.2.2 Efficacy Summary at Week 96: Virologic and Immunologic Responses

Antiretroviral Efficacy at Week 96

The antiretroviral efficacy of DOR 100 mg at Week 96, as measured by the proportion of participants with HIV-1 RNA <50 copies/mL, was higher than that of DRV+r [Table 2.7.3-trtmtnve96wk: 3], supporting the conclusion of the non-inferiority of DOR to DRV+r previously established at Week 48. In the analysis using the FDA snapshot approach, 73.1% and 66.0% of participants in the DOR and DRV+r groups, respectively, achieved HIV-1 RNA <50 copies/mL. The treatment difference (DOR – DRV+r) was 7.1% (95% confidence interval [CI]: 0.5, 13.7).

The antiretroviral efficacy of DOR 100 mg at Week 96, as measured by the proportion of participants achieving the endpoint of HIV-1 RNA <40 copies/mL, was higher than that of DRV+r. Specifically, 72.0% and 64.4% of participants in the DOR and DRV+r groups, respectively, using the FDA snapshot approach, achieved HIV-1 RNA <40 copies/mL, with a treatment difference of 7.6% (95% CI: 1.0, 14.2).

Comparable antiretroviral efficacy results in the DOR and DRV+r groups were also seen with a threshold of <200 copies/mL.

Immunologic Efficacy at Week 96

The immunologic efficacy of DOR 100 mg, as measured by the change from baseline to Week 96 in $CD4^+$ T-cell count (using the OF approach), was comparable to that of DRV+r: mean increases from baseline were 224 and 207 cells/mm^3, respectively [Table 2.7.3-trtmtnve96wk: 3].

Table 2.7.3-trtmtnve96wk: 3

P018: Efficacy Analysis at Week 96

Parameter	Missing Data Approach[†]	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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2.1.2.3 Antiretroviral Efficacy Over Time Through Week 96

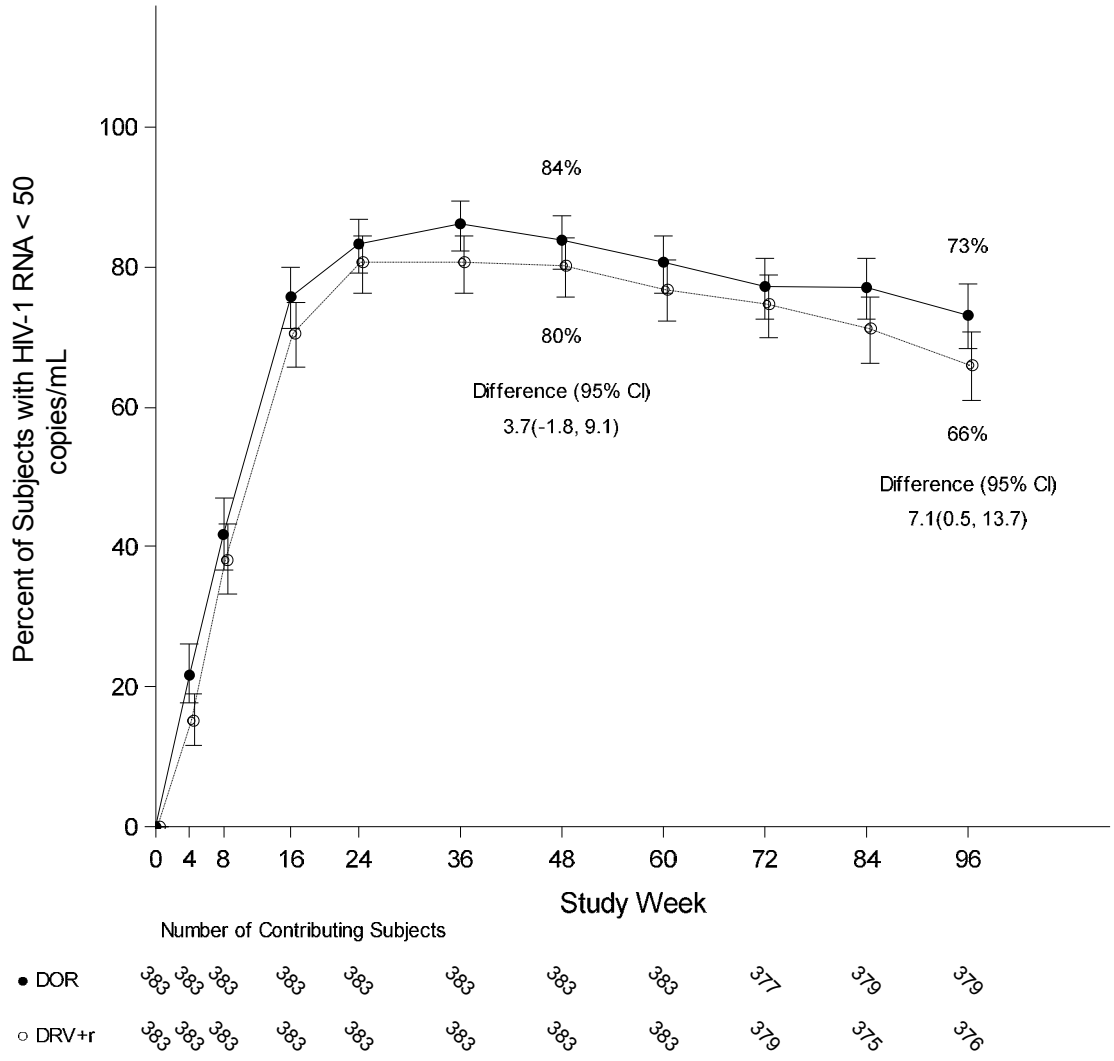
The proportion of participants in the DOR group who achieved HIV-1 RNA <50 copies/mL increased from baseline through Week 24, demonstrating a response that was robust and comparable to that of DRV+r. The proportions of participants who achieved HIV-1 RNA <50 copies/mL over time through Week 96, using the FDA snapshot approach, were comparable for the DOR and DRV+r treatment groups at most time points. At all measured time points, including Week 96, as described above, the observed proportion of participants who had HIV RNA below 50 copies/mL was higher in the DOR group than in the DRV+r group [Figure 2.7.3-trtmtnve96wk: 2]. Additional details are available in the CSR [Ref. 5.3.5.1: P018MK1439: 11.1.2.1.1].

Comparable antiretroviral efficacy over time in the DOR and DRV+r groups was also seen when HIV-1 RNA thresholds of <40 copies/mL and <200 copies/mL were used as endpoints [Ref. 5.3.5.1: P018MK1439: 11.1.2.1.1].

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Figure 2.7.3-trtmtnve96wk: 2

P018: Proportion of Subjects With HIV-1 RNA < 50 copies/mL Over Time
FDA Snapshot Approach

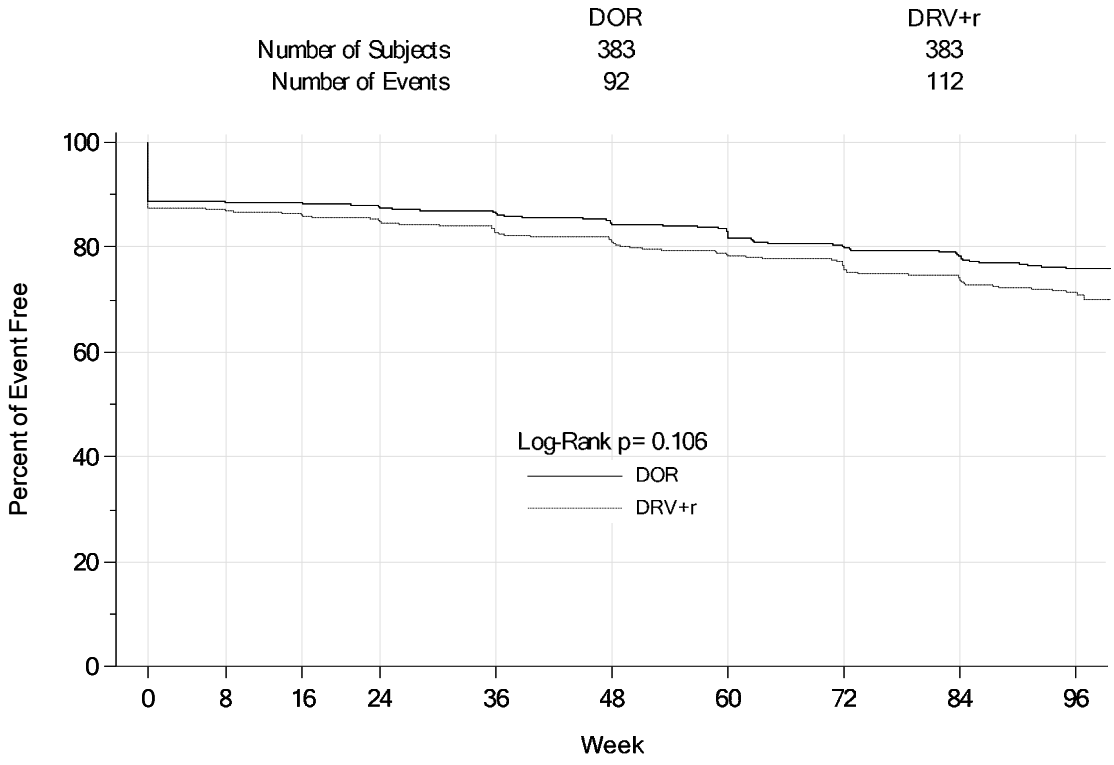


2.1.2.4 Time to Loss of Virologic Response

Time to loss of virologic response (TLOVR), using an HIV-1 RNA threshold of 50 copies/mL, is presented in a Kaplan-Meier plot, including a non-multiplicity-adjusted p-value. The risk of loss-of-response was comparable in the DOR and DRV+r groups through Week 96 [Figure 2.7.3-trtmtnve96wk: 3].

Figure 2.7.3-trtmtnve96wk: 3

P018: Kaplan-Meier Plot for Time to Loss of Virologic Response



Number of subjects at risk

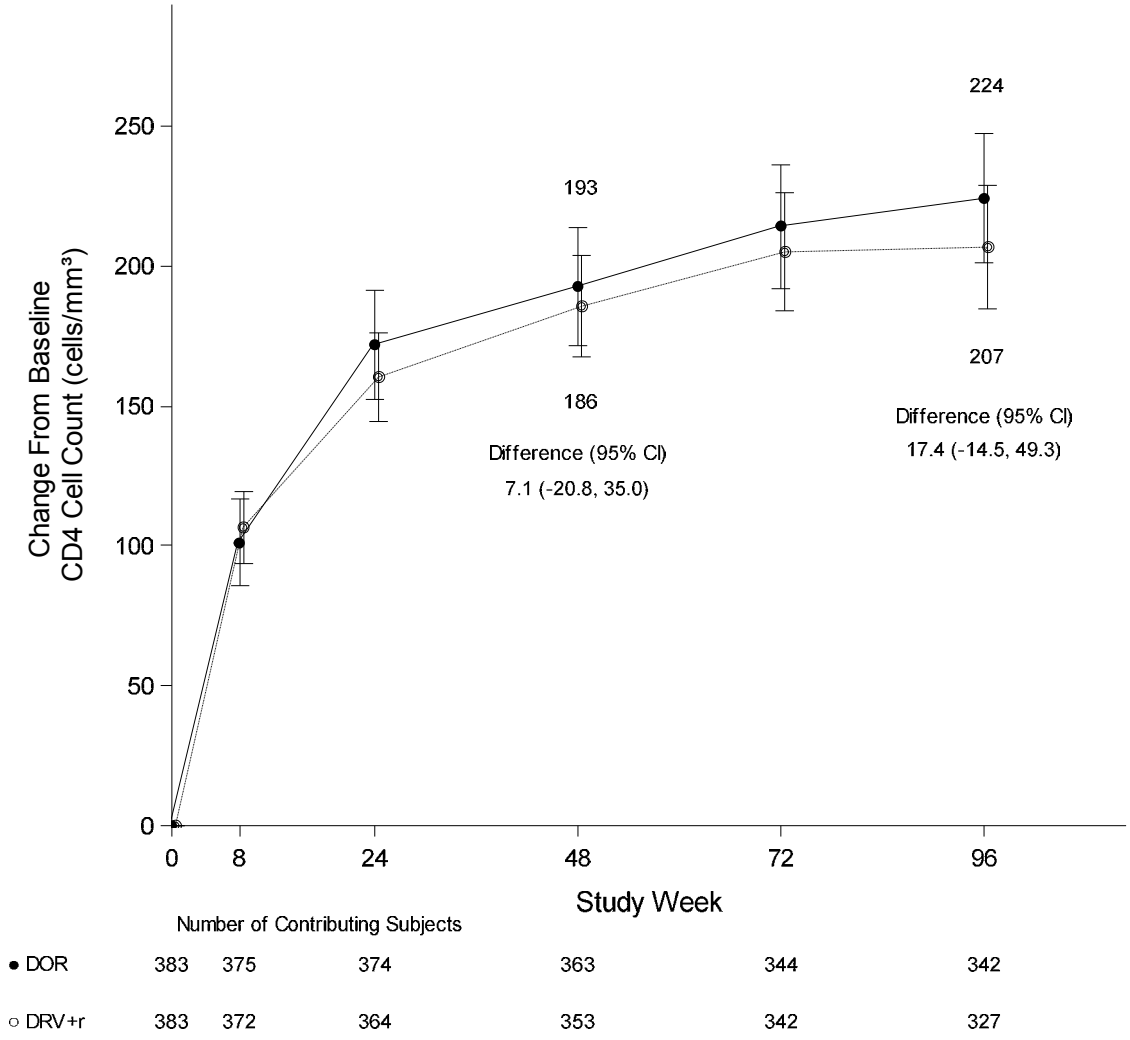
DOR	383	340	339	336	332	324	318	307	298	223
DRV+r	383	334	330	326	317	312	301	293	280	201

2.1.2.5 Immunologic Response Through Week 96

Comparable increases from baseline in $CD4^+$ T-cell count were observed at each time point through Week 96 for the DOR and DRV+r treatment groups, with mean increases from baseline at Week 96 of 224 and 207 cells/mm^3, respectively [Figure 2.7.3-trtmtnve96wk: 4].

Figure 2.7.3-trtmtnve96wk: 4

P018: Change From Baseline in $CD4^+$ T-Cell Count (cells/mm³) Over Time
Observed Failure Approach



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2.1.2.6 Protocol-Defined Virologic Failure and Development of Viral Drug Resistance Through Week 96

Numbers of participants with PDVF (with participants classified as rebounders or non-responders) are summarized below; the majority of participants in both the DOR and DRV+r groups who met PDVF criteria were rebounders. For participants who were required to discontinue study drug due to PDVF and for participants who discontinued for other reasons, details of genotypic and phenotypic assessments of viral drug resistance are summarized below. Further details on viral resistance data are provided in the study report [Ref. 5.3.5.1: P018MK1439: 11.1.4].

Participants With Protocol-Defined Virologic Failure

Through Week 96, rates of PDVF were low and comparable in the DOR (8.9%) and DRV+r (11.2%) treatment groups. The majority of participants with PDVF in each treatment group were rebounders who had initially responded to treatment, while few were non-responders [Table 2.7.3-trtmtnve96wk: 4].

More than half the participants who met either rebound or non-response PDVF criteria in each treatment group had HIV-1 RNA <200 copies/mL at the time of virologic failure confirmation (56% in the DOR group and 60% in the DRV+r group). In the majority of participants who met the rebound definition of PDVF in both treatment groups, HIV-1 RNA levels decreased between the viral failure visit and the viral failure confirmation visit [Ref. 5.3.5.1: P018MK1439: 16.2.6.1].

Table 2.7.3-trtmtnve96wk: 4

P018: Number of Subjects with Protocol Defined Virologic Failure (Weeks 0-96)

	Doravirine 100 mg QD N=(383) n (%)			Darunavir 800 mg + ritonavir 100 mg QD N=(383) n (%)		
	Confirmation HIV-1 RNA ≥50 and ≤200 copies/mL	Confirmation HIV-1 RNA >200 copies/mL	Total	Confirmation HIV-1 RNA ≥50 and ≤200 copies/mL	Confirmation HIV-1 RNA >200 copies/mL	Total
Virologic Failure (confirmed)† by Week 24						
Non-Responder	0 (0.0)	2 (0.5)	2 (0.5)	0 (0.0)	2 (0.5)	2 (0.5)
Rebounder	7 (1.8)	3 (0.8)	10 (2.6)	4 (1.0)	2 (0.5)	6 (1.6)
Virologic Failure (confirmed)† by Week 36						
Non-Responder	0 (0.0)	2 (0.5)	2 (0.5)	0 (0.0)	3 (0.8)	3 (0.8)
Rebounder	9 (2.3)	5 (1.3)	14 (3.7)	10 (2.6)	4 (1.0)	14 (3.7)
Virologic Failure (confirmed)† by Week 48						
Non-Responder	0 (0.0)	3 (0.8)	3 (0.8)	1 (0.3)	4 (1.0)	5 (1.3)
Rebounder	12 (3.1)	5 (1.3)	17 (4.4)	13 (3.4)	6 (1.6)	19 (5.0)
Virologic Failure (confirmed)† by Week 60						
Non-Responder	0 (0.0)	3 (0.8)	3 (0.8)	1 (0.3)	4 (1.0)	5 (1.3)
Rebounder	16 (4.2)	7 (1.8)	23 (6.0)	17 (4.4)	7 (1.8)	24 (6.3)
Virologic Failure (confirmed)† by Week 72						
Non-Responder	0 (0.0)	3 (0.8)	3 (0.8)	1 (0.3)	4 (1.0)	5 (1.3)
Rebounder	18 (4.7)	8 (2.1)	26 (6.8)	21 (5.5)	9 (2.3)	30 (7.8)
Virologic Failure (confirmed)† by Week 84						
Non-Responder	0 (0.0)	3 (0.8)	3 (0.8)	1 (0.3)	4 (1.0)	5 (1.3)
Rebounder	18 (4.7)	10 (2.6)	28 (7.3)	23 (6.0)	11 (2.9)	34 (8.9)
Virologic Failure (confirmed)† by Week 96						
Non-Responder	0 (0.0)	3 (0.8)	3 (0.8)	1 (0.3)	4 (1.0)	5 (1.3)
Rebounder	19 (5.0)	12 (3.1)	31 (8.1)	25 (6.5)	13 (3.4)	38 (9.9)

† Protocol defined virologic failure (PDVF) for this study is defined as one of the following: 1) Rebounder: Confirmed (two consecutive measures at least one week apart) HIV-1 RNA ≥ 50 copies/mL after initial response of HIV-1 RNA <50 copies/mL at any time during the study; Or 2) Non responder: Confirmed (two consecutive measures at least one week apart) HIV -1 RNA ≥ 200 copies/mL at Week 24 or Week 36; OR Confirmed (two consecutive measures at least one week apart) HIV-1 RNA ≥ 50 copies/mL at Week 48.

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; advf]

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Viral Drug Resistance in Participants With Protocol-Defined Virologic Failure

Of the 11 participants in the DOR group who met criteria for PDVF and had samples tested for virologic resistance, all had successful genotype testing and 10 had successful phenotype testing. Of the 14 participants in the DRV+r group, who met criteria for PDVF and had samples tested for virologic resistance, 13 had successful testing for genotype and/or phenotype. Detailed listings by participant are found in the CSR [Ref. 5.3.5.1: P018MK1439: 11.1.4.2.1].

Virus from 1 of the 11 DOR-treated participants with PDVF and resistance-testing results was found to have primary genotypic and phenotypic resistance to DOR (via V106A and P225H mutations) and to FTC/3TC. Across the other NNRTIs tested, this isolate was also phenotypically resistant to NVP but not to EFV, ETR or RPV. No other genotypic or phenotypic resistance to DOR was observed in the DOR group.

No HIV-1 genotypic primary mutation associated with DRV resistance was identified in viruses from the 13 DRV+r treated participants with PDVF and successfully tested viral isolates. The virus isolated from 1 participant had primary phenotypic resistance to FTC/3TC (genotypic results were not available).

Viral Drug Resistance in Participants Who Discontinued for Reasons Other Than Protocol-Defined Virologic Failure

Viral isolates from participants who discontinued from study treatment for reasons other than meeting PDVF criteria were also assessed for genotypic and phenotypic drug resistance. Of the 61 participants in the DOR group and the 71 participants in the DRV+r group who discontinued for reasons other than PDVF, 4 and 6 participants, respectively, had resistance testing successfully performed.

Descriptions of resistance data for each of these 10 participants, as well as detailed listings of resistance data, by participant, for both treatment groups, are found in the CSR [Ref. 5.3.5.1: P018MK1439: 11.1.4.2.2].

Among the 4 DOR-treated participants with results from resistance testing, virus from 1 participant, 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. Virus from a second participant, discontinued at Week 2 due to an AE of rash, had phenotypic resistance to DOR (based on IC50 increase of approximately 2.8-fold with respect to wild type virus) as defined by the central laboratory's assay, although no genotypic change in reverse transcriptase was identified. At baseline the participant's virus demonstrated a 2.2-fold increase in IC50 with respect to wild type virus. Over a 2-week period of treatment the participant had an approximately 1 $\log_{10}$ decline in HIV-1 RNA. Based on the viral response, lack of genotypic mutations to DOR, minimal change in IC50 from baseline, and insufficient data to inform a clinical cutoff for DOR phenotypic resistance, it is considered that this participant did not develop resistance to DOR.

Among participants treated with DRV+r who discontinued for reasons other than meeting PDVF criteria, no primary genotypic resistance mutation and no phenotypic resistance to DRV or to the NRTI components was identified.

2.1.2.7 Efficacy in Subgroups by Demographic and Prognostic Factors

When efficacy in P018 at Week 96 was assessed *across* treatment groups using the OF approach by various baseline demographic and prognostic factors, specifically age, gender, region, race, and ethnicity, screening and baseline HIV-1 RNA (≤ or >100,000 copies/mL), baseline $CD4^+$ T-cell count, chronic hepatitis B/C status, and viral subtype, comparable efficacy was seen in the DOR and DRV+r groups for the sub-populations defined by these factors [Ref. 5.3.5.1: P018MK1439: Table 11-6] [Ref. 5.3.5.1: P018MK1439: Figure 14.2-9], 14.2-10, 14.2-11, 14.2-12]. Results were also comparable between treatment groups when the FDA snapshot approach was used.

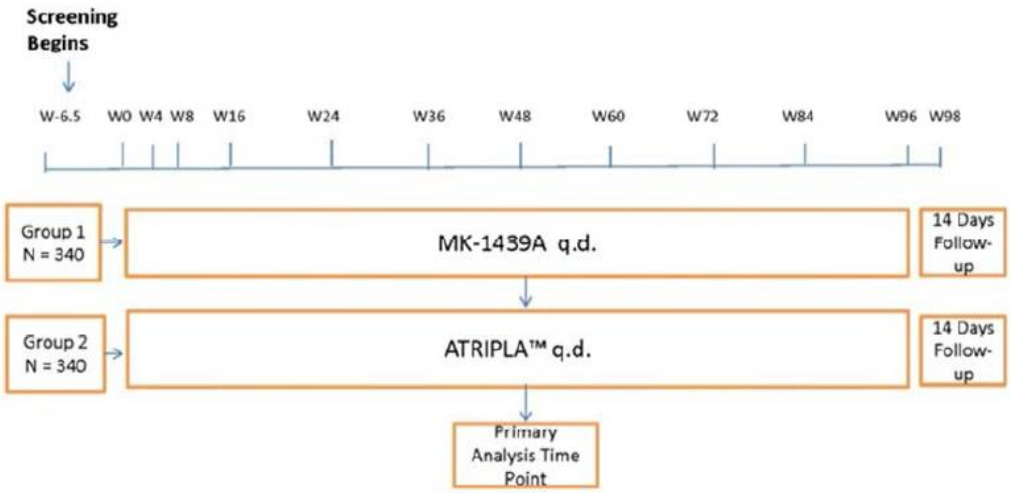
2.2 Protocol 021: Phase 3 Trial – Comparison With EFV/TDF/FTC

2.2.1 Protocol 021 Study Design

P021 is a Phase 3, multicenter, double-blind, randomized, active-controlled trial in HIV-1-infected, treatment-naïve men and women, 18 years of age or older, with an HIV-1 RNA level of ≥1000 copies/mL at screening. A total of 734 participants were stratified by screening HIV-1 RNA level (≤ or >100,000 copies/mL) and hepatitis B and/or C co-infection status (yes or no) and randomized within each of the 4 strata to DOR/3TC/TDF or EFV/FTC/TDF (supplied as ATRIPLA™). Participants received blinded treatment for 96 weeks in the base study, and, if eligible, could have chosen to enter an optional 96-week open-label study extension. All participants had completed the 96-week base study by the time of the database lock for the efficacy endpoint analysis at Week 96. The design of the base study is shown in [Figure 2.7.3-trtmtnve96wk: 5], and objectives relevant to the Week 96 time point are listed in [Table 2.7.3-trtmtnve96wk: 2].

Figure 2.7.3-trtmtnve96wk: 5

Protocol 021 Study Design



2.2.2 Protocol 021 Key Efficacy Results

2.2.2.1 Demographic and Prognostic Characteristics at Baseline

The DOR/3TC/TDF and EFV/FTC/TDF treatment groups were comparable with respect to demographic and prognostic characteristics at baseline [Ref. 5.3.5.1: P021MK1439A: 10.4.1]. The majority of participants were male (84.6%). Participants were predominantly white (47.5%), and had a median age of 31 years (range: 18 to 70 years).

Baseline $CD4^+$ T-cell counts were >200 cells/mm^3 (mean 425 cells/mm^3) for most participants in the DOR/3TC/TDF and EFV/FTC/TDF groups. Similarly, baseline mean plasma HIV-1 RNA levels were comparable for participants in the DOR/3TC/TDF (4.4 $\log_{10}$ copies/mL) and EFV/FTC/TDF (4.5 $\log_{10}$ copies/mL) groups; the proportions of participants with baseline HIV-1 RNA >100,000 copies/mL were 20.1% and 22.5%, respectively.

2.2.2.2 Efficacy Summary at Week 96: Virologic and Immunologic Responses

Antiretroviral Efficacy at Week 96

The antiretroviral efficacy of DOR/3TC/TDF at Week 96, as measured by the proportion of participants with HIV-1 RNA <50 copies/mL, was comparable to EFV/FTC/TDF [Table 2.7.3-trtmtnve96wk: 5], supporting the non-inferiority of DOR/3TC/TDF to EFV/FTC/TDF established at Week 48. Using the FDA snapshot approach, HIV-1 RNA <50 copies/mL was achieved by 77.5% and 73.6% of participants in the DOR/3TC/TDF and EFV/FTC/TDF groups, respectively, with a treatment difference of 3.8% (95% CI: -2.4, 10.0).

When using the threshold of HIV-1 RNA <40 copies/mL, DOR/3TC/TDF continued to demonstrate antiretroviral efficacy comparable to that of EFV/FTC/TDF at Week 96. Specifically, 76.1% and 72.8% of participants in the DOR/3TC/TDF and EFV/FTC/TDF groups, respectively, achieved HIV-1 RNA <40 copies/mL using the FDA snapshot approach; the treatment difference was 3.3% (95% CI: -3.1, 9.6).

Comparable antiretroviral efficacy results among participants 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 96.

Immunologic Efficacy at Week 96

The immunologic efficacy of DOR/3TC/TDF, as measured by the change from baseline to Week 96 in $CD4^+$ T-cell count (using the OF approach), was comparable to that of EFV/FTC/TDF; mean increases from baseline were 238 and 223 cells/mm^3 among participants in the DOR/3TC/TDF and EFV/FTC/TDF groups, respectively [Table 2.7.3-trtmtnve96wk: 5].

Table 2.7.3-trtmtnve96wk: 5

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/mm^3)	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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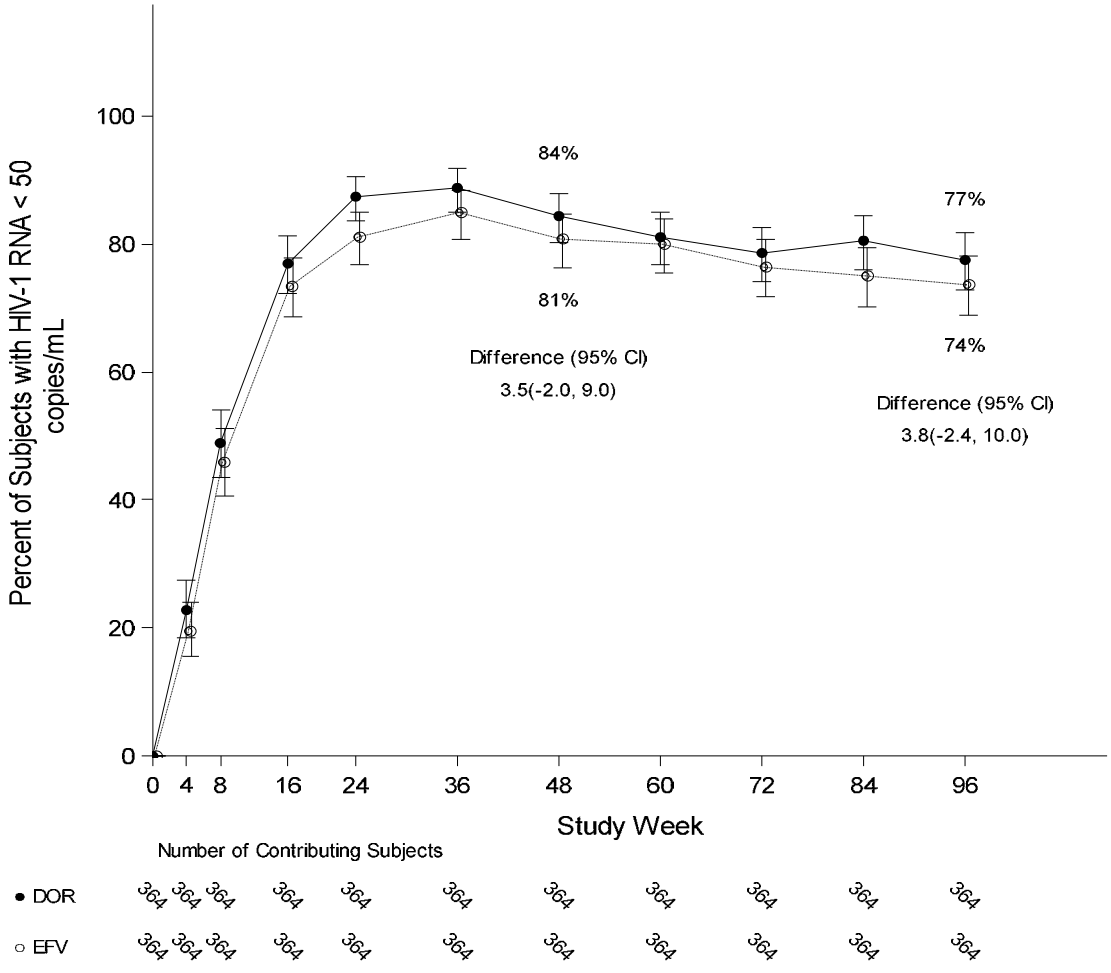
2.2.2.3 Antiretroviral Efficacy Through Week 96

The proportions of participants achieving HIV-1 RNA <50 copies/mL over time through Week 96, using the FDA snapshot approach, were comparable for the DOR/3TC/TDF and EFV/FTC/TDF groups [Figure 2.7.3-trtmtnve96wk: 6].

Comparable antiretroviral efficacy over time was seen in the 2 treatment groups when HIV-1 RNA thresholds of <40 copies/mL and <200 copies/mL were used [Ref. 5.3.5.1: P021MK1439A: 11.1.2.1.1].

Figure 2.7.3-trtmtnve96wk: 6

Proportion of Subjects With HIV-1 RNA < 50 copies/mL Over Time
FDA Snapshot Approach
Weeks 0-96; Base Study (Double Blind)



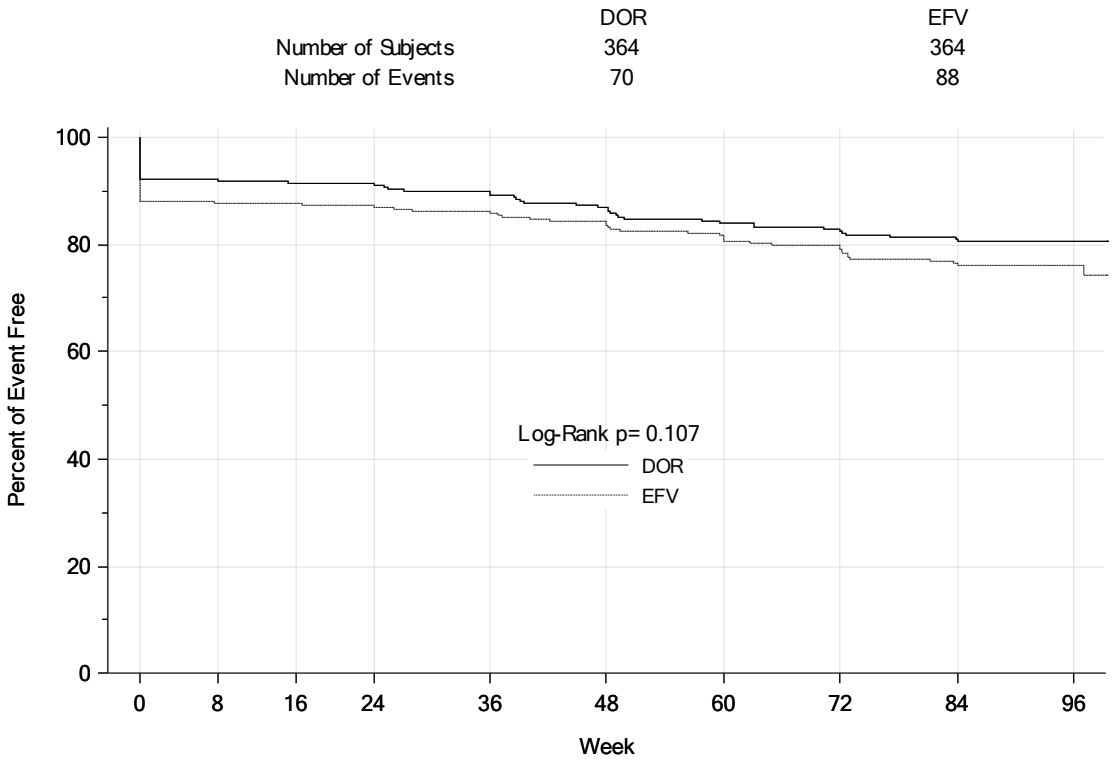
DOR=DOR/3TC/TDF QD; EFV=EFV/FTC/TDF QD
Source: [P021MK1439A: analysis-adsl; adrna]

2.2.2.4 Time to Loss of Virologic Response

TLOVR, using an HIV-1 RNA threshold of 50 copies/mL, was assessed by Kaplan-Meier product-limit estimates and by the log-rank test (non-multiplicity-adjusted p-value) and Cox models. The risk of loss-of-response events was comparable in the DOR/3TC/TDF and EFV/FTC/TDF treatment groups through Week 96 [Figure 2.7.3-trtmtnve96wk: 7].

Figure 2.7.3-trtmtnve96wk: 7

Kaplan-Meier plot for Time to Loss of Virologic Response
Base Study (Double Blind)



DOR: DOR/3TC/TDF QD; EFV: EFV/FTC/TDF QD
Source: [P021MK1439A: analysis-adtte]

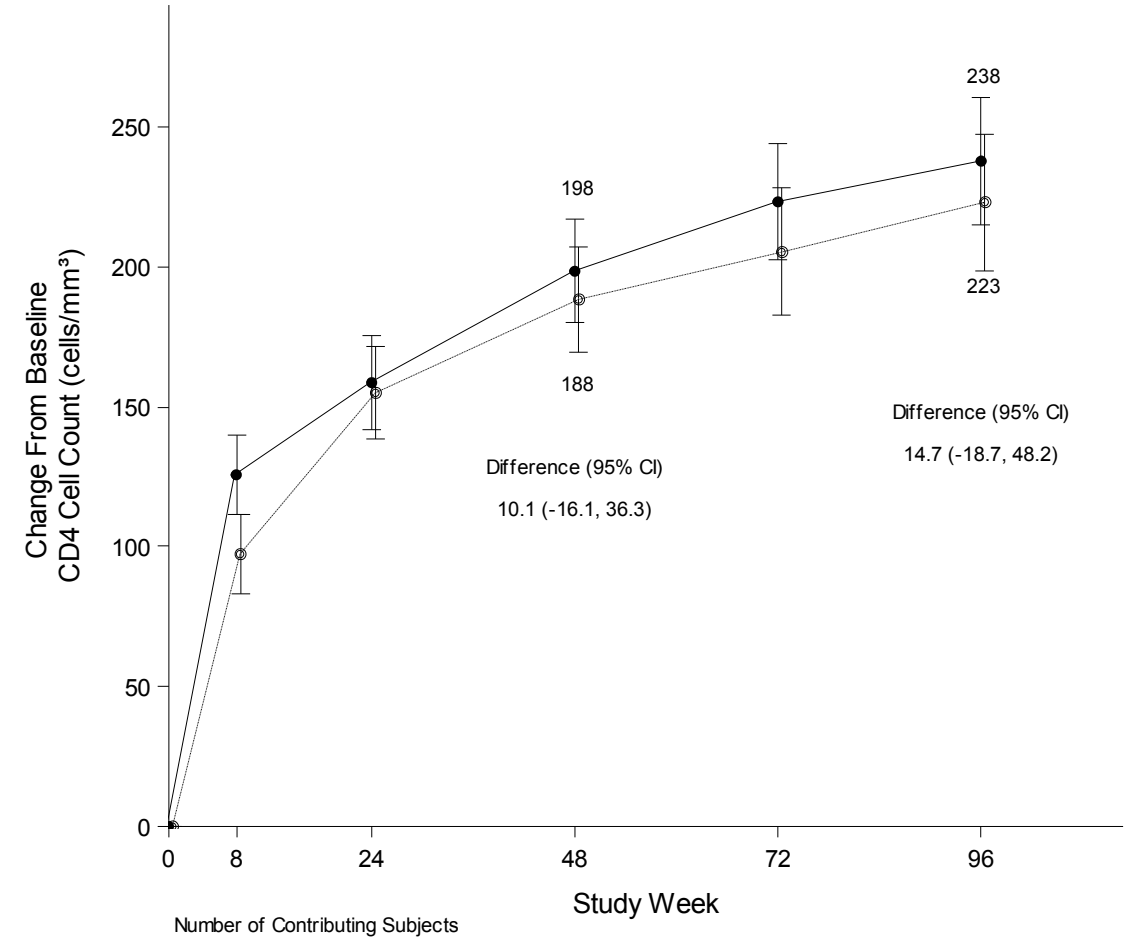
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2.2.2.5 Immunologic Response Through Week 96

Comparable increases from baseline in $CD4^+$ T-cell count were observed at each time point through Week 96 for the DOR/3TC/TDF and EFV/FTC/TDF groups, with mean increases from baseline at Week 96 of 238 and 223 cells/mm^3, respectively [Figure 2.7.3-trtmtnve96wk: 8].

Figure 2.7.3-trtmtnve96wk: 8

Change From Baseline in CD4 Cell Count (cells/mm³) Over Time
Observed Failure Approach
Weeks 0-96; Base Study (Double Blind)



DOR=DOR/3TC/TDF QD; EFV=EFV/FTC/TDF QD
Source: [P021MK1439A: analysis-adsl; adcd4]

2.2.2.6 Protocol-Defined Virologic Failure and Evaluation of Viral Drug Resistance

Numbers of participants with PDVF (with participants classified as rebounders or non-responders) are summarized below. The majority of participants in both the DOR/3TC/TDF group and EFV/FTC/TDF group who met PDVF criteria were rebounders. For participants who were required to discontinue study drug due to PDVF and for participants who discontinued for other reasons, details of genotypic and phenotypic assessments of viral drug resistance are summarized below. Further details are provided in the study report [Ref. 5.3.5.1: P021MK1439A: 11.1.4].

Participants With Protocol-Defined Virologic Failure

Through Week 96, rates of PDVF were low and comparable in the DOR/3TC/TDF (8.3%) and EFV/FTC/TDF (7.7%) treatment groups [Table 2.7.3-trtmtnve96wk: 6].

Among participants who met the rebound definition of PDVF, a majority in each treatment group had HIV-1 RNA ≤200 copies/mL at the viral failure confirmation visit [Table 2.7.3-trtmtnve96wk: 6].

Table 2.7.3-trtmtnve96wk: 6

Number of Subjects with Protocol Defined Virologic Failure
Weeks 0-96; Base Study (Double Blind)

	DOR/3TC/TDF QD N=(364) n (%)			EFV/FTC/TDF QD N=(364) n (%)		
	Confirmation HIV-1 RNA ≥50 and ≤200 copies/mL	Confirmation HIV-1 RNA >200 copies/mL	Total	Confirmation HIV-1 RNA ≥50 and ≤200 copies/mL	Confirmation HIV-1 RNA >200 copies/mL	Total
Virologic Failure (confirmed)† by Week 24						
Non-Responder	0 (0.0)	5 (1.4)	5 (1.4)	0 (0.0)	4 (1.1)	4 (1.1)
Rebounder	3 (0.8)	2 (0.5)	5 (1.4)	1 (0.3)	3 (0.8)	4 (1.1)
Virologic Failure (confirmed)† by Week 36						
Non-Responder	0 (0.0)	6 (1.6)	6 (1.6)	0 (0.0)	4 (1.1)	4 (1.1)
Rebounder	5 (1.4)	3 (0.8)	8 (2.2)	3 (0.8)	3 (0.8)	6 (1.6)
Virologic Failure (confirmed)† by Week 48						
Non-Responder	0 (0.0)	6 (1.6)	6 (1.6)	0 (0.0)	4 (1.1)	4 (1.1)
Rebounder	9 (2.5)	6 (1.6)	15 (4.1)	4 (1.1)	6 (1.6)	10 (2.7)
Virologic Failure (confirmed)† by Week 60						
Non-Responder	0 (0.0)	6 (1.6)	6 (1.6)	0 (0.0)	4 (1.1)	4 (1.1)
Rebounder	10 (2.7)	8 (2.2)	18 (4.9)	7 (1.9)	6 (1.6)	13 (3.6)
Virologic Failure (confirmed)† by Week 72						
Non-Responder	0 (0.0)	6 (1.6)	6 (1.6)	0 (0.0)	4 (1.1)	4 (1.1)
Rebounder	15 (4.1)	8 (2.2)	23 (6.3)	11 (3.0)	8 (2.2)	19 (5.2)
Virologic Failure (confirmed)† by Week 84						
Non-Responder	0 (0.0)	6 (1.6)	6 (1.6)	0 (0.0)	4 (1.1)	4 (1.1)
Rebounder	16 (4.4)	9 (2.5)	25 (6.9)	12 (3.3)	10 (2.7)	22 (6.0)
Virologic Failure (confirmed)† by Week 96						

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Number of Subjects with Protocol Defined Virologic Failure
Weeks 0-96; Base Study (Double Blind)

	DOR/3TC/TDF QD N=(364) n (%)			EFV/FTC/TDF QD N=(364) n (%)		
	Confirmation HIV-1 RNA ≥50 and ≤200 copies/mL	Confirmation HIV-1 RNA >200 copies/mL	Total	Confirmation HIV-1 RNA ≥50 and ≤200 copies/mL	Confirmation HIV-1 RNA >200 copies/mL	Total
Non-Responder	0 (0.0)	6 (1.6)	6 (1.6)	0 (0.0)	4 (1.1)	4 (1.1)
Rebounder	18 (4.9)	10 (2.7)	28 (7.7)	14 (3.8)	10 (2.7)	24 (6.6)

† Protocol defined virologic failure (PDVF) for this study is defined as one of the following: 1) Rebounder: Confirmed (two consecutive measures at least one week apart) HIV-1 RNA ≥ 50 copies/mL after initial response of HIV-1 RNA <50 copies/mL at any time during the study; Or 2) Non responder: Confirmed (two consecutive measures at least one week apart) HIV -1 RNA ≥ 200 copies/mL at Week 24 or Week 36; OR Confirmed (two consecutive measures at least one week apart) HIV-1 RNA ≥ 50 copies/mL at Week 48.

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; advf]

Viral Drug Resistance in Participants With Protocol-Defined Virologic Failure

Of the participants in the DOR/3TC/TDF group who met PDVF criteria, results from viral drug resistance testing (genotyping and/or phenotyping) were available for 22 participants. Of the participants in the EFV/FTC/TDF group who met PDVF criteria, results from viral drug resistance testing (genotyping and/or phenotyping) were available for 15 participants. Detailed listings by participant, for both treatment groups, are found in the CSR [Ref. 5.3.5.1: P021MK1439A: 16.2.6].

Through Week 96, among participants in the DOR/3TC/TDF group with PDVF, genotypic mutations associated with DOR resistance were identified in viral isolates from 7 participants, with phenotypic resistance to DOR identified in 6 of these participants. Of the 7 participants with genotypic mutations associated with DOR resistance, genotypic resistance with or without phenotypic resistance to FTC and 3TC was seen in 6 participants. Brief summaries of viral drug resistance in these participants are found in the study report [Ref. 5.3.5.1: P021MK1439A: 11.1.4.2.1.1]. No additional participants with viral resistance to DOR were identified between Week 48 and Week 96 in the DOR/3TC/TDF group.

Through Week 96, among participants in the EFV group with PDVF, genotypic mutations associated with EFV resistance were identified in viral isolates from 10 participants, with phenotypic resistance to EFV identified in 9 of these participants. In 5 of these participants, genotypic with or without phenotypic resistance to FTC was seen; 2 of these participants' viral isolates demonstrated genotypic resistance to tenofovir. Additional details are found in [Ref. 5.3.5.1: P021MK1439A: 11.1.4.2.1.2]. One new participant with viral resistance to EFV was identified between Week 48 and Week 96 in the EFV/FTC/TDF group.

Viral Drug Resistance in Participants Who Discontinued for Reasons Other Than Protocol-Defined Virologic Failure

Viral isolates from participants who discontinued from study treatment for reasons other than meeting PDVF criteria (and who had HIV-1 RNA >400 copies/mL at the discontinuation visit) were also assessed for genotypic and phenotypic drug resistance. Of the participants in the DOR/3TC/TDF group who discontinued without meeting criteria for PDVF, 13 participants had results from resistance testing available. Of these 13, 11 had successful genotype testing and 12 had successful phenotype testing. Of the participants in the EFV/FTC/TDF group who discontinued without meeting criteria for PDVF, 22 had results from resistance testing available. Of these 22, 18 had successful genotype testing and 17 had successful phenotype testing.

Through Week 96, virus from 1 of the 11 DOR/3TC/TDF samples tested was found to have primary genotypic resistance to DOR. None of the tested samples had phenotypic resistance to DOR or phenotypic resistance to NRTIs.

Through Week 96, virus from 4 of the 18 EFV/FTC/TDF samples tested was found to have EFV resistance associated mutations. Four of the 17 tested samples had EFV phenotypic resistance. Two samples had primary genotypic or phenotypic resistance to NRTIs.

Detailed listings by participant are found in the CSR [Ref. 5.3.5.1: P021MK1439A: 16.2.6].

2.2.2.7 Efficacy in Subgroups by Demographic and Prognostic Factors

Efficacy at Week 96 (proportions of participants with HIV-1 RNA <50 copies/mL), using the OF approach, was assessed by various baseline demographic and prognostic factors – age, gender, region, race/ethnicity, screening/baseline HIV-1 RNA (≤ or >100,000 copies/mL), baseline $CD4^+$ T-cell count, chronic hepatitis B/C status, and viral subtype). Comparable results (based on 95% CIs around the differences between treatment groups that include 0) were observed in the DOR/3TC/TDF and the EFV/FTC/TDF treatment groups across all of the subgroups [Ref. 5.3.5.1: P021MK1439A: Table 11-7] [Ref. 5.3.5.1: P021MK1439A: Figure 14.2-10, 14.2-11, 14.2-12, 14.2-13].

The proportions of participants who achieved each of the HIV-1 RNA thresholds (<50, <40, and <200 copies/mL) were generally comparable across treatment groups for baseline prognostic and demographic factors. These results are generally consistent with the results for the overall treatment group differences using the FDA snapshot approach [Ref. 5.3.5.1: P021MK1439A: Table 11-7].

3 COMPARISON AND ANALYSES OF RESULTS ACROSS STUDIES

This section provides integrated data and analyses from the pivotal Phase 3 trials, P018 and P021, in which a pooled DOR group is compared with the DRV+r group from P018 and with the EFV/FTC/TDF group from P021.

3.1 Rationale for Pooling Strategy for Efficacy Analyses

The 2 Phase 3 trials, P018 and P021, are similar in design and enrollment criteria, and have the same efficacy endpoints, definition of PDVF, and approach to handling participants with PDVF, thus justifying the pooling of their data.

Participants in P018 and P021 are referred to as the "pooled efficacy population". Participants who received DOR in P018 or DOR/3TC/TDF in P021 are referred to as the "DOR Regimen" group.

3.2 Trial Populations

3.2.1 Participant Disposition in the Pooled Efficacy Population

Comparable proportions of participants across treatment groups discontinued from the trial for any reason by Week 96 [Table 2.7.3-trtmtnve96wk: 7]. While overall proportions of participants who discontinued were generally balanced across treatment groups (21.1% to 28.6%), a higher proportion of participants discontinued due to an AE in the EFV/FTC/TDF group (7.1%) than in the DOR Regimen group (2.3%).

Table 2.7.3-trtmtnve96wk: 7

Disposition of Subjects
Efficacy Pool (P018 and P021 Combined)
Weeks 0-96, Base Study (Double Blind)

	DOR Regimen (P018, P021)		DRV+r (P018)		EFV/FTC/TDF (P021)	
	n	(%)	n	(%)	n	(%)
Total Randomized	753		384		366	
Not Treated	6	(0.8)	1	(0.3)	2	(0.5)
Treated	747	(99.2)	383	(99.7)	364	(99.5)
Discontinued Study	159	(21.1)	110	(28.6)	88	(24.0)
Adverse Event	17	(2.3)	14	(3.6)	26	(7.1)
Death	4	(0.5)	1	(0.3)	4	(1.1)
Lack Of Efficacy	52	(6.9)	32	(8.3)	23	(6.3)
Lost To Follow-Up	34	(4.5)	24	(6.3)	8	(2.2)
Non-Compliance With Study Drug	10	(1.3)	6	(1.6)	4	(1.1)
Physician Decision	4	(0.5)	4	(1.0)	2	(0.5)
Pregnancy	4	(0.5)	1	(0.3)	2	(0.5)
Protocol Deviation	5	(0.7)	6	(1.6)	2	(0.5)
Withdrawal By Subject	29	(3.9)	22	(5.7)	17	(4.6)
Completed Base Study	588	(78.1)	273	(71.1)	276	(75.4)
Entered Study Extension	551	(73.2)	233	(60.7)	269	(73.5)
Did not Enter Study Extension	37	(4.9)	40	(10.4)	7	(1.9)

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

Source: [ISE: analysis-adsl; dsplus]

3.2.2 Baseline Demographic and Prognostic Characteristics in the Pooled Efficacy Population

The pooled efficacy population reflects the enrollment of the pivotal trials, with a participant population representative of the global target population in regard to geographic, racial, ethnic, gender and age characteristics. Participants were enrolled in P018 and/or P021 in North America, South America, Europe and Russia, Asia, South Africa, and Australia/New Zealand, although with different levels of enrollment in each region. The overall participant population also reflects the target population with regard to virologic and other baseline factors such as HIV-1 subtype and baseline viral load and $CD4^+$ T-cell level.

Demographic and prognostic characteristics were comparable across the DOR Regimen group and both comparator groups with the exception of various racial and regional subgroups [Table 2.7.3-trtmtnve96wk: 8]. Because data from the DRV+r and EFV/FTC/TDF groups for this integrated analysis were each from a different single trial, the differences noted reflect differences in regional enrollment between the 2 trials.

Across treatment groups, most participants were male; the racial group with the largest proportion of participants in each treatment group was white. The median age was between 30 and 34 years (range: 18 to 70 years).

P018 and P021 each had 2 stratification factors for randomization; the common factor was screening HIV-1 RNA of ≤ or >100,000 copies/mL. Approximately 75% of participants in each treatment group were in the stratum of screening HIV-1 RNA ≤100,000 copies/mL. The additional stratification factor in P018 was the investigator-chosen NRTI regimen and, in P021, co-infection with HBV and/or HCV.

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Table 2.7.3-trtmtnve96wk: 8

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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3.3 Results From Pooled Efficacy Population

There were no hypotheses associated with the efficacy analyses for the pooled efficacy population. In both P018 and P021, the primary efficacy hypothesis evaluated the noninferiority of DOR to the active comparator at Week 48 with respect to antiretroviral efficacy, as measured by the proportion of participants with HIV-1 RNA <50 copies/mL. Results from P018 and P021 showed that DOR and DOR/3TC/TDF, respectively, met the non-inferiority criterion at Week 48 for the efficacy hypothesis for each trial [Ref. 5.4: 04WHL3, 050SC7], which were further supported by the Week 96 results within each trial.

3.3.1 Efficacy Summary at Week 96: Virologic and Immunologic Responses

Antiretroviral efficacy was comparable across the DOR Regimen group and the comparator groups with respect to the secondary endpoint (proportion of participants with HIV-1 RNA <50 copies/mL at Week 96 using the FDA snapshot approach): 75.2%, 66.0% and 73.6% in the DOR Regimen, DRV+r and EFV/FTC/TDF groups, respectively [Table 2.7.3-trtmtnve96wk: 9]. Antiretroviral efficacy was also comparable across the 3 treatment groups with respect to related secondary and exploratory endpoints (proportions of participants with HIV-1 RNA <40 and <200 copies/mL at Week 96). Efficacy results were consistent across the different missing-data approaches used (FDA snapshot approach and OF approach).

Immunologic efficacy at Week 96 was also comparable across the DOR Regimen group and the comparator groups; mean change 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 2.7.3-trtmtnve96wk: 9].

Virologic outcome at Week 96 is based on the FDA snapshot algorithm and uses an HIV-1 RNA threshold of 50 copies/mL. Among participants who did not achieve HIV-1 RNA <50 copies/mL, comparable proportions of participants across the treatment groups either had HIV-1 RNA data at Week 96 but did not reach the virologic threshold or had no data at Week 96 (24.6%, 33.4%, and 26.4% in the DOR Regimen, DRV+r, and EFV/FTC/TDF groups, respectively). Among those with no data at Week 96, a higher proportion of participants who discontinued due to an AE was observed in the EFV group compared with the DOR and DRV+r groups [Table 2.7.3-trtmtnve96wk: 10].

Table 2.7.3-trtmtnve96wk: 9

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]

Table 2.7.3-trtmtnve96wk: 10

Virologic Outcome at Week 96
Efficacy Pool (P018 and P021 Combined)
FDA Snapshot Approach

Outcome	DOR Regimen (P018, P021) (N=747) n	(%)	DRV+r (P018) (N=383) n	(%)	EFV/FTC/TDF (P021) (N=364) n	(%)
HIV-1 RNA <50 copies/mL	559	(74.8)	248	(64.8)	268	(73.6)
HIV-1 RNA ≥ 50 copies/mL[†]	120	(16.1)	76	(19.8)	44	(12.1)
No Virologic Data at Week 96 Window	64	(8.6)	52	(13.6)	52	(14.3)
Reasons						
Discontinued study due to AE or Death[‡]	21	(2.8)	14	(3.7)	30	(8.2)
Discontinued study for Other Reasons[§]	39	(5.2)	33	(8.6)	20	(5.5)
On study but missing data in window	4	(0.5)	5	(1.3)	2	(0.5)

[†] 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 96, subjects who discontinued study drug or study before Week 96 for lack or loss of efficacy and subjects with HIV-1 RNA equal to or above 50 copies/mL in the Week 96 window (relative day 631, ie, last day of double-blind treatment period).

[‡] Includes subjects who discontinued because of adverse event (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 consists of: lost to follow-up, non-compliance with study drug, physician decision, pregnancy, protocol deviation, screen failure, withdrawal by subject.

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 (Percent) of subjects in each category.

Source: [ISE: analysis-adsl; adrna]

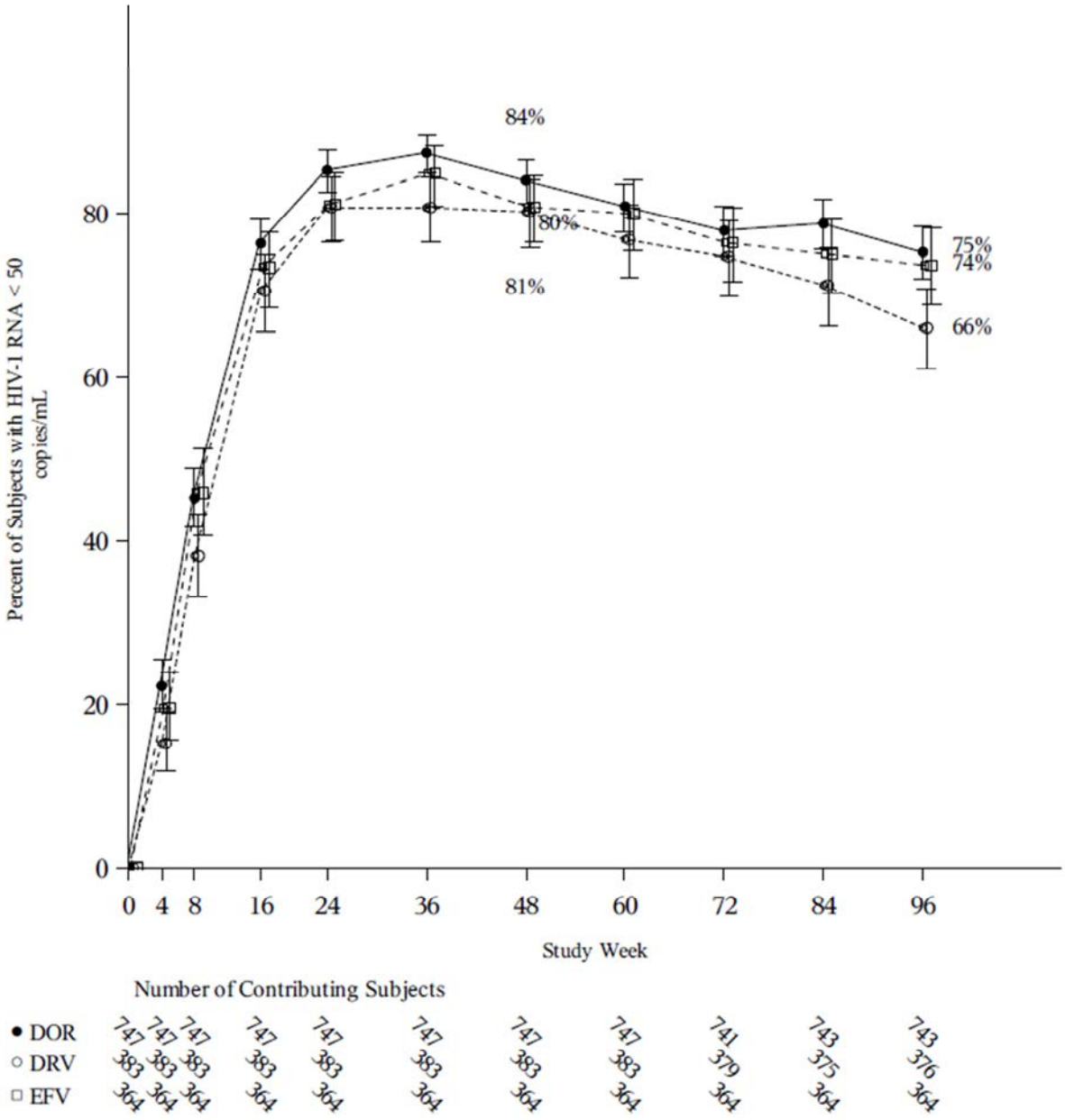
3.3.2 Antiretroviral Efficacy Over Time Through Week 96

Using the FDA snapshot approach and the threshold of HIV-1 RNA <50 copies/mL, responses were comparable across groups at each time point [Figure 2.7.3-trtmtnve96wk: 9].

A consistent pattern of antiretroviral efficacy over time was seen across all groups when HIV-1 RNA thresholds of <40 and <200 copies/mL were used. Analyses using the OF approach to missing data with each of these thresholds also showed a consistent pattern of antiretroviral efficacy over time [Sec. 5.3.5.3.2.3.3.2-trtmtnve96wk].

Figure 2.7.3-trtmtnve96wk: 9

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)



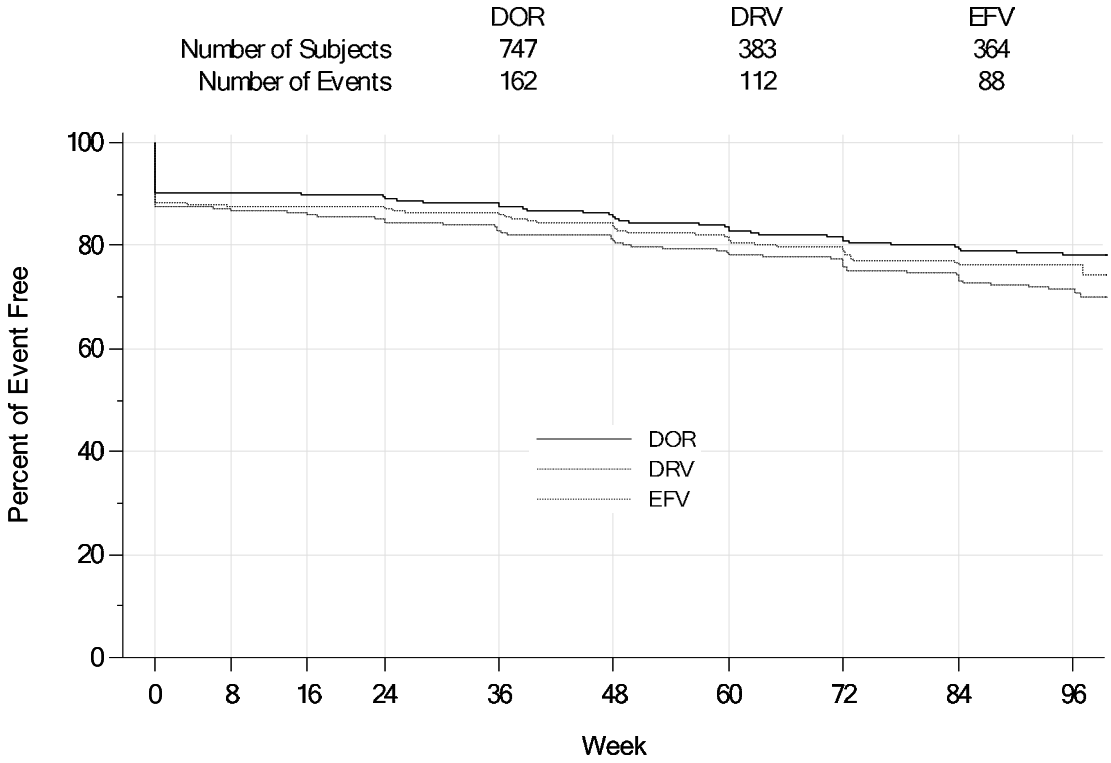
DOR=DOR Regimen (P018, P021); DRV=DRV+r (P018); EFV=EFV/FTC/TDF (P021)
Source: [ISE: analysis-adsl; adrna]

3.3.3 Time to Loss of Virologic Response

As seen in the Kaplan-Meier plot of TLOVR, the risk of loss-of-response was comparable across the DOR Regimen, DRV+r, and EFV/FTC/TDF treatment groups, with no clinically meaningful difference seen across the groups [Figure 2.7.3-trtmtnve96wk: 10].

Figure 2.7.3-trtmtnve96wk: 10

Kaplan-Meier Plot for Time to Loss of Virologic Response
Efficacy Pool (P018 and P021 Combined)



Number of subjects at risk

DOR	747	675	672	669	659	640	624	609	591	454
DRV	383	334	330	326	317	312	301	293	280	201
EFV	364	319	319	318	314	306	297	290	278	207

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

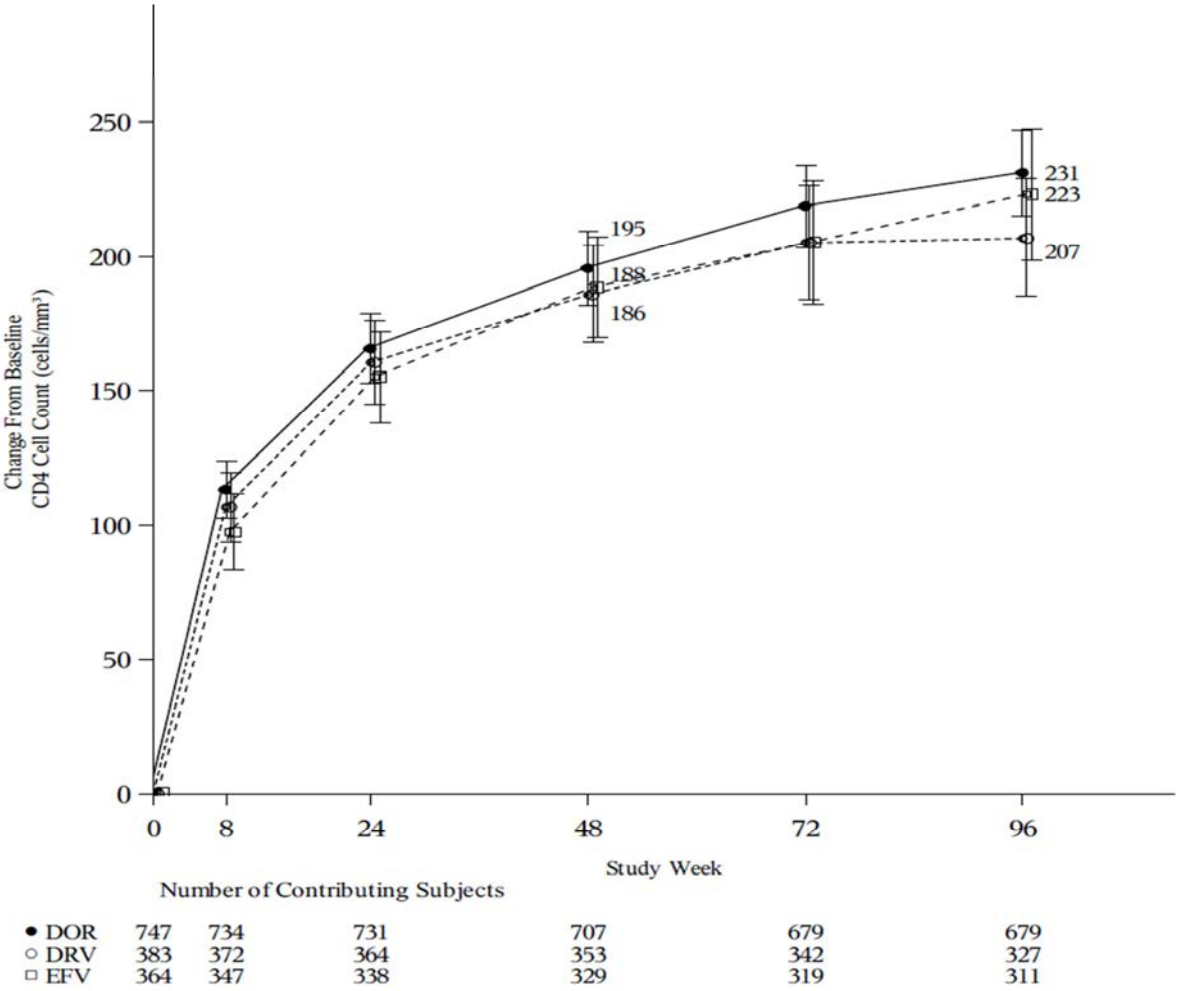
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3.3.4 Immunologic Response Through Week 96

Immunologic efficacy, as measured by change from baseline in $CD4^+$ T-cell count at Weeks 8, 24, 48, 72, and 96 was comparable across the DOR Regimen group, the DRV+r group and the EFV/FTC/TDF group. Specifically, a clinically meaningful change from baseline was seen by Week 8 in each group (113, 107, and 97 cells/mm^3, respectively), with further increases through Week 96 (231, 207, and 223 cells/mm^3, respectively, at Week 96) [Figure 2.7.3-trtmtnve96wk: 11].

Figure 2.7.3-trtmtnve96wk: 11

Change From Baseline in CD4 Cell Count (cells/mm³) Over Time
Efficacy Pool (P018 and P021 Combined)
Observed Failure 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; adcd4]

3.3.5 Protocol-Defined Virologic Failure and Evaluation of Viral Drug Resistance

Participants With Protocol-Defined Virologic Failure

Numbers of participants with PDVF are summarized below for the pooled efficacy population. For this integrated analysis, participants with PDVF were defined as either rebounders or non-responders, with the same definitions as in the individual P018 and P021 trials [Sec. 2.7.3-trtmtnve96wk: 1.4.1.3].

Proportions of participants who met the criterion for PDVF by Week 96 were low and comparable across the DOR Regimen group, the DRV+r group and the EFV/FTC/TDF group [Table 2.7.3-trtmtnve96wk: 11]. A majority of participants in all 3 groups were rebounders who had initially responded to treatment. It is notable that between two-thirds of participants with PDVF in the DOR Regimen and DRV+r groups had low-level viremia, ie, HIV-1 RNA between 50 and 200 copies/mL, at the time of virologic failure confirmation, as did approximately half of participants with PDVF in the EFV/FTC/TDF group [Table 2.7.3-trtmtnve96wk: 11]. This observation is consistent with the possibility that the viremia meeting PDVF criteria was due to non-compliance with study medication.

Further characterization of levels of HIV-1 RNA among participants who met PDVF criteria is provided in the individual study reports [Ref. 5.3.5.1: P018MK1439: 11.1.4.1] [Ref. 5.3.5.1: P021MK1439A: 11.1.4.1].

Table 2.7.3-trtmtnve96wk: 11

Number of Subjects with Protocol Defined Virologic Failure
Efficacy Pool (P018 and P021 Combined)
Weeks 0-96, Base Study (Double Blind)

	DOR Regimen (P018, P021) N=(747) n (%)			DRV+r (P018) N=(383) n (%)			EFV/FTC/TDF (P021) N=(364) n (%)		
	Confirmation HIV-1 RNA ≥50 and ≤200 copies/mL	Confirmation HIV-1 RNA >200 copies/mL	Total	Confirmation HIV-1 RNA ≥50 and ≤200 copies/mL	Confirmation HIV-1 RNA >200 copies/mL	Total	Confirmation HIV-1 RNA ≥50 and ≤200 copies/mL	Confirmation HIV-1 RNA >200 copies/mL	Total
Virologic Failure (confirmed)† by Week 24									
Non-Responder	0 (0.0)	7 (0.9)	7 (0.9)	0 (0.0)	2 (0.5)	2 (0.5)	0 (0.0)	4 (1.1)	4 (1.1)
Rebounder	10 (1.3)	5 (0.7)	15 (2.0)	4 (1.0)	2 (0.5)	6 (1.6)	1 (0.3)	3 (0.8)	4 (1.1)
Virologic Failure (confirmed)† by Week 36									
Non-Responder	0 (0.0)	8 (1.1)	8 (1.1)	0 (0.0)	3 (0.8)	3 (0.8)	0 (0.0)	4 (1.1)	4 (1.1)
Rebounder	14 (1.9)	8 (1.1)	22 (2.9)	10 (2.6)	4 (1.0)	14 (3.7)	3 (0.8)	3 (0.8)	6 (1.6)
Virologic Failure (confirmed)† by Week 48									
Non-Responder	0 (0.0)	9 (1.2)	9 (1.2)	1 (0.3)	4 (1.0)	5 (1.3)	0 (0.0)	4 (1.1)	4 (1.1)
Rebounder	21 (2.8)	11 (1.5)	32 (4.3)	13 (3.4)	6 (1.6)	19 (5.0)	4 (1.1)	6 (1.6)	10 (2.7)
Virologic Failure (confirmed)† by Week 60									
Non-Responder	0 (0.0)	9 (1.2)	9 (1.2)	1 (0.3)	4 (1.0)	5 (1.3)	0 (0.0)	4 (1.1)	4 (1.1)
Rebounder	26 (3.5)	15 (2.0)	41 (5.5)	17 (4.4)	7 (1.8)	24 (6.3)	7 (1.9)	6 (1.6)	13 (3.6)
Virologic Failure (confirmed)† by Week 72									
Non-Responder	0 (0.0)	9 (1.2)	9 (1.2)	1 (0.3)	4 (1.0)	5 (1.3)	0 (0.0)	4 (1.1)	4 (1.1)
Rebounder	33 (4.4)	16 (2.1)	49 (6.6)	21 (5.5)	9 (2.3)	30 (7.8)	11 (3.0)	8 (2.2)	19 (5.2)
Virologic Failure (confirmed)† by Week 84									
Non-Responder	0 (0.0)	9 (1.2)	9 (1.2)	1 (0.3)	4 (1.0)	5 (1.3)	0 (0.0)	4 (1.1)	4 (1.1)
Rebounder	34 (4.6)	19 (2.5)	53 (7.1)	23 (6.0)	11 (2.9)	34 (8.9)	12 (3.3)	10 (2.7)	22 (6.0)
Virologic Failure (confirmed)† by Week 96									
Non-Responder	0 (0.0)	9 (1.2)	9 (1.2)	1 (0.3)	4 (1.0)	5 (1.3)	0 (0.0)	4 (1.1)	4 (1.1)
Rebounder	37 (5.0)	22 (2.9)	59 (7.9)	25 (6.5)	13 (3.4)	38 (9.9)	14 (3.8)	10 (2.7)	24 (6.6)

† Protocol defined virologic failure (PDVF) for this study is defined as one of the following: 1) Rebounder: Confirmed (two consecutive measures at least one week apart) HIV-1 RNA ≥ 50 copies/mL after initial response of HIV-1 RNA <50 copies/mL at any time during the study; Or 2) Non responder: Confirmed (two consecutive measures at least one week apart) HIV -1 RNA ≥ 200 copies/mL at Week 24 or Week 36; OR Confirmed (two consecutive measures at least one week apart) HIV-1 RNA ≥ 50 copies/mL at Week 48.

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; advf]

Development of Viral Drug Resistance

Viral drug resistance was assessed for participants in P018 and P021 who met PDVF criteria or who discontinued for a reason other than PDVF. Among participants in P018 and P021 treated with DOR or DOR/3TC/TDF, 47 participants had genotype and/or phenotypic testing results available.

Viral resistance data from HIV-1 isolates collected during the treatment period are described within the individual trial summaries above [Sec. 2.7.3-trtmtnve96wk: 2]. A listing of post-baseline viral resistance data, for each participant who developed genotypic resistance to any study drug in his/her treatment regimen is provided below [Table 2.7.3-trtmtnve96wk: 12], [Table 2.7.3-trtmtnve96wk: 13]. Listings by participant of resistance-related data from both baseline (screening) and post-baseline time points, including polymorphisms not considered related to viral resistance, are provided in each of the study reports for all participants with genotypic and/or phenotypic resistance to DOR or to EFV [Ref. 5.3.5.1: P018MK1439: 16.2.6] [Ref. 5.3.5.1: P021MK1439A: 16.2.6].

Among 747 participants in P018 and P021 treated with DOR or DOR/3TC/TDF, a low frequency of RT mutations known to be associated with DOR resistance was observed. Through 96 weeks of therapy, HIV-1 isolates from 10 (1.3%) participants had at least 1 DOR resistance mutation, with phenotypic resistance to DOR observed in 8 (1.1%) of these [Figure 2.7.3-trtmtnve96wk: 12]. Eight of the 10 participants who had a DOR resistance mutation also showed NRTI genotypic or phenotypic resistance.

The RT amino acid position that was most frequently observed to have a resistance-associated substitution among DOR-treated participants was V106 (with a majority having the V106I substitution). Substitutions at the V106 codon were often seen in combination with F227C.

Figure 2.7.3-trtmtnve96wk: 12

Resistance Among Doravirine-Treated Participants in P018 and P021

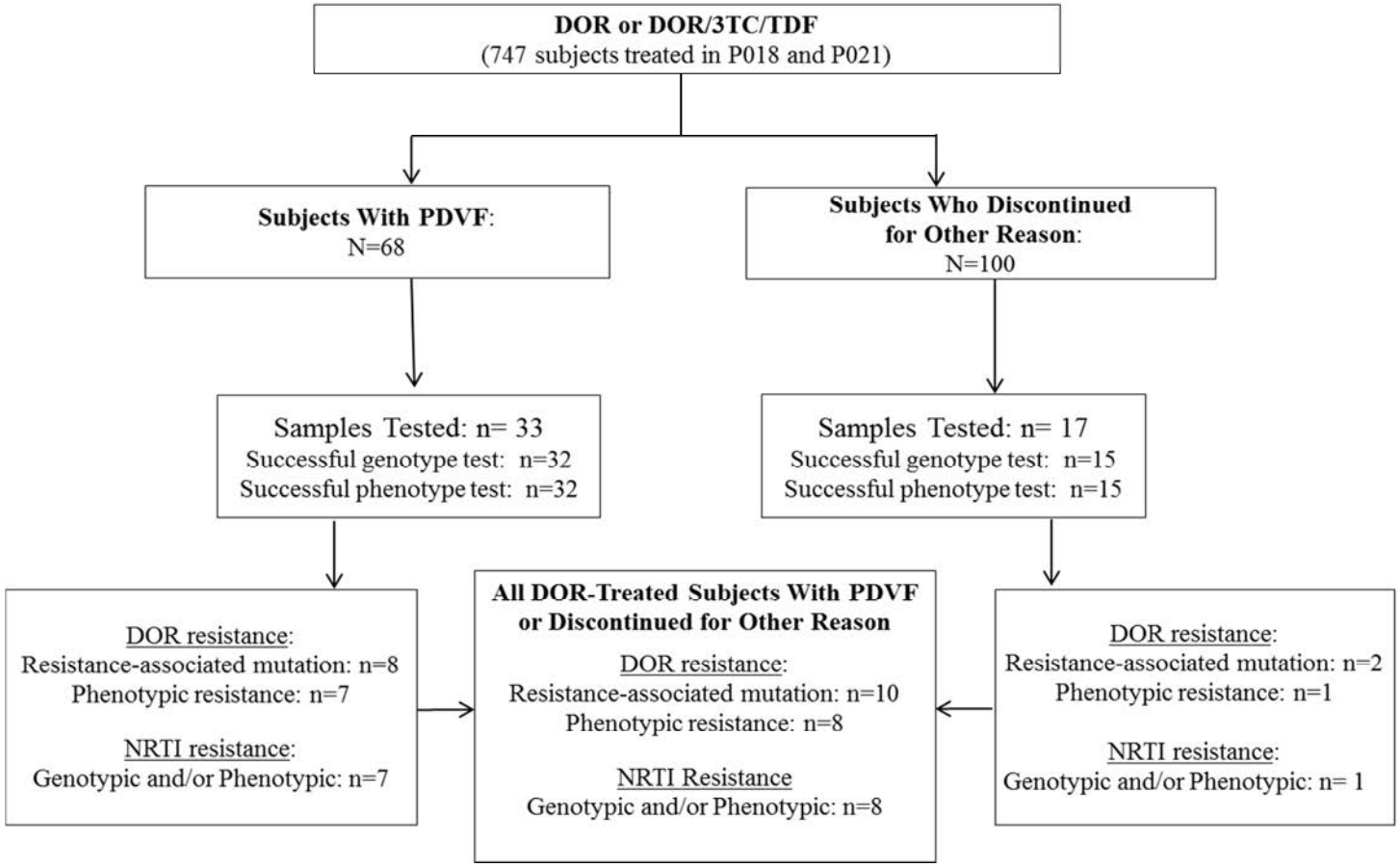


Table 2.7.3-trtmtnve96wk: 12

Week 96 Post-Baseline Resistance Data
Protocol 018

Subject HIV-1 Subtype	PDVF Type or D/C (Reason): Week of PDVF or D/C Visit	Day Sample Collected Viral Load[a]	**DOR Susceptibility** [Subjects Treated w/DOR] Genotypic Resistance [RT Mutation]	 Phenotypic Resistance IC_{50} Fold Diff[b]	**Comparator Susceptibility** [Subjects Treated w/EFV or DRV+r] Genotypic Resistance[d]	 Phenotypic Resistance IC_{50} Fold Diff[b]	**NRTI Susceptibility** [c] Genotypic Resistance [RT Mutation]	 Phenotypic Resistance IC_{50} Fold Diff[b]
Subjects Treated With DOR P018[e]								
A Subtype B	Rebounder PDVF: Wk 60	D.539 1,591 c/mL	V106A, P225H	R(>95.05)			FTC:V118I, M184I TDF:None	R(35.00) S(0.51)
B Subtype B	D/C(Non-Compliance With Study Drug): Wk 24	D.169 55,708 c/mL	V106I, H221Y, F227C	R(>96.61)			FTC:M184V TDF:None	R(>57.89) S(0.42)
Subjects Treated With Darunavir + ritonavir (DRV+r): Trial P018								
C Subtype A	Rebounder PDVF: Wk 48	D.421 431 c/mL			None	Failed(Failed)	3TC:A62V ABC:None	Failed(Failed) Failed(Failed)
D Subtype A1	Rebounder PDVF: Wk 84	D.631 427 c/mL			Failed	S(0.45)	FTC:Failed TDF:Failed	R(>78.83) S(0.57)

Abbreviations: D/C = discontinuation; PDVF = protocol-defined viral failure; PR = HIV-1 protease gene; PS = partially susceptible; RT = HIV-1 reverse transcriptase gene;

a: Viral load is measured as HIV-1 RNA copies/mL.

b: If the fold difference in IC50 with respect to wild-type virus for a given study drug was less than the threshold used to define phenotypic resistance, the virus was considered susceptible to that drug ('S').

c: Data on NRTI susceptibility are provided for only the NRTIs in each subject's treatment regimen.

d: PR mutations for DRV+r; RT mutations for EFV.

e: One DOR-treated subject described in the P018 study report is excluded from this table because the subject's HIV-1 isolate is not considered to have developed resistance to DOR for the purposes of this pooled analysis. The subject with observed phenotypic resistance to DOR (2.8-fold change at Day 29 relative to wild-type virus) is not considered to have developed resistance to DOR based on the observed virologic response, lack of genotypic mutations associated with DOR resistance , minimal change in IC50 from baseline (baseline IC50 FC was 2.2) and insufficient clinical data to define a clinical cutoff for DOR phenotypic resistance [Ref. 5.3.5.1: P018MK1439: 11.1.4.2.2].

Note: Subjects in P018 and P021 were required to be discontinued from the trial if they met PDVF criteria.

Table 2.7.3-trtmtnve96wk: 13

Week 96 Post-Baseline Resistance Data
Protocol 021

Subject HIV-1 Subtype	PDVF Type or D/C (Reason): Week of PDVF or D/C Visit	Day Sample Collected Viral Load[a]	**DOR Susceptibility** [Subjects Treated w/DOR] Genotypic Resistance [RT Mutation]	 Phenotypic Resistance IC_{50} Fold Diff[b]	**Comparator Susceptibility** [Subjects Treated w/EFV or DRV+r] Genotypic Resistance[d]	 Phenotypic Resistance IC_{50} Fold Diff[b]	**NRTI Susceptibility** [c] Genotypic Resistance [RT Mutation]	 Phenotypic Resistance IC_{50} Fold Diff[b]
Subjects Treated With DOR or DOR/3TC/TDF: Trials P021[e]								
A Subtype AE	Rebounder PDVF: Wk 48	D.330 431 c/mL	Y188L	R(>104.95)			3TC:M184V TDF:None	R(>98.65) S(0.72)
A Subtype AE	Rebounder PDVF: Wk 48	D.366 1,256 c/mL	Y188L	R(>181.58)			3TC:M41L, M184V TDF:M41L	R(>102.62) S(0.78)
B Subtype C	Non-Responder PDVF: Wk 36	D.338 7,498 c/mL	Y318Y/F	S(0.35)			3TC:A62V TDF:A62V	S(0.75) S(0.78)
C Subtype B	Non-Responder PDVF: Wk 24	D.172 4,669 c/mL	V106I, F227C	R(18.00)			3TC:None TDF:None	S(2.69) S(0.33)
C Subtype B	Non-Responder PDVF: Wk 24	D.195 12,691 c/mL	V106I, F227C	R(>105.49)			3TC:None TDF:None	S(3.07) S(0.32)
C Subtype B	Non-Responder PDVF: Wk 24	D.243 13,380 c/mL	V106I, H221H/Y, F227C	R(>102.28)			3TC:M184M/V TDF:None	S(3.43) S(0.45)
D Subtype F1	D/C(Physician Decision): Wk 4	D.8 472 c/mL	V106I	S(0.84)			3TC:None TDF:None	S(0.85) S(0.76)
E Subtype B	Non-Responder PDVF: Wk 24	D.120 12,173 c/mL	A98A/G, V106V/I, H221H/Y, F227C	R(>102.28)			3TC:M184V TDF:None	R(>125.28) S(0.56)
E Subtype B	Non-Responder PDVF: Wk 24	D.169 33,250 c/mL	A98A/G, H221H/Y, F227C	R(>88.43)			3TC:M184V TDF:None	R(>113.04) S(0.57)

Week 96 Post-Baseline Resistance Data
Protocol 021

Subject HIV-1 Subtype	PDVF Type or D/C (Reason): Week of PDVF or D/C Visit	Day Sample Collected Viral Load[a]	**DOR Susceptibility** [Subjects Treated w/DOR]		**Comparator Susceptibility** [Subjects Treated w/EFV or DRV+r]		**NRTI Susceptibility [c]**	
			Genotypic Resistance [RT Mutation]	Phenotypic Resistance IC_{50} Fold Diff[b]	Genotypic Resistance[d]	Phenotypic Resistance IC_{50} Fold Diff[b]	Genotypic Resistance [RT Mutation]	Phenotypic Resistance IC_{50} Fold Diff[b]
E Subtype B	Non-Responder PDVF: Wk 24	D.182 34,944 c/mL	A98G, V106V/I, H221H/Y, F227C	R(>109.90)			3TC:M184V TDF:None	R(>116.24) S(0.58)
F Subtype B	Non-Responder PDVF: Wk 24	D.112 12,003 c/mL	V106V/I, F227C	R(>102.28)			3TC:M184V TDF:None	R(>125.28) S(0.50)
F Subtype B	Non-Responder PDVF: Wk 24	D.174 7,527 c/mL	F227C	R(>176.19)			3TC:M184V TDF:None	R(>103.66) S(0.38)
F Subtype B	Non-Responder PDVF: Wk 24	D.251 6,254 c/mL	A98A/G, F227C	R(>93.31)			3TC:M184V TDF:None	R(>74.87) S(0.47)
F Subtype B	Non-Responder PDVF: Wk 24	D.335 14,791 c/mL	A98A/G, F227F/C	R(>97.08)			3TC:V75V/I, M184V TDF:None	R(>107.12) S(0.58)
G Subtype B	Non-Responder PDVF: Wk 24	D.114 88,103 c/mL	A98A/G, V106A, P225H	R(>102.28)			3TC:K65R TDF:K65R	R(4.93) PS(1.65)
G Subtype B	Non-Responder PDVF: Wk 24	D.176 80,038 c/mL	A98A/G, V106V/A, P225P/H	R(32.00)			3TC:None TDF:None	S(1.23) S(1.04)
G Subtype B	Non-Responder PDVF: Wk 24	D.212 106,092 c/mL	V106A, P225H, Y318Y/F	R(>210.82)			3TC:K65R TDF:K65R	R(12.00) PS(1.59)
H Subtype B	D/C(Withdrawal By Subject): Wk 24	D.169 246,237 c/mL	None	S(0.79)			3TC:None TDF:None	S(1.11) S(0.96)
I Subtype C	Non-Responder PDVF: Wk 24	D.114 781 c/mL	None	S(0.44)			3TC:None TDF:None	S(0.94) S(0.81)

Week 96 Post-Baseline Resistance Data
Protocol 021

Subject HIV-1 Subtype	PDVF Type or D/C (Reason): Week of PDVF or D/C Visit	Day Sample Collected Viral Load[a]	**DOR Susceptibility** [Subjects Treated w/DOR] Genotypic Resistance [RT Mutation]	 Phenotypic Resistance IC_{50} Fold Diff[b]	**Comparator Susceptibility** [Subjects Treated w/EFV or DRV+r] Genotypic Resistance[d]	 Phenotypic Resistance IC_{50} Fold Diff[b]	**NRTI Susceptibility** [c] Genotypic Resistance [RT Mutation]	 Phenotypic Resistance IC_{50} Fold Diff[b]
I Subtype C	Non-Responder PDVF: Wk 24	D.170 71,727 c/mL	V106M, V108V/I, F227F/C	R(>103.31)			3TC:None TDF:None	S(2.05) S(0.56)
I Subtype C	Non-Responder PDVF: Wk 24	D.196 32,799 c/mL	V106M/T, F227C/R	R(>98.16)			3TC:K65K/R, M184V TDF:K65K/R	R(>96.85) S(0.42)
Subjects Treated With Efavirenz (EFV): Trials P007, P021								
J Subtype B	D/C(Lost To Follow-Up): Wk 16	D.173 1,610 c/mL			K103N	R(32.00)	FTC:None TDF:None	S(0.98) S(0.70)
K Subtype B	D/C(Lack Of Efficacy): Wk 8	D.118 9,264 c/mL			K103N	R(20.00)	FTC:None TDF:None	S(0.95) S(0.87)
L Subtype B	D/C(Withdrawal By Subject): Wk 60	D.421 259,425 c/mL			K103N	R(9.57)	FTC:None TDF:None	S(1.10) S(0.77)
L Subtype B	D/C(Withdrawal By Subject): Wk 60	D.449 17,338 c/mL			None	R(9.51)	FTC:None TDF:None	R(>63.14) S(0.35)
M Subtype B	Rebounder PDVF: Wk 48	D.336 407 c/mL			K103N	R(6.44)	FTC:None TDF:None	S(1.05) S(0.82)
N Subtype B	Rebounder PDVF: Wk 60	D.585 4,144 c/mL			K103N, V179V/D, N348I	R(7.33)	FTC:None TDF:None	S(1.41) S(0.62)
O Subtype B	Rebounder PDVF: Wk 48	D.346 31,823 c/mL			K103N, E138E/G	R(11.00)	FTC:None TDF:None	S(1.06) S(0.84)

Week 96 Post-Baseline Resistance Data
Protocol 021

Subject HIV-1 Subtype	PDVF Type or D/C (Reason): Week of PDVF or D/C Visit	Day Sample Collected Viral Load[a]	**DOR Susceptibility** [Subjects Treated w/DOR]		**Comparator Susceptibility** [Subjects Treated w/EFV or DRV+r]		**NRTI Susceptibility**[c]	
			Genotypic Resistance [RT Mutation]	Phenotypic Resistance IC_{50} Fold Diff[b]	Genotypic Resistance[d]	Phenotypic Resistance IC_{50} Fold Diff[b]	Genotypic Resistance [RT Mutation]	Phenotypic Resistance IC_{50} Fold Diff[b]
O Subtype B	Rebounder PDVF: Wk 48	D.374 4,909 c/mL			K103N, E138E/G	R(11.00)	FTC:None TDF:None	S(1.00) S(0.87)
P Subtype Complex	Rebounder PDVF: Wk 24	D.240 3,459 c/mL			K103N	R(5.34)	FTC:None TDF:None	S(0.95) S(0.95)
Q Subtype C	Rebounder PDVF: Wk 16	D.186 16,960 c/mL			K103N	R(11.00)	FTC:None TDF:None	S(0.71) S(0.84)
R Subtype B	Rebounder PDVF: Wk 48	D.339 4,037 c/mL			G190E	Failed(Failed)	FTC:V118I, M184V TDF:None	Failed(Failed) Failed(Failed)
R Subtype B	Rebounder PDVF: Wk 48	D.365 9,566 c/mL			G190E	Failed(Failed)	FTC:V118I, M184V TDF:None	Failed(Failed) Failed(Failed)
S Subtype B	Non-Responder PDVF: Wk 24	D.167 841 c/mL			K103N	R(5.94)	FTC:M184V TDF:None	R(>71.75) S(0.51)
S Subtype B	Non-Responder PDVF: Wk 24	D.188 4,017 c/mL			K103N	R(6.77)	FTC:M184V TDF:None	R(>90.30) S(0.55)
T Subtype B	Non-Responder PDVF: Wk 24	D.188 2,649 c/mL			K103N, M230L	R(>83.16)	FTC:M184V TDF:None	R(>92.78) S(0.50)
T Subtype B	Non-Responder PDVF: Wk 24	D.232 585 c/mL			K103N, M230L	R(>91.81)	FTC:M184V TDF:None	R(>90.30) S(0.58)
U Subtype B	Non-Responder PDVF: Wk 24	D.169 87,443 c/mL			G190E	R(>92.01)	FTC:M184I, K219K/E TDF:D67D/G, K70K/E	R(>63.29) S(0.47)

Week 96 Post-Baseline Resistance Data
Protocol 021

Subject HIV-1 Subtype	PDVF Type or D/C (Reason): Week of PDVF or D/C Visit	Day Sample Collected Viral Load[a]	**DOR Susceptibility** [Subjects Treated w/DOR] Genotypic Resistance [RT Mutation]	 Phenotypic Resistance IC_{50} Fold Diff[b]	**Comparator Susceptibility** [Subjects Treated w/EFV or DRV+r] Genotypic Resistance[d]	 Phenotypic Resistance IC_{50} Fold Diff[b]	**NRTI Susceptibility**[c] Genotypic Resistance [RT Mutation]	 Phenotypic Resistance IC_{50} Fold Diff[b]
U Subtype B	Non-Responder PDVF: Wk 24	D.178 57,519 c/mL			G190E	R(>112.53)	FTC:M184I, K219K/E TDF:D67D/G, D67G, K70E	R(>90.27) S(0.37)
V Subtype B	Non-Responder PDVF: Wk 24	D.172 952 c/mL			K103N	R(12.00)	FTC:None TDF:None	S(1.11) S(0.80)
V Subtype B	Non-Responder PDVF: Wk 24	D.212 11,224 c/mL			K103N, V108V/I, T369T/A/I/V	R(22.00)	FTC:K65K/R, M184M/I TDF:K65K/R	R(81.00) S(0.64)
W Subtype AE	D/C(Withdrawal By Subject): Wk 36	D.213 27,565 c/mL			K101K/N, K103N, P225P/H	R(11.00)	FTC:None TDF:None	S(0.97) S(0.92)
W Subtype AE	D/C(Withdrawal By Subject): Wk 36	D.276 136,633 c/mL			K101K/N, K103N, P225P/H	R(24.00)	FTC:None TDF:None	S(1.27) S(1.02)

Abbreviations: D/C = discontinuation; PDVF = protocol-defined viral failure; PR = HIV-1 protease gene; PS = partially susceptible; RT = HIV-1 reverse transcriptase gene;

a: Viral load is measured as HIV-1 RNA copies/mL.

b: If the fold difference in IC50 with respect to wild-type virus for a given study drug was less than the threshold used to define phenotypic resistance, the virus was considered susceptible to that drug ('S').

c: Data on NRTI susceptibility are provided for only the NRTIs in each subject's treatment regimen.

d: PR mutations for DRV+r; RT mutations for EFV.

e: One DOR-treated subject described in the P018 study report is excluded from this table because the subject's HIV-1 isolate is not considered to have developed resistance to DOR for the purposes of this pooled analysis. The subject with observed phenotypic resistance to DOR (2.8-fold change at Day 29 relative to wild-type virus) is not considered to have developed resistance to DOR based on the observed virologic response, lack of genotypic mutations associated with DOR resistance , minimal change in IC50 from baseline (baseline IC50 FC was 2.2) and insufficient clinical data to define a clinical cutoff for DOR phenotypic resistance [Ref. 5.3.5.1: P018MK1439: 11.1.4.2.2].

Note: Subjects in P018 and P021 were required to be discontinued from the trial if they met PDVF criteria.

3.4 Analyses of Results in Subpopulations of the Pooled Efficacy Population

Subgroup analysis using the OF approach to missing data did not identify clinically meaningful differences in antiretroviral efficacy (proportion of participants with HIV-1 RNA <50 copies/mL) across the 3 treatment groups for the subpopulations defined by various demographic and prognostic factors [Table 5.3.5.3.2-trtmtnve96wk: 26].

When thresholds of HIV-1 RNA 40 and 200 copies/mL were used to evaluate antiretroviral response, results were consistent with those for the 50 copies/mL threshold, ie, there was a lack of meaningful differences across subgroups [Table 5.3.5.3.2-trtmtnve96wk: 25] [Table 5.3.5.3.2-trtmtnve96wk: 27].

Similarly, there were no meaningful differences in immunologic efficacy observed across treatment groups for all demographic and prognostic factors [Table 5.3.5.3.2-trtmtnve96wk: 23].

Analyses of efficacy at Week 96 by subgroup (including estimates of treatment differences) are presented as forest plots (as well as in tables) in the individual CSRs [Ref. 5.3.5.1: P018MK1439: 11.1.3] [Ref. 5.3.5.1: P021MK1439A: 11.1.3].

4 ANALYSIS OF CLINICAL INFORMATION RELEVANT TO DOSING RECOMMENDATIONS

The recommended dosage of DOR is one 100-mg tablet taken orally QD with or without food. The recommended dose of DOR/3TC/TDF is 1 tablet (containing 100 mg of DOR, 300 mg of 3TC, and 300 mg TDF) taken orally QD with or without food.

The Week 96 data presented in this application support the antiretroviral efficacy of DOR, as a single agent used in combination with other antiretroviral agents, or as part of the FDC DOR/3TC/TDF at the recommended dosage. Therefore, the dosing recommendations are unchanged.

5 PERSISTENCE OF EFFICACY AND/OR TOLERANCE EFFECTS

DOR in combination with other antiretroviral agents and DOR/3TC/TDF demonstrated robust antiretroviral and immunologic responses that were demonstrated to be non-inferior to those of DRV+r and EFV (each in combination with other antiretroviral agents) at Week 48. This response was sustained through 96 weeks of treatment based on data from P018 [Sec. 2.7.3-trtmtnve96wk: 2.2.2.3] and P021 [Sec. 2.7.3-trtmtnve96wk: 3.3.2].

5.1 Sustained Response Through Week 96 (P018 and P021)

Robust antiretroviral efficacy of DOR at Week 96 was seen in the integrated (P018 + P021) data, as evidenced by the proportions of participants in the DOR Regimen group who achieved HIV-1 RNA <50 copies/mL (using the FDA snapshot approach to missing data). Consistent evidence of sustained robust antiretroviral efficacy through Week 96 was seen when HIV-1 RNA thresholds of <40 copies/mL and <200 copies/mL were used [Table 5.3.5.3.2-trtmtnve96wk: 16] [Table 5.3.5.3.2-trtmtnve96wk: 18]. There were no notable

differences in antiretroviral efficacy at any time point between the DOR Regimen group and the control groups (DRV+r and EFV/FTC/TDF), regardless of HIV-1 RNA threshold.

Results of the TLOVR analysis at Week 96 are consistent with the results for antiretroviral efficacy [Sec. 2.7.3-trtmtnve96wk: 3.3.3].

The change from baseline in $CD4^+$ T-cell count (using the OF approach to missing data) increased over time for the DOR Regimen group in both P018 and P021 [Figure 2.7.3-trtmtnve96wk: 11]. The time course of this change from baseline in $CD4^+$ T-cell count was comparable to that seen in each of the control groups (DRV+r and EFV/FTC/TDF, respectively).

6 CONCLUSIONS

DOR 100 mg QD, as a single entity (administered in combination therapy 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 is 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) through Week 48, which are further supported by the Week 96 results within each trial. The following conclusions can be drawn from the pivotal Phase 3 trials (P018 and P021):

- DOR and DOR/3TC/TDF have efficacy comparable to DRV+r and EFV with respect to the proportion of participants with HIV-1 RNA <50 copies/mL at Week 96, supporting the non-inferiority of DOR and DOR/3TC/TDF to DRV+r and EFV previously established at Week 48.
- DOR and DOR/3TC/TDF have efficacy comparable to that of DRV+r and EFV with respect to:
    - Proportion of participants with HIV-1 RNA <40 copies/mL and HIV-1 RNA <200 copies/mL at Week 96.
    - Increase from baseline in $CD4^+$ T-cell counts at Week 96.
- Efficacy of DOR and DOR/3TC/TDF was consistent across various subpopulations.
- 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 resistance to DOR was rare.

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2.7　臨床概要

2.7.4　臨床的安全性

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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
ALT	Alanine transaminase
ASaT	All Subjects as Treated (analysis population)
AST	Aspartate transaminase
CD4	Cluster of differentiation 4
CI	Confidence interval
CNS	Central nervous system
CPSOS	Clinical Pharmacology Summary of Safety
CSR	Clinical study report
CYP	Cytochrome P450
DAIDS	Division of Acquired Immunodeficiency Syndrome
DBL	Database lock
DILI	Drug-induced liver injury
DOR	Doravirine (MK-1439)
DOR/3TC/TDF	Doravirine/ lamivudine/ tenofovir disoproxil fumarate (MK-1439A)
DRV+r	Darunavir boosted with ritonavir
ECI	Event of clinical interest
EFV	Efavirenz
EFV/FTC/TDF	Fixed-dose combination of EFV, emtricitabine and tenofovir disoproxil fumarate
FDC	Fixed-dose combination
FTC	Emtricitabine
HCV	Hepatitis C virus
HDL-C	High-density lipoprotein cholesterol
HIV-1	Human Immunodeficiency Virus type 1
IRIS	Immune reconstitution syndrome

Abbreviation/Term	Definition
iSAP	Integrated statistical analysis plan
ISS	Integrated Summary of Safety
LDL-C	Low-density lipoprotein cholesterol
LLN	Lower limit of normal range
MedDRA	Medical Dictionary for Regulatory Activities
MK-1439A	Fixed-dose combination of DOR, 3TC, and TDF
MSP	Main safety pool
NNRTI	Nonnucleoside reverse transcriptase inhibitor
NRTI	Nucleos(t)ide reverse transcriptase inhibitors
PDLC	Predefined limit of change
PI	Protease inhibitor
PK	Pharmacokinetic(s)
QD	Once daily
RNA	Ribonucleic acid
SAE	Serious adverse event
SOC	System organ class
SSP	Special safety pool
TDF	Tenofovir disoproxil fumarate
ULN	Upper limit of normal (range)

SUMMARY OF CLINICAL SAFETY

1 EXPOSURE TO DOR AND DOR/3TC/TDF

1.1 Overall Safety Evaluation Plan and Safety Study Summaries

1.1.1 Overview of the Clinical Program

Doravirine (DOR, also known as MK-1439) 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 in antiretroviral treatment-naïve adults aged 18 years and older. It is being developed as both the single agent DOR (100 mg) and as a fixed-dose combination (FDC) with lamivudine (3TC, 300 mg) and tenofovir disoproxil fumarate (TDF, 300 mg) (also known as MK-1439A but hereafter referred to as DOR/3TC/TDF).

DOR (in combination with other antiretroviral medicinal products) and DOR/3TC/TDF are being developed in a hybrid clinical development program that includes mutually supportive Phase 2 and Phase 3 trials of the DOR single entity and DOR/3TC/TDF.

The trials supporting this Application and contributing data to this Summary of Clinical Safety include 36 Phase 1 trials, 1 Phase 2b dose-ranging trial (Protocol 007 [P007]), and 2 Phase 3 trials (P018 and P021). A total of 1657 subjects received at least 1 dose of DOR or DOR/3TC/TDF in these trials ([Table 2.7.4: 1], [Table 2.7.4: 2]). The subjects are included as follows:

- 678 subjects in 36 Phase 1 trials.
  - Of the 678 subjects, 650 were healthy subjects. Other subject populations included 12 subjects infected with HIV-1, 8 subjects with moderate hepatic impairment, and 8 subjects with severe renal impairment.
- 232 subjects in P007, a Phase 2 trial that was conducted as a 2-part dose-ranging trial in treatment-naïve HIV-1 infected subjects.
  - Part I: 166 subjects received DOR (in QD doses of 25 mg [40 subjects], 50 mg [43 subjects], 100 mg [42 subjects], and 200 mg [41 subjects]) and 42 subjects received efavirenz (EFV), each in combination with open label emtricitabine (FTC)/TDF (supplied as TRUVADA™).
  - Part II: After dose selection, Part I subjects who were in the DOR 25 mg, 50 mg and 200 mg dose treatment groups who continued in the trial were switched to the 100 mg dose of DOR at their next planned study visit between Week 36 and Week 72, while maintaining the study blind. An additional 132 subjects were randomized (66 in each treatment group) and received treatment with DOR 100 mg QD and EFV in combination with FTC/TDF.

- 747 subjects in two Phase 3 trials, P018 and P021 (treatment-naïve HIV-1 infected subjects).
  - Safety follow-up in both trials through Week 48 is provided to support this Application. The trials are ongoing to evaluate long term safety and efficacy through Week 96. These two international, multicenter, trials were conducted at different investigation sites. Out of 125 participating sites in P018 and 126 participating sites in P021, there were only 39 sites that participated in both trials.
  - P018 is a Phase 3, multicenter, double-blind, randomized, active comparator controlled trial to evaluate the safety and efficacy of DOR 100 mg QD versus darunavir 800 mg QD plus ritonavir 100 mg QD (DRV+r), each in combination with FTC/TDF (supplied as TRUVADA™) or abacavir (ABC)/3TC (supplied as either EPZICOM™ or KIVEXA™). A total of 766 treatment-naïve HIV-1 infected subjects received treatment (383 in the DOR treatment group, 383 in the DRV+r treatment group).
  - P021 is a Phase 3, multicenter, double-blind, randomized, active comparator controlled clinical trial to evaluate the safety and efficacy of DOR/3TC/TDF QD versus EFV/FTC/TDF (supplied as ATRIPLA™) QD. A total of 728 treatment-naïve HIV-1 infected subjects received treatment (364 in the DOR/3TC/TDF treatment group, 364 in the EFV/FTC/TDF treatment group).

Trial designs and pharmacokinetic (PK) and pharmacodynamic results for the Phase 1 trials are summarized in [Sec. 2.7.1] and [Sec. 2.7.2]. Additional details of the trial designs for P007, P018, and P021 can be found in the individual clinical study reports (CSRs, [Ref. 5.3.5.1: P007V01MK1439, P018V01MK1439, P021V01MK1439A]).

Limited preliminary safety data from other ongoing trials, including 2 Phase 2 (P028, P030) and 1 Phase 3 (P024) trials, are provided in this Summary of Clinical Safety [Table 2.7.4: 1]. As of the cut-off dates for this Application, no milestones were reached for the planned analyses of these trials [Table 2.7.4: 3] [Table 2.7.4: 2]. Data from these trials are not included in the individual safety analyses or integrated analysis of this application (see [Sec. 2.7.4.1.1.2]), the only reported data are narratives of adverse events (AEs) leading to discontinuation, serious AEs, and deaths.

- 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 for a total duration of 36 weeks (base study). All subjects who complete the base study are eligible for the study extension and, if they provide consent, will receive open-label DOR/3TC/TDF for another 96 weeks. There are two treatment groups. Subjects were assigned randomly in a 1:1 ratio to either the Immediate Switch Group or to the Deferred Switch Group.
  - Immediate Switch Group: Immediate Switch (at Study Day 1) from a baseline regimen of EFV/FTC/TDF or its components to DOR/3TC/TDF (+ a placebo matched to EFV/FTC/TDF to maintain blinding) for 12 weeks followed by treatment with open-label DOR/3TC/TDF for an additional 12 weeks.

- Deferred Switch Group: Subjects to receive EFV/FTC/TDF (+ a placebo matched to DOR/3TC/TDF to maintain blinding) for the first 12 weeks of the study followed by treatment with open-label DOR/3TC/TDF for 24 weeks.

- P030 is a Phase 2 trial to evaluate the safety and efficacy of DOR/3TC/TDF in antiretroviral treatment-naïve subjects with HIV-1 infection with selected NNRTI transmitted resistance mutations. The trial includes a 96 week base study and a 96 week trial extension to collect long-term efficacy and safety data with DOR/3TC/TDF.

- P024 is a Phase 3 trial to evaluate a switch from a baseline regimen of a boosted protease inhibitor (PI), NNRTI, or integrase inhibitor based regimen to DOR/3TC/TDF in virologically-suppressed, HIV-1-infected subjects for 48 weeks (base study). All subjects who complete the base study are eligible for the study extension to receive open-label DOR/3TC/TDF for an additional 96 weeks. Subjects were assigned randomly in a 2:1 ratio to either an immediate switch to MK-1439A on Study Day 1 (Immediate Switch Group) or a delayed switch to MK-1439A at Study Week 24 (Delayed Switch Group).

Table 2.7.4: 1
Summary of Phase 2 and Phase 3 Trials Included in the DOR and DOR/3TC/TDF Clinical Development Program

Trial	Short Description	Trial Design	Treatments (N treated) [Duration]	Key Elements of Subject Population	Status (Data Included in Application)
DOR					
P007	Dose-finding (Phase 2b) in treatment-naïve adult subjects	Part I: Double-blind dose-ranging, subjects randomized to 1 of the 5 treatment arms (4 dose groups of DOR, EFV) Part II: Double-blind, additional subjects randomized to the selected dose of DOR or to EFV	Part I: QD doses of DOR 25 mg (n=40), 50 mg (n=43), 100 mg (n = 42), 200 mg (n=41) or EFV (n=42), each with FTC/TDF (total N=208) [at least 24 weeks] After dose selection, Part I subjects who were in the DOR 25 mg, 50 mg and 200 mg dose treatment groups who continued in the trial were switched to the 100 mg dose of DOR at their next planned study visit between Week 36 and Week 72 Part II: DOR 100 mg (n=66) or EFV (n=66), each QD with FTC/TDF [up to 96 weeks] . Subjects who received 100mg DOR only in both Parts I and II (n=108)	International multicenter study in treatment naïve HIV-1 infected subjects aged 18 or older.	Complete (96-week data)
P018	Pivotal (Phase 3) in treatment-naïve adult subjects	Multicenter, double-blind, randomized, active comparator controlled Subjects randomized 1:1 to DOR or DRV+r	DOR 100 mg QD with FTC/TDF or ABC/3TC (n = 383) DRV+r (800 mg DRV+100mg r) with FTC/TDF or ABC/3TC (n = 383) [Base study for 96 weeks followed by 96-week open label study extension]	International multicenter study in treatment naïve HIV-1 infected subjects aged 18 or older.	Ongoing (48-week data, DBL [redacted] 20[redacted])

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Trial	Short Description	Trial Design	Treatments (N treated) [Duration]	Key Elements of Subject Population	Status (Data Included in Application)
DOR/3TC/TDF					
P021	Pivotal (Phase 3) in treatment-naïve adult subjects	Multicenter, double-blind, randomized, active controlled Subjects randomized 1:1 to DOR/3TC/TDF or EFV/FTC/TDF	DOR/3TC/TDF (DOR 100 mg/ TDF 300 mg/ 3TC 300 mg) QD (n=364) EFV/FTC/TDF (EFV 600 mg/ FTC 200 mg/ TDF 300 mg) QD (n = 364) [96-week base study followed by 96-week open label extension]	International study in treatment naïve HIV-1 infected subjects aged 18 or older.	Ongoing (48-week data, DBL [redacted] 20[redacted])
P024	Phase 3 efficacy switch in virologically suppressed subjects	Multicenter, open-label, randomized, active- controlled Immediate switch to DOR/3TC/TDF on Study Day 1 or delayed switch to DOR/3TC/TDF at Study Week 24	Immediate switch group: Immediate switch (at Study Day 1) from baseline regimen to DOR/3TC/TDF (n = 446) Delayed Switch Group: Subjects continue their baseline regimen for 24 weeks and then switch to DOR/3TC/TDF (n = 233 subjects overall; 127 subjects in this group have completed 24 weeks of baseline regimen and switched to DOR/3TC/TDF) [48-week base study followed by 96-week open label extension] Trial fully enrolled; subjects expected to complete 48 weeks treatment in Q1 2018.	International study in HIV-1 infected subjects aged 18 or older and virologically suppressed while on a boosted PI, NNRTI, or integrase inhibitor based regimen.	Ongoing (Safety narratives for subjects who experienced an SAE [including death] or discontinued due to AEs [drug related or not related])
P028	Phase 2b safety switch in virologically suppressed subjects	Multicenter, double blind (with in-house blinding), randomized, active-controlled, Immediate switch to DOR/3TC/TDF on Study Day 1 (Immediate Switch Group) or continued treatment with EFV regimen for 12 weeks followed by switch to open label DOR/3TC/TDF (Deferred Switch Group).	Immediate Switch Group : Immediate switch (at Study Day 1) from a baseline EFV regimen to DOR/3TC/TDF for 12 weeks followed by treatment with open-label DOR/3TC/TDF for an additional 12 weeks Deferred Switch Group: Subjects receive EFV regimen for 12 weeks followed by treatment with open-label DOR/3TC/TDF 24 weeks. [36-week base trial followed by 96–week extension.] As of the data cutoff, 19 subjects had completed blinded treatment (10 subjects in Immediate Switch Group and 9 subjects from the Deferred Switch Group were switched to DOR/3TC/TDF	International (not in United States) multicenter study in HIV-1 infected subjects aged 18 or older and virologically suppressed while on an EFV regimen and who have CNS intolerance.	Ongoing and enrolling (Safety narratives for subjects who experienced an SAE [including death] or discontinued due to AEs [drug related or not related])

Trial	Short Description	Trial Design	Treatments (N treated) [Duration]	Key Elements of Subject Population	Status (Data Included in Application)
P030	Phase 2 in treatment-naïve subjects with transmitted resistance to NNRTI	Multicenter, single-arm, open-label Long-term efficacy and safety data of DOR/3TC/TDF.	DOR/3TC/TDF QD (n =10) [96 week base trial and a 96 week trial extension]	International multicenter study in treatment-naïve HIV-1 infected subjects aged 18 or older and with transmitted resistance to NNRTI.	Ongoing (Safety narratives for subjects who experienced an SAE [including death] or discontinued due to AEs [drug related or not related])
Abbreviations: AE = adverse event; CNS = central nervous system; DBL = database lock; DOR = doravirine; EFV = efavirenz; HIV-1 = Human Immunodeficiency Virus type 1; NNRTI = non-nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; QD = once daily; SAE = serious adverse event; 3TC = lamivudine 300 mg; TDF = tenofovir disoproxil fumarate 300 mg					

Table 2.7.4: 2
Summary of Subjects who Received Doravirine (as either DOR or DOR/3TC/TDF) in the Clinical Development Program
All Trials (Completed & Ongoing)

	Subjects Who Received DOR or DOR/3TC/TDF (N)[a]
Phase 1	**678**
Phase 2	**261**
P007 – Total	232
(P007 100 mg only) [b]	(108)
P028[c]	19
P030[c]	10
Phase 3	**1320**
P018	383
P021	364
P024[c]	573
Total Overall Clinical Program	**2259**
Treatment-naive HIV-1 Subjects	1593
Total in P007, P018, P021 (Integrated Safety Populations)	**979**
DOR 100 mg only	615
DOR/3TC/TDF	364

a. Subjects who received ≥1 of any dose of doravirine as either DOR or DOR/3TC/TDF.
b. Subjects who received 100 mg in Part I/Part II combined
c. Studies are ongoing, safety narratives provided for subjects who experienced an SAE(s) or discontinued due to an AE are included in the application.

Abbreviations: AE = adverse event; DOR = doravirine; DOR/3TC/TDF = doravirine/ lamivudine/ tenofovir disoproxil fumarate; HIV-1= Human Immunodeficiency Virus type 1; SAE = serious AE

Table 2.7.4: 3
Last Patient Last Visit/ Data Cutoff Date and Database Lock Dates
for Phase 2 and Phase 3 Trials

Trial	Last Patient Last Visit Date/ Data Cutoff Date	Database Lock Date
P007 Week 96 analysis	22-Mar-2016	[redacted]-20[redacted] (Week 96)
P018 Week 48 analysis	29-Sep-2016	[redacted]-20[redacted]
P021 Week 48 analysis	20-Mar-2017	[redacted]-20[redacted]
P024	[redacted]-20[redacted]	[redacted]-20[redacted]
P028	[redacted]-20[redacted]	[redacted]-20[redacted]
P030	[redacted]-20[redacted]	[redacted]-20[redacted]
P007: Last subject last visit (LSLV) date is the last visit of last subject P018 and P021: Last subject's last visit for primary endpoint analysis P024, P028 and P030: Data cutoff date of [redacted] is used as the cut off for events in scope occurring on or before that date.		

1.1.2 Organization, Content and Analysis Population of this Safety Summary

Safety data are presented in the following order in each of the results sections of this Summary of Clinical Safety.

- Summary of safety results from Phase 1 trials.
- Summary of safety results from individual trials P007 (100 mg arm), P018, and P021.
- Summary of the integrated safety data (see [Sec. 2.7.4.1.1.3]).

Phase 1 trials are not individually summarized in the Summary of Clinical Safety; an overview of safety data across the Phase 1 program can be found in the Clinical Pharmacology Summary of Safety (CPSOS [Sec. 5.3.5.3.1-trtmtnve48wk]). Information for Phase 2b and Phase 3 trials P007, P018, and P021 can be found in the individual CSRs ([Ref. 5.3.5.1: P007V01MK1439, P018V01MK1439, P021V01MK1439A]).

Content

The following are presented for the individually summarized Phase 2b and Phase 3 trials and for the integrated safety data:

- Adverse events (AEs), including:
  - Common AEs
  - Deaths
  - Other serious adverse events (SAEs)
  - AEs leading to discontinuation
  - AEs of special interest which consist of central nervous system (CNS)/ neuropsychiatric AEs (comparison of DOR with EFV in trials P007 and P021)

- Laboratory Evaluations, including:
  - Pre-defined limit of change (PDLC) evaluations
  - Change from baseline for laboratory parameters
  - Change from baseline in fasting lipids for the Phase 3 trials (P018 and P021)
- Vital Signs, physical findings, and other observations, including:
  - Summary of vital signs, physical examinations, and other evaluations
  - Data for safety in special groups

Analysis Population

The All Subjects as Treated (ASaT) population was used for the analysis of safety data in the trials, and consisted of all randomized subjects who received at least 1 dose of study treatment. Subjects were included in the treatment group corresponding to the study treatment they actually received for the analysis of safety data using the ASaT population. Subjects who received the incorrect study medication for the entire treatment period were to be included in the treatment group corresponding to the study medication actually received. In these trials, few subjects received incorrect study medication for a short period of time due to dispensing errors that were corrected later, as discussed in the P018 and P021 CSRs [Ref. 5.3.5.1: P018V01MK1439: 10.2] [Ref. 5.3.5.1: P021V01MK1439A: 10.2]; no subject received the incorrect study medication for the entire treatment period. Therefore, the treatment group assignment in the ASaT population is the same as in the treatment group to which the subjects were randomized.

An analysis of the differences between treatment groups was done for AEs that occurred at an incidence of ≥4 subjects in at least 1 treatment group. The threshold of at least 4 events was chosen because the 95% confidence interval (CI) for the between-group difference in percent incidence will always include zero when treatment groups of equal size each have less than 4 events and thus would add little to the interpretation of potentially meaningful differences.

For the 3 ongoing trials (P028, P024, and P030), milestones for planned analyses had not been reached as of the cut-off date for this application. As such, only narratives for subjects who experienced deaths, other SAEs, and discontinuations due to AEs are presented in [Sec. 2.7.4.2.6].Of note, only narratives for subjects in P024 are provided as none of the subjects in P028 and P030 met any of these reporting categories. Data reported in the narratives are preliminary.

1.1.3 Overall Safety Assessment- Data Integration Plan

Safety data from trials P007, P018 and P021 are integrated in this Application, for the purpose of supporting the proposed indications for DOR and DOR/3TC/TDF. P007 includes complete data through Week 96; P018 and P021 include 48-week data, and these trials are still ongoing.

The Integrated Statistical Analysis Plan (iSAP) for the Integrated Summary of Safety (ISS) is provided in [Ref. 5.3.5.3: 04LVBJ]. Integrated data for the Phase 2b (all subjects who received only the 100 mg dose) and Phase 3 trials included in this dossier are presented as per the iSAP.

Integrated safety analyses were conducted for 2 pools of subjects, the Main Safety Pool (MSP) and the Special Safety Pool (SSP) [Table 2.7.4: 4]. The trials and treatment groups included in each pool are also depicted in [Figure 2.7.4: 1].

The MSP is the primary pool for the evaluation of all AEs and includes data from trials P007, P018, and P021. The DRV+r treatment group from P018 was not combined with the EFV-based treatment groups from P007 and P021 as these 2 treatments are associated with different safety profiles with regard to specific AEs and laboratory measurements. Combining these treatment groups could have diluted the specific signals from each drug. No formal statistical testing was performed. Descriptive summary data are presented for each treatment group.

The SSP is used for the analyses of the proportion of subjects who discontinued from trials P007 and P021 due to AEs through Week 48 (pre-specified hypothesis in the iSAP, including P007 and P021), the time to discontinuation from the trials due to AEs through Week 48, and neuropsychiatric events using a pre-specified list of AEs. The P007 and P021 trials both have an EFV treatment group, and since EFV is associated with neuropsychiatric events, the SSP population was used to evaluate neuropsychiatric events.

Table 2.7.4: 4
Integrated Safety Populations
Main Safety Pool and Special Safety Pool

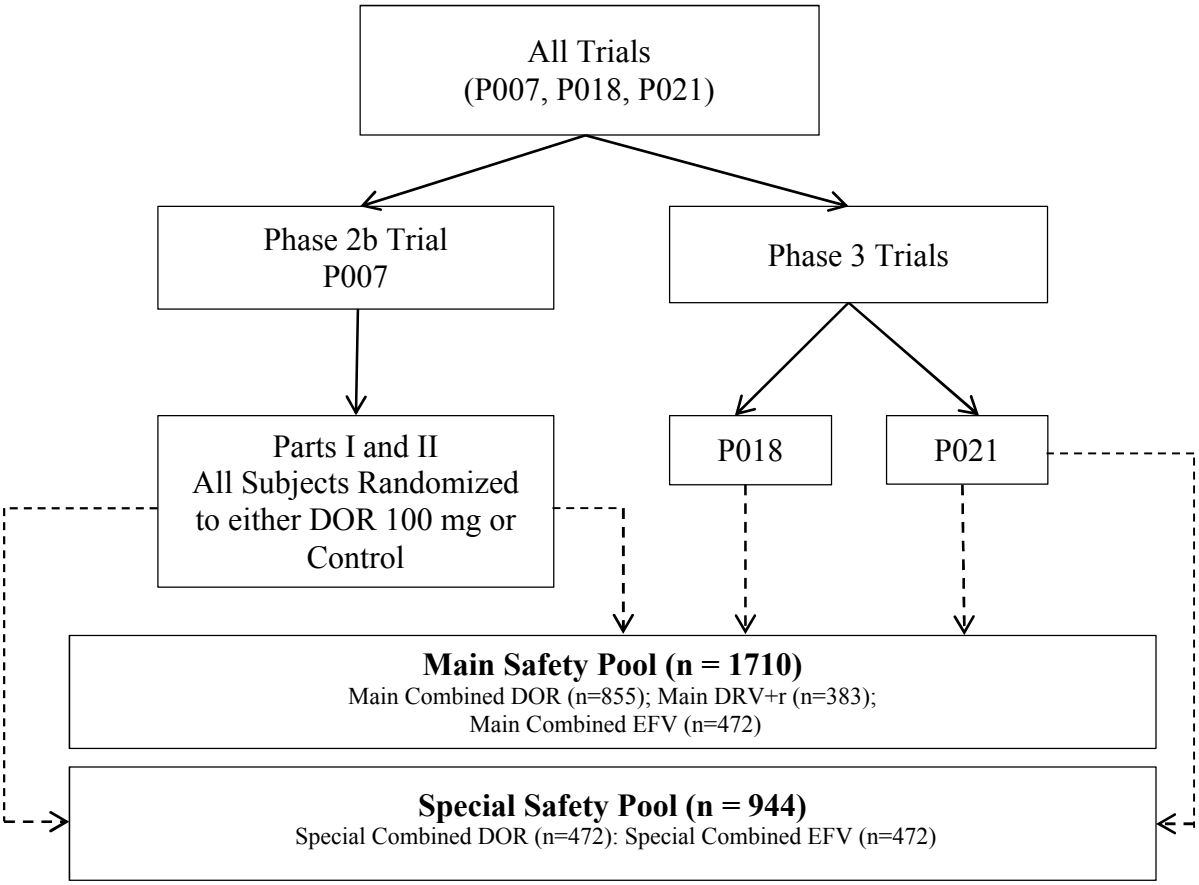
Objective	Analysis	Trials Involved	Combined Treatment groups (N)
Main Safety Pool (n = 1710 subjects)			
DOR / DOR/3TC/TDF vs. Controls	AEs, AEs by specific terms and SOC, PDLC, and change in laboratory measurement and vital signs (estimate by treatment group)[a]	P007 (100 mg arm), P018, P021	Main Combined DOR: DOR and DOR/3TC/TDF (N=855) (P007 100 mg arm=108 subjects + P018=383 subjects + P021=364 subjects) Main DRV+r: Darunavir (DRV+r) regimen (n =383) Main Combined EFV: EFV regimen (n=472) (P007=108 subjects P021=364 subjects)
Special Safety Pool= 944 subjects			
DOR / DOR/3TC/TDF vs. Controls	Proportion of subjects discontinuing due to AE[b] and time to discontinuation due to AE by Week 48.[c] Proportion of subjects with neuropsychiatric events by Week 8 and Week 48.[d]	P007 (100 mg arm), P021	Special Combined DOR: DOR and DOR/3TC/TDF (N =472) (P007 100 mg arm= 108 participants + P021= 364 participants) Special Combined EFV: EFV regimen (n =472) (P007=108 subjects P021=364 subjects)

a. Descriptive statistics, no formal statistical testing.
b. Tier 1 endpoint, p-values and 95% Confidence Intervals (CI) provided
c. Kaplan-Meier product-limit estimates provided
d. 95% CI for between-treatment differences provided

Abbreviations: AE = adverse event; DOR = doravirine; DRV+r = Darunavir boosted with ritonavir; EVF = efavirenz; PDLC = Predefined Limit of Change; SOC = System Organ Class; 3TC = lamivudine 300 mg; TDF = tenofovir disoproxil fumarate 300 mg

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Figure 2.7.4: 1
Diagram of Integrated Safety Populations



Main Combined DOR Treatment Group (P018, and P021, and from 100 mg arm 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 from 100 mg arm 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 from 100 mg arm P007): EFV600 mg administered with FTC/TDF, or EFV/FTC/TDF

1.1.4 Overall Safety Evaluation Plan

For each trial, safety monitoring was performed by the investigator(s) at each study visit. AEs were coded by the Medical Dictionary for Regulatory Activities (MedDRA) 19.1. Specific (if they caused the subject to be excluded from the trial, or were the result of a protocol-specified intervention) AEs were recorded from the time the consent form was signed, but before treatment allocation/randomization. All AEs were recorded from randomization through the pre-specified post-dose period. Subjects who discontinued early were requested to complete an end of treatment visit, and AEs were reported through this visit.

Subjects were asked about any AEs during their study visits, and the information was recorded on case report forms. The investigator assessed if there was or was not a reasonable possibility that the AE was related to study therapy. Drug-related AEs were those assessed by the investigator to be related to study therapy. For each trial, guidelines for grading the intensity of AEs are presented in the protocol [Ref. 5.3.5.1: P007V01MK1439: 16.1.1] [Ref. 5.3.5.1: P018V01MK1439: 16.1.1] [Ref. 5.3.5.1: P021V01MK1439A: 16.1.1]. Adverse events were graded by the investigator as being of mild, moderate, or severe intensity.

Serious AEs were to be reported within 24 hours to the Sponsor. Each SAE was fully investigated and, if considered drug-related by the investigator, a decision was made as to whether the risk/benefit warranted the subject's continuation in the study. Decisions to temporarily withhold or reinitiate therapy because of an AE were reviewed on a case-by-case basis by the investigator.

For the Phase 2b and Phase 3 trials, following each visit, investigators received laboratory test results from the central laboratory. Guidelines for grading the severity of laboratory abnormalities are based on the Division of Acquired Immunodeficiency Syndrome (DAIDS) common toxicity criteria. Investigators assessed whether laboratory values outside the normal range were AEs. Clinical laboratory values that were protocol-specified events of clinical interest (ECI) and/or resulted in discontinuation of study drug were recorded as AEs.

1.2 Overall Extent of Exposure to DOR

Phase 1 Clinical Pharmacology Trials

In the Phase 1 program, DOR was evaluated in 32 trials and DOR/3TC/TDF was evaluated in 4 trials. Overall, 678 subjects received at least a single dose of DOR or DOR/3TC/TDF. A total of 592 subjects received at least 1 dose of DOR as the single entity without co-administration of 3TC and TDF and 101 subjects received at least 1 dose of DOR in combination with 3TC and TDF (either as DOR/3TC/TDF or co-administration of the individual components) [Sec. 2.7.2.1.2].

Of the 592 subjects who received DOR as the single entity, 407 subjects received single doses (385 received a single dose ≥100 mg) and 197 subjects received multiple doses of DOR (179 subjects received multiple doses ≥100 mg). Note: 12 subjects are counted in both the single-dose and multiple-dose groups ([Appendix 5.3.5.3.1-trtmtnve48wk: 1], [Appendix 5.3.5.3.1-trtmtnve48wk: 3]).

Of the 101 subjects who received at least 1 dose of DOR in combination with 3TC and TDF, 86 subjects received the DOR/3TC/TDF FDC tablet. All 86 subjects who received DOR/3TC/TDF received single doses ([Appendix 5.3.5.3.1-trtmtnve48wk: 2]). Note: Due to the nature of Phase 1 trials, subjects may have been exposed to more than 1 treatment.

Descriptions of the 36 Phase 1 trials can be found in [Sec. 2.7.1] and [Sec. 2.7.2]. The extent of exposure and the disposition for all subjects in the Phase 1 trials are summarized in the CPSOS ([Sec. 5.3.5.3.1-trtmtnve48wk]).

Phase 2 and Phase 3 trials

DOR was administered as a single entity in trials P007 and P018. A total of 614 subjects received any dose of DOR for a mean duration of 455.5 days in these trials [Table 2.7.4: 5]. This includes 232 subjects from P007 who received any dose of DOR in Part I and Part II ([Ref. 5.3.5.1: P007V01MK1439: Table 12-3]) and all 383 subjects from P018 ([Ref. 5.3.5.1: P018V01MK1439: Table 12-1]) who received DOR.

A total of 364 subjects received DOR as DOR/3TC/TDF for a mean duration of 387.1 days in P021 [Table 2.7.4: 6].

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Table 2.7.4: 5
Extent of Exposure to DOR by Dose
P007 and P018 Combined

DOR	≤ 4 wks	> 4 wks to 8 wks	> 8 wks to 16 wks	> 16 wks to 24 wks	> 24 wks to 36 wks	> 36 wks to 48 wks	> 48 wks	Total Subjects	Duration Range	Mean Duration
Any Dose	20	10	12	10	22	58	482	614	1 to 701 days	455.5 days
25 mg	3	2	0	1	2	22	12	42	1 to 421 days	296.2 days
50 mg	4	0	1	1	7	17	14	44	2 to 504 days	301.3 days
100 mg	14	9	12	10	37	100	406	588	1 to 685 days	409.1 days
200 mg	14	0	1	1	5	15	18	54	1 to 494 days	247.7 days
300 mg	1	0	0	0	0	0	0	1	1 to 1 days	1.0 days
Other	1	0	0	0	0	0	0	1	6 to 6 days	6.0 days

Each subject who received DOR is counted once on the "Any Dose" row in the column that reflects the total duration of exposure to DOR.

Each subject is counted again on one or more specific dose category rows that correspond to the actual dose(s) received. On each applicable specific dose row, the subject is counted once in the column that reflects the duration of exposure to that specific dose.

Source: [ISS: analysis-adsl; explus]

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Table 2.7.4: 6
Extent of Exposure to DOR/3TC/TDF by Dose
P021

DOR/3TC/TDF	≤ 4 wks	> 4 wks to 8 wks	> 8 wks to 16 wks	> 16 wks to 24 wks	> 24 wks to 36 wks	> 36 wks to 48 wks	> 48 wks	Total Subjects	Duration Range	Mean Duration
Any Dose	6	7	5	6	12	67	261	364	1 to 589 days	387.1 days
DOR 100 mg/lamivudine 300 mg/TDF 300 mg	6	7	5	7	12	66	261	364	1 to 589 days	386.7 days
DOR 200 mg/lamivudine 600 mg/TDF 600 mg	42	0	1	0	0	0	0	43	1 to 58 days	3.1 days

Each subject who received DOR/3TC/TDF is counted once on the "Any Dose" row in the column that reflects the total duration of exposure to DOR/3TC/TDF.

Each subject is counted again on one or more specific dose category rows that correspond to the actual dose(s) received. On each applicable specific dose row, the subject is counted once in the column that reflects the duration of exposure to that specific dose.

Source: [ISS: analysis-adsl; explus]

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Subject Disposition

The disposition of subjects in the individual trials P007, P018, and P021 can be found in [Ref. 5.3.5.1: P007V01MK1439: Table 10-4] [Ref. 5.3.5.1: P018V01MK1439: Table 14.1-1] [Ref. 5.3.5.1: P021V01MK1439A: Table 14.1-1].

Main Safety Pool

Overall, 99.3% of the randomized subjects in the Combined DOR group, 99.7% of the subjects in the DRV+r group and 99.4% of the subjects in the EFV group received treatment and are included in the MSP [Table 2.7.4: 7].

Similar proportions of subjects discontinued from the study by Week 48 in all three treatment groups [Table 2.7.4: 7]. The proportion of subjects who discontinued from the study due to AEs was higher in the EFV group (6.1%) compared with the DOR (2.0%).

The proportion of subjects who discontinued from the study due to lack of efficacy was similar in the 3 treatment groups.

The disposition of subjects in the MSP for all available data is shown in [Table 5.3.5.3.3-trtmtnve48wk: 4].

Table 2.7.4: 7
Disposition of Subjects
Main Safety Pool (P007 (DOR 100 mg QD Group) and P018 and P021 Combined)
Weeks 0-48

	Main Combined DOR		Main DRV+r		Main Combined EFV	
	n	(%)	n	(%)	n	(%)
Total Randomized	861		384		475	
Not Treated	6	(0.7)	1	(0.3)	3	(0.6)
Treated	855	(99.3)	383	(99.7)	472	(99.4)
Discontinued Study	121	(14.1)	71	(18.5)	77	(16.2)
Adverse Event	17	(2.0)	12	(3.1)	29	(6.1)
Death	2	(0.2)	0	(0.0)	3	(0.6)
Lack Of Efficacy	30	(3.5)	14	(3.6)	11	(2.3)
Lost To Follow-Up	26	(3.0)	19	(4.9)	11	(2.3)
Non-Compliance With Study Drug	13	(1.5)	4	(1.0)	2	(0.4)
Physician Decision	5	(0.6)	3	(0.8)	3	(0.6)
Pregnancy	2	(0.2)	0	(0.0)	1	(0.2)
Protocol Deviation	5	(0.6)	6	(1.6)	2	(0.4)
Withdrawal By Subject	21	(2.4)	13	(3.4)	15	(3.2)

n (%) = Number (percent) of subjects in each sub-category.
Main Combined DOR: DOR 100 mg administered with FTC/TDF in P007 and P018 or ABC/3TC in P018, or fixed dose combination of DOR/ 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: EFV 600 mg administered with FTC/TDF in P007, or fixed dose combination of EFV/emtricitabine/tenofovir disoproxil fumarate 600/200/300 mg in P021.

Source: [ISS: analysis-adsl; dsplus]

Special Safety Pool

Overall, 472 (99.2%) of the subjects in the Special Combined DOR treatment group and 472 (99.4%) of the subjects in the Special Combined EFV treatment group received treatment in the SSP [Table 2.7.4: 8].

A similar proportion of subjects in the Special Combined EFV treatment group (16.2%) discontinued from the study by Week 48 compared with the Special Combined DOR treatment group (13.7%). The proportion of subjects who discontinued from the study due to AEs was slightly higher in the Special Combined EFV group (6.1%) compared with the Special Combined DOR group (2.7%).

The disposition of subjects in the SSP for all available data is shown in [Table 5.3.5.3.3-trtmtnve48wk: 6].

Table 2.7.4: 8
Disposition of Subjects
Special Safety Pool (P007 (DOR 100 mg q.d. Group) and Protocol 021 Combined)
Weeks 0-48

	Special Combined DOR		Special Combined EFV	
	n	(%)	n	(%)
Total Randomized	476		475	
Not Treated	4	(0.8)	3	(0.6)
Treated	472	(99.2)	472	(99.4)
Discontinued Study	65	(13.7)	77	(16.2)
Adverse Event	13	(2.7)	29	(6.1)
Death	1	(0.2)	3	(0.6)
Lack Of Efficacy	18	(3.8)	11	(2.3)
Lost To Follow-Up	9	(1.9)	11	(2.3)
Non-Compliance With Study Drug	6	(1.3)	2	(0.4)
Physician Decision	2	(0.4)	3	(0.6)
Pregnancy	1	(0.2)	1	(0.2)
Protocol Deviation	4	(0.8)	2	(0.4)
Withdrawal By Subject	11	(2.3)	15	(3.2)

n (%) = Number (percent) of subjects in each sub-category.
Special Combined DOR: DOR 100 mg administered with FTC/TDF in P007, or fixed dose combination of DOR/lamivudine/tenofovir disoproxil fumarate 100/300/300 mg in P021.
Special Combined EFV: EFV 600 mg administered with FTC/TDF in P007, or fixed dose combination of EFV/emtricitabine/tenofovir disoproxil fumarate 600/200/300 mg in P021.

Source: [ISS: analysis-adsl; dsplus]

1.3 Demographic and Other Characteristics of Study Population

Phase 1 Clinical Pharmacology Trials

Most (n =650) of the 678 subjects who received DOR or DOR/3TC/TDF in the Phase 1 trials were healthy adult subjects with no secondary diagnoses. P019 included a cohort of 8 subjects with moderate hepatic insufficiency (a score of 7 to 9 on the Child-Pugh scale), and P051 included a cohort of 8 subjects with severe renal insufficiency (estimated glomerular filtration rate of <30 mL/min/1.73 m^2) [Ref. 5.3.3.3: P019: 9.3.1] [Ref. 5.3.3.3: P051MK1439: 9.3.1]. Twelve subjects in P005 were treatment naïve HIV-1 infected subjects [Ref. 5.3.4.1: P005V01: 9.3.1].

Overall, the percentage of male and female subjects was 62.1% and 37.9%, respectively. The mean age was 39.5 years (range 19 to 78 years). The largest percentage of subjects was white (62.9%) followed by black or African American (29.6%), Asian (3.7%), and multi-racial (3.1%) [Table 5.3.5.3.1-trtmtnve48wk: 6].

Baseline demographic data [Table 5.3.5.3.1-trtmtnve48wk: 6] from the 36 pooled Phase 1 clinical pharmacology trials are summarized in the CPSOS [Sec. 5.3.5.3.1-trtmtnve48wk].

Descriptions of Phase 1 clinical pharmacology trials can be found in [Sec. 2.7.1] and [Sec. 2.7.2].

Phase 2 and Phase 3 Trials

Baseline Demographic Characteristics

Demographic and baseline disease characteristics for subjects in the individual trials (P007, P018, and P021) can be found in [Ref. 5.3.5.1: P007V01MK1439: Table 10-8], [Ref. 5.3.5.1: P018V01MK1439: Table 10-5], and [Ref. 5.3.5.1: P021V01MK1439A: Table 10-5].

Main Safety Pool

Overall, the integrated treatment groups were generally well balanced with respect to demographic baseline characteristics [Table 2.7.4: 9]. There was a higher proportion of males compared with females in all 3 treatment groups. Demographics and baseline characteristics were consistent across the 3 groups with regard to gender and age. There was a higher proportion of white and Asian subjects for the Main Combined DOR and the Main Combined EFV groups compared with the Main DRV+r. The higher proportion of Asian is explained due to increased enrollment in Asia in P021. The higher proportion of whites is explained due to enrollment in the US and Europe for both trials.

Special Safety Pool

The demographic and baseline disease characteristics for the subjects in the SSP were similar to those subjects in the MSP [Table 2.7.4: 10].

Table 2.7.4: 9
Subject Baseline Characteristics
Main Safety Pool (P007 (DOR 100 mg q.d. Group) and P018 and P021 Combined)

	Main Combined DOR (N = 855)	Main DRV+r (N = 383)	Main Combined EFV (N = 472)
Gender n (%)			
Male	723 (84.6)	326 (85.1)	412 (87.3)
Female	132 (15.4)	57 (14.9)	60 (12.7)
Race n (%)			
American Indian or Alaska Native	13 (1.5)	3 (0.8)	6 (1.3)
Asian	71 (8.3)	7 (1.8)	67 (14.2)
Black or African American	169 (19.8)	88 (23.0)	85 (18.0)
Multiple	57 (6.7)	2 (0.5)	57 (12.1)
Native Hawaiian or Other Pacific Islander	1 (0.1)	2 (0.5)	0 (0.0)
White	543 (63.5)	280 (73.1)	257 (54.4)
Missing	1 (0.1)	1 (0.3)	0 (0.0)
Ethnicity n (%)			
Hispanic or Latino	234 (27.4)	86 (22.5)	137 (29.0)
Not Hispanic or Latino	610 (71.3)	290 (75.7)	328 (69.5)
Unknown	11 (1.3)	7 (1.8)	7 (1.5)
Region n (%)			
Africa	60 (7.0)	22 (5.7)	27 (5.7)
Asia/Pacific	80 (9.4)	3 (0.8)	72 (15.3)
Europe	323 (37.8)	179 (46.7)	148 (31.4)
Latin America	127 (14.9)	33 (8.6)	87 (18.4)
North America	265 (31.0)	146 (38.1)	138 (29.2)
Age (years)			
18 to 64	850 (99.4)	379 (99.0)	470 (99.6)
>=65	5 (0.6)	4 (1.0)	2 (0.4)
Mean (SD)	34.5 (10.6)	35.7 (10.7)	33.2 (9.8)
Median (min, max)	32.0 (18, 70)	34.0 (18, 69)	31.0 (18, 69)
Baseline CD4 Cell Count (cells/mm^3)			
N†	855	383	472
Mean (SD)	433.5 (209.7)	411.9 (229.6)	422.9 (206.0)
Median (min, max)	410.0 (19, 1822)	393.0 (19, 1303)	393.5 (19, 1452)
Baseline CD4 Cell Counts n (%)			
<=50 cells/mm^3	15 (1.8)	19 (5.0)	10 (2.1)
>50 cells/mm^3 and <=200 cells/mm^3	78 (9.1)	48 (12.5)	46 (9.7)
>200 cells/mm^3	762 (89.1)	316 (82.5)	416 (88.1)
Baseline Plasma HIV-1 RNA (log_{10} copies/mL)			
N†	855	382	472
Mean (SD)	4.4 (0.7)	4.4 (0.7)	4.5 (0.7)
Median (min, max)	4.4 (2.0, 6.5)	4.4 (2.4, 6.5)	4.5 (2.6, 6.7)

Subject Baseline Characteristics
Main Safety Pool (P007 (DOR 100 mg q.d. Group) and P018 and P021 Combined)

	Main Combined DOR (N = 855)	Main DRV+r (N = 383)	Main Combined EFV (N = 472)
Baseline Plasma HIV-1 RNA (copies/mL)			
N[†]	855	382	472
Geometric Mean	26892.1	26630.5	31279.8
Median (min, max)	26458.0 (105, 3106564)	27357.0 (235, 3272236)	31302.0 (403, 4631008)
Baseline Plasma HIV-1 RNA n (%)			
<=100,000 copies/mL	664 (77.7)	308 (80.4)	358 (75.8)
>100,000 copies/mL	191 (22.3)	74 (19.3)	114 (24.2)
Missing	0 (0.0)	1 (0.3)	0 (0.0)
Baseline Plasma HIV-1 RNA n (%)			
<=500,000 copies/mL	817 (95.6)	370 (96.6)	446 (94.5)
>500,000 copies/mL	38 (4.4)	12 (3.1)	26 (5.5)
Missing	0 (0.0)	1 (0.3)	0 (0.0)
History of AIDS n (%)			
Yes	86 (10.1)	37 (9.7)	60 (12.7)
No	769 (89.9)	346 (90.3)	412 (87.3)
Stratum n (%)			
Screening HIV-1 RNA<= 100,000	635 (74.3)	289 (75.5)	342 (72.5)
Screening HIV-1 RNA> 100,000	220 (25.7)	94 (24.5)	130 (27.5)
Baseline Hepatitis Status[††]			
Hep B and/or C Positive	22 (2.6)	18 (4.7)	9 (1.9)
Hep B Positive Only	13 (1.5)	12 (3.1)	8 (1.7)
Hep C Positive Only	9 (1.1)	6 (1.6)	1 (0.2)
Hep B and C Negative	833 (97.4)	365 (95.3)	463 (98.1)
Viral Subtype n (%)			
Clade B	573 (67.0)	272 (71.0)	339 (71.8)
Non-Clade B	280 (32.7)	111 (29.0)	133 (28.2)
Missing	2 (0.2)	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. P007 did not allow active hepatitis B and/or C positive subjects to be enrolled. Subjects with non-reactive hepatitis B surface antigen test and undetectable HCV RNA PCR test or without such tests were classified as hepatitis B and C negative.

Main Combined DOR: DOR 100 mg administered with FTC/TDF in P007 and P018 or ABC/3TC in P018, or fixed dose combination of DOR/ 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: EFV 600 mg administered with FTC/TDF in P007, or fixed dose combination of EFV/emtricitabine/tenofovir disoproxil fumarate 600/200/300 mg in P021.

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

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

Source: [ISS: analysis-adsl]

Table 2.7.4: 10
Subject Baseline Characteristics
Special Safety Pool (P007 (DOR 100 mg q.d. Group) and P021 Combined)

	Special Combined DOR (N = 472)	Special Combined EFV (N = 472)
Gender n (%)		
Male	404 (85.6)	412 (87.3)
Female	68 (14.4)	60 (12.7)
Race n (%)		
American Indian or Alaska Native	10 (2.1)	6 (1.3)
Asian	64 (13.6)	67 (14.2)
Black or African American	83 (17.6)	85 (18.0)
Multiple	51 (10.8)	57 (12.1)
White	263 (55.7)	257 (54.4)
Missing	1 (0.2)	0 (0.0)
Ethnicity n (%)		
Hispanic or Latino	141 (29.9)	137 (29.0)
Not Hispanic or Latino	326 (69.1)	328 (69.5)
Unknown	5 (1.1)	7 (1.5)
Region n (%)		
Africa	37 (7.8)	27 (5.7)
Asia/Pacific	68 (14.4)	72 (15.3)
Europe	153 (32.4)	148 (31.4)
Latin America	89 (18.9)	87 (18.4)
North America	125 (26.5)	138 (29.2)
Age (years)		
18 to 64	469 (99.4)	470 (99.6)
>=65	3 (0.6)	2 (0.4)
Mean (SD)	34.3 (10.7)	33.2 (9.8)
Median (min, max)	32.0 (18, 70)	31.0 (18, 69)
Baseline CD4 Cell Count (cells/mm^3)		
N†	472	472
Mean (SD)	434.2 (211.0)	422.9 (206.0)
Median (min, max)	410.5 (19, 1399)	393.5 (19, 1452)
Baseline CD4 Cell Counts n (%)		
<=50 cells/mm^3	9 (1.9)	10 (2.1)
>50 cells/mm^3 and <=200 cells/mm^3	42 (8.9)	46 (9.7)
>200 cells/mm^3	421 (89.2)	416 (88.1)
Baseline Plasma HIV-1 RNA (log_{10} copies/mL)		
N†	472	472
Mean (SD)	4.4 (0.7)	4.5 (0.7)
Median (min, max)	4.4 (2.4, 6.5)	4.5 (2.6, 6.7)

Subject Baseline Characteristics
Special Safety Pool (P007 (DOR 100 mg q.d. Group) and P021 Combined)

	Special Combined DOR (N = 472)	Special Combined EFV (N = 472)
Baseline Plasma HIV-1 RNA (copies/mL)		
N[†]	472	472
Geometric Mean	26871.4	31279.8
Median (min, max)	25955.5 (259, 3106564)	31302.0 (403, 4631008)
Baseline Plasma HIV-1 RNA n (%)		
<=100,000 copies/mL	364 (77.1)	358 (75.8)
>100,000 copies/mL	108 (22.9)	114 (24.2)
Baseline Plasma HIV-1 RNA n (%)		
<=500,000 copies/mL	451 (95.6)	446 (94.5)
>500,000 copies/mL	21 (4.4)	26 (5.5)
History of AIDS n (%)		
Yes	50 (10.6)	60 (12.7)
No	422 (89.4)	412 (87.3)
Stratum n (%)		
Screening HIV-1 RNA<= 100,000	345 (73.1)	342 (72.5)
Screening HIV-1 RNA> 100,000	127 (26.9)	130 (27.5)
Baseline Hepatitis Status[††]		
Hep B and/or C Positive	11 (2.3)	9 (1.9)
Hep B Positive Only	9 (1.9)	8 (1.7)
Hep C Positive Only	2 (0.4)	1 (0.2)
Hep B and C Negative	461 (97.7)	463 (98.1)
Viral Subtype n (%)		
Clade B	307 (65.0)	339 (71.8)
Non-Clade B	163 (34.5)	133 (28.2)
Missing	2 (0.4)	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. P007 did not allow active hepatitis B and/or C positive subjects to be enrolled. Subjects with non-reactive hepatitis B surface antigen test and undetectable HCV RNA PCR test or without such tests were classified as hepatitis B and C negative.

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

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

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

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

Source: [ISS: analysis-adsl]

Medical History

The proportion of subjects with medical history in the individual trials (P007, P018, P021) can be found in [Ref. 5.3.5.1: P007V01MK1439: Table 10-9] [Ref. 5.3.5.1: P018V01MK1439: Table 10-6] [Ref. 5.3.5.1: P021V01MK1439A: Table 10-6].

Main Safety Pool

Overall, proportions of subjects with secondary diagnoses were similar across treatment groups in the MSP. The most commonly reported medical history conditions in the 3 treatment groups were syphilis, acquired immunodeficiency syndrome (AIDS), and hypertension. Numbers and percentages of subjects with medical history present in ≥5% of subjects in any treatment group and in ≥0% of subjects in each treatment group in the MSP are presented in [Table 5.3.5.3.3-trtmtnve48wk: 9] and [Table 5.3.5.3.3-trtmtnve48wk: 10].

Special Safety Pool

The proportion of subjects with secondary diagnoses overall were similar across treatment groups in the SSP. The medical history of the subjects in the SSP was similar to that of the subjects in the MSP, as these subjects are also part of the MSP.

Numbers and percentages of subjects with medical history present in ≥5% of subjects in either treatment group and in >0% of subjects in either treatment group in the SSP are presented in [Table 5.3.5.3.3-trtmtnve48wk: 11], and [Table 5.3.5.3.3-trtmtnve48wk: 12].

Prior Medications

The proportion of subjects with any prior medications in the individual trials (P007, P018, P021) can be found in [Ref. 5.3.5.1: P007V01MK1439: Table 10-11] [Ref. 5.3.5.1: P018V01MK1439: Table 10-7] [Ref. 5.3.5.1: P021V01MK1439A: Table 10-7].

Main Safety Pool

Similar proportions of subjects in each main treatment group received 1 or more prior medications in the MSP (Main Combined DOR [57.4%], Main DVR+r [55.6%] Main Combined EFV [57.6%]) [Table 2.7.4: 11] [Table 5.3.5.3.3-trtmtnve48wk: 14].

Although some differences were observed between treatments groups in proportions of subjects who reported specific medications, these differences were not considered to be clinically important. The most commonly reported prior medications in the Main Combined DOR, Main DVR+r and Main Combined EFV treatment groups were in the classes of antibacterials for systemic use, analgesics, and anti-inflammatory and anti-rheumatic products.

Table 2.7.4: 11
Subjects With Specific Prior Medications
(Incidence ≥5% in One or More Treatment Groups)
Main Safety Pool (P007 (DOR 100 mg q.d. Group) and P018 and P021 Combined)

	Main Combined DOR		Main DRV+r		Main Combined EFV	
	n	(%)	n	(%)	n	(%)
Subjects in population	855		383		472	
With one or more prior medications	491	(57.4)	213	(55.6)	272	(57.6)
With no prior medication	364	(42.6)	170	(44.4)	200	(42.4)
alimentary tract and metabolism						
drugs for acid related disorders	**34**	**(4.0)**	**23**	**(6.0)**	**19**	**(4.0)**
vitamins	**112**	**(13.1)**	**62**	**(16.2)**	**67**	**(14.2)**
vitamins (unspecified)	52	(6.1)	26	(6.8)	26	(5.5)
antiinfectives for systemic use						
antibacterials for systemic use	**157**	**(18.4)**	**83**	**(21.7)**	**94**	**(19.9)**
azithromycin	28	(3.3)	23	(6.0)	9	(1.9)
sulfamethoxazole (+) trimethoprim	58	(6.8)	36	(9.4)	31	(6.6)
vaccines	**51**	**(6.0)**	**18**	**(4.7)**	**32**	**(6.8)**
musculoskeletal system						
antiinflammatory and antirheumatic products	**71**	**(8.3)**	**29**	**(7.6)**	**39**	**(8.3)**
ibuprofen	46	(5.4)	18	(4.7)	22	(4.7)
nervous system						
analgesics	**85**	**(9.9)**	**38**	**(9.9)**	**63**	**(13.3)**
acetaminophen	38	(4.4)	11	(2.9)	32	(6.8)
psychoanaleptics	**47**	**(5.5)**	**21**	**(5.5)**	**23**	**(4.9)**
psycholeptics	**48**	**(5.6)**	**23**	**(6.0)**	**33**	**(7.0)**
respiratory system						
antihistamines for systemic use	**49**	**(5.7)**	**23**	**(6.0)**	**31**	**(6.6)**
drugs for obstructive airway diseases	**33**	**(3.9)**	**31**	**(8.1)**	**15**	**(3.2)**

Every subject is counted a single time for each applicable specific prior medication. A subject with multiple prior medications within a medication category is counted a single time for that category.

A medication class or specific medication 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: DOR 100 mg administered with FTC/TDF in P007 and P018 or ABC/3TC in P018, or fixed dose combination of DOR/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: EFV 600 mg administered with FTC/TDF in P007, or fixed dose combination of EFV/emtricitabine/tenofovir disoproxil fumarate 600/200/300 mg in P021.

Source: [ISS: analysis-adsl; cmplus]

Special Safety Pool

A similar distribution of subjects in both treatment groups in the SSP reported specific prior medications (Special Combined DOR: 60.4%, Special Combined EFV: 57.6%) [Table 2.7.4: 12] [Table 5.3.5.3.3-trtmtnve48wk: 16]. No clinically important differences were observed between treatment groups in the proportion of subjects with any prior therapy or in the proportions of subjects with specific prior medications.

Table 2.7.4: 12
Subjects With Specific Prior Medications
(Incidence ≥5% in One or More Treatment Groups)
Special Safety Pool (P007 (DOR 100 mg q.d. Group) and P021 Combined)

	Special Combined DOR		Special Combined EFV	
	n	(%)	n	(%)
Subjects in population	472		472	
With one or more prior medications	285	(60.4)	272	(57.6)
With no prior medication	187	(39.6)	200	(42.4)
alimentary tract and metabolism				
vitamins	**57**	**(12.1)**	**67**	**(14.2)**
vitamins (unspecified)	20	(4.2)	26	(5.5)
antiinfectives for systemic use				
antibacterials for systemic use	**87**	**(18.4)**	**94**	**(19.9)**
sulfamethoxazole (+) trimethoprim	32	(6.8)	31	(6.6)
vaccines	**37**	**(7.8)**	**32**	**(6.8)**
cardiovascular system				
lipid modifying agents	**24**	**(5.1)**	**17**	**(3.6)**
genitourinary system and sex hormones				
sex hormones and modulators of the genital system	**25**	**(5.3)**	**17**	**(3.6)**
musculoskeletal system				
antiinflammatory and antirheumatic products	**43**	**(9.1)**	**39**	**(8.3)**
ibuprofen	24	(5.1)	22	(4.7)
nervous system				
analgesics	**53**	**(11.2)**	**63**	**(13.3)**
acetaminophen	27	(5.7)	32	(6.8)
psychoanaleptics	**28**	**(5.9)**	**23**	**(4.9)**
psycholeptics	**29**	**(6.1)**	**33**	**(7.0)**
respiratory system				
antihistamines for systemic use	**29**	**(6.1)**	**31**	**(6.6)**

Every subject is counted a single time for each applicable specific prior medication. A subject with multiple prior medications within a medication category is counted a single time for that category.
A medication class or specific medication 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.
Special Combined DOR: DOR 100 mg administered with FTC/TDF in P007, or fixed dose combination of DOR/lamivudine/tenofovir disoproxil fumarate 100/300/300 mg in P021.
Special Combined EFV: EFV 600 mg administered with FTC/TDF in P007, or fixed dose combination of EFV/emtricitabine/tenofovir disoproxil fumarate 600/200/300 mg in P021.

Source: [ISS: analysis-adsl; cmplus]

Concomitant Medications

The proportion of subjects with any concomitant medications in P007, P018, and P021 can be found in [Ref. 5.3.5.1: P007V01MK1439: Table 10-13] [Ref. 5.3.5.1: P018V01MK1439: Table 10-8] [Ref. 5.3.5.1: P021V01MK1439A: Table 10-8].

Main Safety Pool

Most subjects in the Main Combined DOR, Main DRV+r, and Main Combined EFV treatment groups (84.9%, 79.6%, and 87.9%, respectively) received concomitant medications [Table 2.7.4: 13] [Table 5.3.5.3.3-trtmtnve48wk: 18].

No clinically important differences between treatment groups in the proportions of subjects with any concomitant therapy or with specific concomitant therapies were observed. The most commonly reported classes of concomitant therapies in the 3 treatment groups were systemic antibacterials, analgesics, and vaccines. Antivirals for systemic use were all similarly taken by subjects in the Main Combined DOR, Main DRV+r, and Main Combined EFV treatment groups (12.2%, 12.8%, and 15.3%, respectively). While some differences were observed between treatments groups in proportions of subjects who reported concomitant medication use, these differences were not considered being clinically important.

Special Safety Pool

In the SSP, the proportion of subjects with any concomitant therapy or in the proportions of subjects with specific concomitant therapies [Table 2.7.4: 14] [Table 5.3.5.3.3-trtmtnve48wk: 20] were generally similar to those in the MSP [Table 2.7.4: 13] [Table 5.3.5.3.3-trtmtnve48wk: 18]. There were no clinically important differences between treatment groups in the SSP in the proportions of subjects with any concomitant therapy or in the proportions of subjects with specific concomitant therapies.

Table 2.7.4: 13
Subjects With Specific Concomitant Medications
(Incidence ≥5% in One or More Treatment Groups)
Main Safety Pool (P007 (DOR 100 mg q.d. Group) and P018 and P021 Combined)

	Main Combined DOR		Main DRV+r		Main Combined EFV	
	n	(%)	n	(%)	n	(%)
Subjects in population	855		383		472	
With one or more concomitant medications	726	(84.9)	305	(79.6)	415	(87.9)
With no concomitant medication	129	(15.1)	78	(20.4)	57	(12.1)
alimentary tract and metabolism						
antidiarrheals, intestinal antiinflammatory/antiinfective agents	**67**	**(7.8)**	**24**	**(6.3)**	**33**	**(7.0)**
drugs for acid related disorders	**94**	**(11.0)**	**42**	**(11.0)**	**55**	**(11.7)**
drugs for functional gastrointestinal disorders	**45**	**(5.3)**	**14**	**(3.7)**	**29**	**(6.1)**
vitamins	**159**	**(18.6)**	**81**	**(21.1)**	**82**	**(17.4)**
vitamins (unspecified)	58	(6.8)	34	(8.9)	32	(6.8)
antiinfectives for systemic use						
antibacterials for systemic use	**378**	**(44.2)**	**161**	**(42.0)**	**219**	**(46.4)**
amoxicillin	66	(7.7)	32	(8.4)	48	(10.2)
amoxicillin (+) clavulanate potassium	45	(5.3)	22	(5.7)	35	(7.4)
azithromycin	93	(10.9)	42	(11.0)	53	(11.2)
doxycycline	46	(5.4)	12	(3.1)	20	(4.2)
sulfamethoxazole (+) trimethoprim	66	(7.7)	45	(11.7)	37	(7.8)
antimycotics for systemic use	**24**	**(2.8)**	**21**	**(5.5)**	**9**	**(1.9)**
fluconazole	22	(2.6)	21	(5.5)	9	(1.9)
antivirals for systemic use	**104**	**(12.2)**	**49**	**(12.8)**	**72**	**(15.3)**
vaccines	**217**	**(25.4)**	**73**	**(19.1)**	**128**	**(27.1)**
influenza virus split virion 3v vaccine inactivated	27	(3.2)	5	(1.3)	25	(5.3)
influenza virus vaccine (unspecified)	72	(8.4)	29	(7.6)	50	(10.6)
cardiovascular system						
agents acting on the renin-angiotensin system	**54**	**(6.3)**	**20**	**(5.2)**	**21**	**(4.4)**
lipid modifying agents	**48**	**(5.6)**	**24**	**(6.3)**	**30**	**(6.4)**
dermatologicals						
antifungals for dermatological use	**73**	**(8.5)**	**39**	**(10.2)**	**36**	**(7.6)**
corticosteroids, dermatological preparations	**52**	**(6.1)**	**24**	**(6.3)**	**25**	**(5.3)**
genitourinary system and sex hormones						
sex hormones and modulators of the genital system	**42**	**(4.9)**	**16**	**(4.2)**	**25**	**(5.3)**
musculoskeletal system						

Subjects With Specific Concomitant Medications
(Incidence ≥5% in One or More Treatment Groups)
Main Safety Pool (P007 (DOR 100 mg q.d. Group) and P018 and P021 Combined)

	Main Combined DOR		Main DRV+r		Main Combined EFV	
	n	(%)	n	(%)	n	(%)
musculoskeletal system						
antiinflammatory and antirheumatic products	**211**	**(24.7)**	**92**	**(24.0)**	**113**	**(23.9)**
ibuprofen	136	(15.9)	61	(15.9)	73	(15.5)
nervous system						
analgesics	**311**	**(36.4)**	**126**	**(32.9)**	**159**	**(33.7)**
acetaminophen	201	(23.5)	62	(16.2)	101	(21.4)
psychoanaleptics	**78**	**(9.1)**	**37**	**(9.7)**	**48**	**(10.2)**
psycholeptics	**99**	**(11.6)**	**46**	**(12.0)**	**80**	**(16.9)**
respiratory system						
antihistamines for systemic use	**145**	**(17.0)**	**66**	**(17.2)**	**117**	**(24.8)**
cetirizine hydrochloride	29	(3.4)	21	(5.5)	35	(7.4)
loratadine	43	(5.0)	8	(2.1)	29	(6.1)
cough and cold preparations	**97**	**(11.3)**	**32**	**(8.4)**	**48**	**(10.2)**
drugs for obstructive airway diseases	**65**	**(7.6)**	**42**	**(11.0)**	**41**	**(8.7)**
albuterol	25	(2.9)	19	(5.0)	15	(3.2)
systemic hormonal preparations, excl. sex hormones and insulins						
corticosteroids for systemic use	**67**	**(7.8)**	**23**	**(6.0)**	**58**	**(12.3)**
various						
all other therapeutic products	**58**	**(6.8)**	**23**	**(6.0)**	**36**	**(7.6)**

Every subject is counted a single time for each applicable specific concomitant medication. A subject with multiple concomitant medications within a medication category is counted a single time for that category.

A medication class or specific medication 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: DOR 100 mg administered with FTC/TDF in P007 and P018 or ABC/3TC in P018, or fixed dose combination of DOR/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: EFV 600 mg administered with FTC/TDF in P007, or fixed dose combination of EFV/emtricitabine/tenofovir disoproxil fumarate 600/200/300 mg in P021.

Source: [ISS: analysis-adsl; cmplus]

Table 2.7.4: 14
Subjects With Specific Concomitant Medications
(Incidence ≥5% in One or More Treatment Groups)
Special Safety Pool (P007 (DOR 100 mg q.d. Group) and P021 Combined)

	Special Combined DOR		Special Combined EFV	
	n	(%)	n	(%)
Subjects in population	472		472	
With one or more concomitant medications	410	(86.9)	415	(87.9)
With no concomitant medication	62	(13.1)	57	(12.1)
alimentary tract and metabolism				
antidiarrheals, intestinal antiinflammatory/antiinfective agents	**37**	**(7.8)**	**33**	**(7.0)**
drugs for acid related disorders	**46**	**(9.7)**	**55**	**(11.7)**
drugs for functional gastrointestinal disorders	**25**	**(5.3)**	**29**	**(6.1)**
vitamins	**89**	**(18.9)**	**82**	**(17.4)**
vitamins (unspecified)	23	(4.9)	32	(6.8)
antiinfectives for systemic use				
antibacterials for systemic use	**215**	**(45.6)**	**219**	**(46.4)**
amoxicillin	38	(8.1)	48	(10.2)
amoxicillin (+) clavulanate potassium	30	(6.4)	35	(7.4)
azithromycin	57	(12.1)	53	(11.2)
doxycycline	26	(5.5)	20	(4.2)
sulfamethoxazole (+) trimethoprim	38	(8.1)	37	(7.8)
antivirals for systemic use	**71**	**(15.0)**	**72**	**(15.3)**
vaccines	**133**	**(28.2)**	**128**	**(27.1)**
influenza virus split virion 3v vaccine inactivated	18	(3.8)	25	(5.3)
influenza virus vaccine (unspecified)	41	(8.7)	50	(10.6)
cardiovascular system				
agents acting on the renin-angiotensin system	**27**	**(5.7)**	**21**	**(4.4)**
lipid modifying agents	**28**	**(5.9)**	**30**	**(6.4)**
dermatologicals				
antifungals for dermatological use	**42**	**(8.9)**	**36**	**(7.6)**
corticosteroids, dermatological preparations	**35**	**(7.4)**	**25**	**(5.3)**
genitourinary system and sex hormones				
sex hormones and modulators of the genital system	**30**	**(6.4)**	**25**	**(5.3)**
musculoskeletal system				
antiinflammatory and antirheumatic products	**126**	**(26.7)**	**113**	**(23.9)**
ibuprofen	76	(16.1)	73	(15.5)
nervous system				
analgesics	**188**	**(39.8)**	**159**	**(33.7)**
acetaminophen	125	(26.5)	101	(21.4)
anesthetics	**24**	**(5.1)**	**18**	**(3.8)**
psychoanaleptics	**48**	**(10.2)**	**48**	**(10.2)**
psycholeptics	**51**	**(10.8)**	**80**	**(16.9)**

Subjects With Specific Concomitant Medications
(Incidence ≥5% in One or More Treatment Groups)
Special Safety Pool (P007 (DOR 100 mg q.d. Group) and P021 Combined)

	Special Combined DOR		Special Combined EFV	
	n	(%)	n	(%)
respiratory system				
antihistamines for systemic use	**79**	**(16.7)**	**117**	**(24.8)**
cetirizine hydrochloride	15	(3.2)	35	(7.4)
loratadine	27	(5.7)	29	(6.1)
cough and cold preparations	**64**	**(13.6)**	**48**	**(10.2)**
drugs for obstructive airway diseases	**40**	**(8.5)**	**41**	**(8.7)**
nasal preparations	**30**	**(6.4)**	**20**	**(4.2)**
systemic hormonal preparations, excl. sex hormones and insulins				
corticosteroids for systemic use	**45**	**(9.5)**	**58**	**(12.3)**
various				
all other therapeutic products	**34**	**(7.2)**	**36**	**(7.6)**

Every subject is counted a single time for each applicable specific concomitant medication. A subject with multiple concomitant medications within a medication category is counted a single time for that category.

A medication class or specific medication 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.

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

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

Source: [ISS: analysis-adsl; cmplus]

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2 ADVERSE EVENTS

2.1 Overview of Adverse Events in the Phase 1 Trials

In the Phase 1 trials, DOR and DOR/3TC/TDF, given as single or multiple doses, alone or co-administered with other therapies, were generally well tolerated with no safety issues identified. No deaths occurred. Three treatment-emergent SAEs were reported following treatment with DOR; 2 were considered to be not related to trial drug by the investigator and 1 (spontaneous abortion) was considered to be related to trial drug. The spontaneous abortion occurred approximately 27 days after the last dose of study drug. The subject's medical history included 7 pregnancies, the outcomes of which were 5 live births, 1 premature birth, and 1 spontaneous abortion. The subject was enrolled into the trial because of having a negative pregnancy screen at the screening visit. Because the subject was pregnant when dosed with all 3 study medications (doravirine, elbasvir, grazoprevir) and there was no identified cause of the fetal loss, relationship of the spontaneous abortion to study drugs could not be ruled out. Therefore, the investigator reported the SAE of spontaneous abortion as being related to doravirine, elbasvir and grazoprevir.

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]). Narratives for the 2 unrelated SAEs can be found in the individual CSRs ([Ref. 5.3.4.1: P005V01: 16.2.7.3], [Ref. 5.3.3.1: P006MK1439: 16.2.7.3]).

Seven subjects discontinued study drug due to a drug-related AE; 1 was considered to be related to DOR alone (headache) and 6 were considered to be related to other trial drugs. See [Table 5.3.5.3.1-trtmtnve48wk: 17] for a listing of all subjects who discontinued due to an AE.

Most reported AEs were transient in nature and rated mild to moderate in intensity. No clear dose-related trends were observed for specific AEs. There may be a trend for an increased incidence of nausea at higher doses of DOR (≥ 200 mg); however, the small sample size in each dose group limit interpretation of these results. The most commonly reported AEs (incidence ≥ 5%) following administration of DOR, DOR/3TC/TDF and DOR + other trial drugs were headache (12.2%) and somnolence (5.3%). Within these dose groups, no other AE was reported for ≥ 5% of subjects. The most commonly reported AE following administration of placebo was headache (16.9%). No other AE was reported for ≥ 5% of subjects in the placebo group [Table 5.3.5.3.1-trtmtnve48wk:13].

A total of 202 (28.9%) subjects reported at least 1 AE that was 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%). Following administration of placebo, the most common drug-related AE was headache (13.3%) [Table 5.3.5.3.1-trtmtnve48wk: 15].

Refer to the CPSOS in [Sec. 5.3.5.3.1-trtmtnve48wk] for a detailed discussion of safety for the Phase 1 clinical pharmacology trials.

2.2 Adverse Events in P007 (Phase 2b Dose-Ranging Trial)

2.2.1 Common Adverse Events

In Part I of P007, the overall safety profile at Week 24 was similar for each of the DOR groups [Ref. 5.3.5.1: P007V01MK1439: Table 12-6]. No evidence of dose related toxicity was observed. Drug-related AEs were reported for a lower proportion of subjects in each of the DOR dose groups (range: 16.7% to 46.5% and 36.7% combined) compared with EFV (57.1%). Overall, the proportion of subjects who discontinued due to drug-related AEs was low (range: 0 to 4.7% for individual doses and 2.4% for DOR combined versus 4.8% for EFV).

At Week 96, the proportion of subjects with 1 or more AEs was comparable across the individual DOR treatment groups, and between the DOR Combined treatment group (91.4%) and the EFV treatment group (96. 3%) [Table 2.7.4: 15].

A lower proportion of subjects with drug-related AEs were observed at Week 96 for any DOR group (DOR Combined 41.4%) compared with the EFV group (58.3%). For the DOR Combined group, a lower proportion of subjects reported SAEs (8.2%) compared with the EFV group (12%), and a lower observed proportion of subjects in the DOR Combined group (4.7%) discontinued from the study due to an AE than in the EFV group (10.2%). No drug-related SAEs were reported in any of the DOR treatment groups, compared with 2.8% of subjects in the EFV group. One subject was discontinued from the trial due to serious drug-related AEs in the EFV treatment group (0.9%). No subjects died during the trial.

Table 2.7.4: 15
Adverse Event Summary
Part I/II Combined (Doravirine All Doses vs. Efavirenz; Weeks 0-96)
All Subjects as Treated (P007)

	Doravirine 25 mg		Doravirine 50 mg		Doravirine 100 mg		Doravirine 200 mg		Doravirine Combined		Efavirenz 600 mg		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	40		43		108		41		232		108		340	
With one or more adverse events	38	(95.0)	41	(95.3)	97	(89.8)	36	(87.8)	212	(91.4)	104	(96.3)	316	(92.9)
With no adverse event	2	(5.0)	2	(4.7)	11	(10.2)	5	(12.2)	20	(8.6)	4	(3.7)	24	(7.1)
With drug-related[†] adverse events	18	(45.0)	21	(48.8)	38	(35.2)	19	(46.3)	96	(41.4)	63	(58.3)	159	(46.8)
With serious adverse events	4	(10.0)	1	(2.3)	11	(10.2)	3	(7.3)	19	(8.2)	13	(12.0)	32	(9.4)
With serious drug-related adverse events	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	3	(2.8)	3	(0.9)
Who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Discontinued due to adverse events	1	(2.5)	4	(9.3)	5	(4.6)	1	(2.4)	11	(4.7)	11	(10.2)	22	(6.5)
Discontinued due to drug-related adverse events	1	(2.5)	2	(4.7)	2	(1.9)	0	(0.0)	5	(2.2)	10	(9.3)	15	(4.4)
Discontinued due to serious adverse events	0	(0.0)	0	(0.0)	3	(2.8)	1	(2.4)	4	(1.7)	1	(0.9)	5	(1.5)
Discontinued due to serious drug-related adverse events	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.9)	1	(0.3)

[†]Determined by the investigator to be drug related.
Note: Both doravirine and efavirenz were administered with TRUVADA™.

Source: [P007V01MK1439: analysis-adsl; adae]

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Overall, the most commonly (≥5% of subjects) reported AEs for DOR were nasopharyngitis, diarrhea, nausea, headache, and dizziness [Ref. 5.3.5.1: P007V01MK1439: Table 14.3-10]. The proportion of subjects reporting dizziness was substantially different between treatment groups: DOR Combined: 12.5% vs EFV: 29.6% [treatment difference -17.1% (-27.1, -8.0)] [Ref. 5.3.5.1: P007V01MK1439: Table 14.3-8]. No other meaningful clinical differences were observed between the treatment groups.

The number and percentage of subjects with AEs through Week 96 with an incidence >0% in 1 or more treatment groups is provided in [Ref. 5.3.5.1: P007V01MK1439: Table 14.3-9]. The number and percentage of subjects with AEs by intensity through Week 96 with an incidence >0% or ≥5% in 1 or more treatment groups is provided in [Ref. 5.3.5.1: P007V01MK1439: Table 14.3-11] and [Ref. 5.3.5.1: P007V01MK1439: Table 14.3-12], respectively.

Drug-Related Adverse Events (Overall)

By Week 96 in P007, the observed proportion of subjects with drug-related AEs was lower in the DOR Combined treatment group (41.4%) compared with the EFV treatment group (58.3%); the lowest proportion of subjects with drug-related AEs was observed in the DOR 100 mg treatment group (35.2%) [Ref. 5.3.5.1: P007V01MK1439: Table 14.3-14] [Table 2.7.4: 16]. Overall, the most commonly reported drug-related AEs for DOR were dizziness, abnormal dreams, and nightmare but they were consistently lower for the DOR Combined treatment group compared to the EFV treatment group, especially dizziness (DOR Combined 5.6% vs EFV 26.9%) and abnormal dreams (DOR Combined 9.1% vs EFV 14.8%).

Adverse events that were considered by the investigator to be drug-related and moderate or severe in intensity were experienced by fewer subjects in the DOR Combined treatment group (13.8%), compared to the EFV treatment group (30.6%) [Ref. 5.3.5.1: P007V01MK1439: Table 14.3-16]. The most common drug-related AE by Week 96 (incidence ≥2%) that was considered by the investigator to be moderate or severe in intensity for the DOR treatment group was insomnia.

Table 2.7.4: 16
Subjects With Drug-Related Adverse Events - Overall:
Related to Blinded Therapy With Doravirine or Efavirenz or Open-Label TRUVADA™
(Incidence ≥5% in One or More Treatment Groups) by System Organ Class
Part I/II Combined (Doravirine All Doses vs. Efavirenz; Weeks 0-96)
All Subjects as Treated (P007)

	Doravirine 25 mg		Doravirine 50 mg		Doravirine 100 mg		Doravirine 200 mg		Doravirine Combined		Efavirenz 600 mg		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	40		43		108		41		232		108		340	
With one or more drug-related adverse events	18	(45.0)	21	(48.8)	38	(35.2)	19	(46.3)	96	(41.4)	63	(58.3)	159	(46.8)
With no drug-related adverse events	22	(55.0)	22	(51.2)	70	(64.8)	22	(53.7)	136	(58.6)	45	(41.7)	181	(53.2)
Gastrointestinal disorders	6	(15.0)	8	(18.6)	12	(11.1)	7	(17.1)	33	(14.2)	20	(18.5)	53	(15.6)
Diarrhoea	4	(10.0)	1	(2.3)	1	(0.9)	2	(4.9)	8	(3.4)	7	(6.5)	15	(4.4)
Nausea	1	(2.5)	4	(9.3)	8	(7.4)	4	(9.8)	17	(7.3)	7	(6.5)	24	(7.1)
General disorders and administration site conditions	4	(10.0)	4	(9.3)	4	(3.7)	6	(14.6)	18	(7.8)	12	(11.1)	30	(8.8)
Fatigue	2	(5.0)	4	(9.3)	4	(3.7)	5	(12.2)	15	(6.5)	5	(4.6)	20	(5.9)

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Subjects With Drug-Related Adverse Events - Overall: Related to Blinded Therapy With Doravirine or Efavirenz or Open-Label TRUVADA™ (Incidence ≥5% in One or More Treatment Groups) by System Organ Class Part I/II Combined (Doravirine All Doses vs. Efavirenz; Weeks 0-96) All Subjects as Treated

	Doravirine 25 mg		Doravirine 50 mg		Doravirine 100 mg		Doravirine 200 mg		Doravirine Combined		Efavirenz 600 mg		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Nervous system disorders	4	(10.0)	8	(18.6)	12	(11.1)	5	(12.2)	29	(12.5)	38	(35.2)	67	(19.7)
Dizziness	1	(2.5)	2	(4.7)	8	(7.4)	2	(4.9)	13	(5.6)	29	(26.9)	42	(12.4)
Headache	0	(0.0)	1	(2.3)	3	(2.8)	3	(7.3)	7	(3.0)	6	(5.6)	13	(3.8)
Somnolence	2	(5.0)	0	(0.0)	1	(0.9)	0	(0.0)	3	(1.3)	1	(0.9)	4	(1.2)
Psychiatric disorders	7	(17.5)	14	(32.6)	22	(20.4)	5	(12.2)	48	(20.7)	34	(31.5)	82	(24.1)
Abnormal dreams	3	(7.5)	9	(20.9)	6	(5.6)	3	(7.3)	21	(9.1)	16	(14.8)	37	(10.9)
Insomnia	1	(2.5)	3	(7.0)	7	(6.5)	2	(4.9)	13	(5.6)	3	(2.8)	16	(4.7)
Nightmare	1	(2.5)	1	(2.3)	6	(5.6)	0	(0.0)	8	(3.4)	9	(8.3)	17	(5.0)
Sleep disorder	1	(2.5)	2	(4.7)	5	(4.6)	0	(0.0)	8	(3.4)	7	(6.5)	15	(4.4)
Reproductive system and breast disorders	2	(5.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.9)	3	(2.8)	5	(1.5)
Skin and subcutaneous tissue disorders	0	(0.0)	0	(0.0)	5	(4.6)	2	(4.9)	7	(3.0)	14	(13.0)	21	(6.2)

Every subject is counted a single time for each applicable specific adverse event. A subject with multiple adverse events within a system organ class is counted a single time for that system organ class.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns is greater than or equal to the percent incidence specified in the report title, after rounding.
Note: Both doravirine and efavirenz were administered with TRUVADA™.

Source: [P007V01MK1439: analysis-adsl; adae]

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2.2.2 Deaths

There were no deaths during the P007 trial.

2.2.3 Other Serious Adverse Events

In P007, the most commonly reported SAEs (Main Combined DOR 8.2%; Main Combined EFV 12%) in any group were in the system organ class (SOC) category of Infections and Infestations, followed by Psychiatric Disorders. SAEs reported for at least 2 or more subjects included suicidal ideation (1 subject in the DOR 100 mg group and 2 subjects in the EFV group) and pharyngotonsillitis (1 subject in the 50 mg DOR group and 1 subject in the EFV group). All other SAEs occurred in 1 subject each.

No drug-related SAEs were reported for any of the DOR treatment groups. Three (2.8%) subjects in the EFV treatment group experienced drug-related SAEs (hepatitis toxic, dizziness, and suicidal ideation).

The number and percentage of subjects with SAEs among treatment groups is presented in [Ref. 5.3.5.1: P007V01MK1439: Table 12-17]. The number and percentage of subjects with drug-related SAEs among treatment groups is presented in [Ref. 5.3.5.1: P007V01MK1439: Table 12-18].

Narratives for subjects with drug-related SAEs in P007 are provided in the CSR [Ref. 5.3.5.1: P007V01MK1439: 16.2.7].

2.2.4 Adverse Events Leading to Discontinuation

The observed proportion of subjects in P007 who discontinued from study medication due to an AE through Week 96 was lower in the DOR Combined group (11 subjects [4.7%]) compared with the EFV group (11 subjects [10.2%]) [Table 2.7.4: 15].

A total of 15 AEs leading to discontinuation were reported for the 11 (4.7%) subjects in the Combined DOR group [Ref. 5.3.5.1: P007V01MK1439: 16.2.7.1-3]. Nine of the AEs were moderate in intensity and 6 were severe. Seven of the 15 AEs were deemed by the investigator to be related to trial medication: asthenia in the DOR 25 mg treatment group; sleep disorder, abdominal pain upper, insomnia, and nausea in the DOR 50 mg group; and fatigue and hallucination in the DOR 100 mg treatment group. Eleven of the 15 resolved, 3 did not resolve, and 1 resolved with sequelae.

A total of 11 AEs leading to discontinuation were reported for 11 (10.2%) subjects in the EFV group. Two of the AEs were mild in intensity, 5 were moderate, and 4 were severe. Ten of the 11 reports AEs were deemed by the investigator to be related to trial medication: $CD4^+$ T cell count decrease, depression, memory impairment, dizziness (2 subjects), hallucination, hepatitis toxic, disturbance in attention, drug eruption, and dysesthesia [Ref. 5.3.5.1: P007V01MK1439: 16.2.7.1-3]. .

The observed proportion of subjects who discontinued the trial due to drug-related AEs in Part I/II combined was generally similar among the DOR groups (range 0 to 4.7, and 2.2% overall for DOR) and highest (9.3%) in the EFV group [Table 2.7.4: 15].

Narratives for subjects with AEs leading to discontinuation are included in the CSR for P007 [Ref. 5.3.5.1: P007V01MK1439: 16.2.7.2-2].

2.2.5 Adverse Events of Special Interest

2.2.5.1 Neuropsychiatric Events

In order to better compare the safety profiles of DOR and EFV, the frequency of subjects experiencing an AE among a pre-specified set of CNS events by Week 8 and by Week 24 was the primary endpoint in P007. This endpoint was subject to inferential testing for statistical significance with p-values and 95% CIs provided for between-group comparisons as pre-specified in the protocol. The pre-specified list of CNS events measured by Week 8 and by Week 24 of treatment included the following MedDRA terms: 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, and concentration impaired [Ref. 5.3.5.1: P007V01MK1439: 9.8.5.2].

By Week 8, the proportion of subjects with CNS events in the DOR 100 mg treatment group was statistically significantly lower than compared with the EFV treatment group (21.4% vs 44.4%, respectively [treatment difference -20.4, p=0.002]) [Table 2.7.4: 17]. Results for Week 24 were also statistically significant favoring the DOR 100 mg group compared with the EFV group (26.9% vs 47.2%, respectively [treatment difference -20.4, p=0.002]).

Table 2.7.4: 17
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]

The majority of the CNS AEs reported by subjects in both treatment groups occurred by Week 8, with only 2% to 3% more subjects reporting CNS events between Week 8 [Table 2.7.4: 18] and Week 24 [Table 2.7.4: 19]. In general, the most commonly reported CNS events for DOR and EFV by Week 24 were dizziness (9.3% vs 28.7%, respectively), insomnia (7.4% vs 2.8%, respectively), abnormal dreams (6.5% vs 16.7%, respectively), and nightmares (6.5% vs. 8.3%, respectively). With the exception of insomnia, all CNS AE terms were reported more frequently in the EFV treatment group.

Based on these data, treatment with DOR is associated with lower rates of CNS AEs than treatment with EFV. This benefit is observed by Week 8 as well as at Week 24.

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Table 2.7.4: 18
Subjects With Central Nervous System Adverse Events (CNS Events) by System Organ Class
Part I/II Combined (Doravirine 100 mg vs. Efavirenz; Weeks 0-8)
All Subjects as Treated (P007)

	Doravirine 100 mg		Efavirenz 600 mg		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	108		108		216	
With one or more Central Nervous System adverse events[†]	26	(24.1)	48	(44.4)	74	(34.3)
With no Central Nervous System adverse events[†]	82	(75.9)	60	(55.6)	142	(65.7)
Nervous system disorders	11	(10.2)	33	(30.6)	44	(20.4)
Disturbance in attention	0	(0.0)	4	(3.7)	4	(1.9)
Dizziness	10	(9.3)	31	(28.7)	41	(19.0)
Somnolence	1	(0.9)	1	(0.9)	2	(0.9)
Psychiatric disorders	19	(17.6)	31	(28.7)	50	(23.1)
Abnormal dreams	7	(6.5)	18	(16.7)	25	(11.6)
Depression	1	(0.9)	2	(1.9)	3	(1.4)
Hallucination	1	(0.9)	3	(2.8)	4	(1.9)
Insomnia	8	(7.4)	3	(2.8)	11	(5.1)
Nightmare	6	(5.6)	9	(8.3)	15	(6.9)
Suicidal ideation	0	(0.0)	1	(0.9)	1	(0.5)

[†] Selected adverse events are from MedDRA terms of depression, nightmare, confusional state, suicidal ideation, suicidal ideation nervous system disorder, psychotic disorder, abnormal dreams, suicide attempt, acute psychosis, delirium, depressed level of consciousness, hallucination, hallucination auditory, hallucination visual, auditory, hallucination visual, completed suicide, suicidal behavior, major depression, depressed mood, depressive symptom, insomnia, disturbance in attention, somnolence, dizziness, concentration impaired.

Subjects are counted once for each unique adverse event and may have had more than one unique adverse event.

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

Source: [P007V01MK1439: analysis-adsl; adae]

Table 2.7.4: 19
Subjects With Central Nervous System Adverse Events (CNS Events)
by System Organ Class
Part I/II Combined (Doravirine 100 mg vs. Efavirenz; Weeks 0-24)
All Subjects as Treated (P007)

	Doravirine 100 mg		Efavirenz 600 mg		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	108		108		216	
With one or more Central Nervous System adverse events[†]	29	(26.9)	51	(47.2)	80	(37.0)
With no Central Nervous System adverse events[†]	79	(73.1)	57	(52.8)	136	(63.0)
Nervous system disorders	12	(11.1)	33	(30.6)	45	(20.8)
Disturbance in attention	1	(0.9)	4	(3.7)	5	(2.3)
Dizziness	10	(9.3)	31	(28.7)	41	(19.0)
Somnolence	1	(0.9)	1	(0.9)	2	(0.9)
Psychiatric disorders	21	(19.4)	34	(31.5)	55	(25.5)
Abnormal dreams	7	(6.5)	19	(17.6)	26	(12.0)
Depressed mood	0	(0.0)	1	(0.9)	1	(0.5)
Depression	2	(1.9)	5	(4.6)	7	(3.2)
Depressive symptom	1	(0.9)	0	(0.0)	1	(0.5)
Hallucination	1	(0.9)	3	(2.8)	4	(1.9)
Insomnia	8	(7.4)	3	(2.8)	11	(5.1)
Nightmare	7	(6.5)	9	(8.3)	16	(7.4)
Suicidal ideation	0	(0.0)	3	(2.8)	3	(1.4)

[†] Selected adverse events are from MedDRA terms of depression, nightmare, confusional state, suicidal ideation, suicidal ideation nervous system disorder, psychotic disorder, abnormal dreams, suicide attempt, acute psychosis, delirium, depressed level of consciousness, hallucination, hallucination auditory, hallucination visual, auditory, hallucination visual, completed suicide, suicidal behavior, major depression, depressed mood, depressive symptom, insomnia, disturbance in attention, somnolence, dizziness, concentration impaired.

Subjects are counted once for each unique adverse event and may have had more than one unique adverse event.

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

Source: [P007V01MK1439: analysis-adsl; adae]

2.2.6 Conclusions

In treatment naïve HIV-1 infected subjects enrolled in P007, DOR at doses of 25 mg, 50 mg, 100 mg, and 200 mg was generally well tolerated for 24 weeks compared with EFV, each in combination with FTC/TDF, with no dose-related toxicities.

Overall (Week 96), DOR (all doses) was generally well tolerated with few discontinuations due to AEs and low rates of SAEs in Part I/II. The proportions of subjects with drug-related AEs in Part I/II combined were generally similar for the DOR treatment groups (rates ranging from 35.2% to 48.8%, and 41.4% overall), and were lower compared with the EFV group (58.3%).

DOR at the final selected dose of 100 mg had a statistically significantly superior CNS safety profile compared to that of EFV, each in combination therapy with FTC/TDF, by Week 8 and by Week 24. A statistically significantly lower proportion of DOR-treated subjects compared to EFV-treated subjects reported CNS adverse events by Week 8 and Week 24 in the pre-specified categories: nervous system disorders and psychiatric disorders.

No subjects died during this trial.

2.3 Adverse Events in P018 (Phase 3 Trial)

2.3.1 Common Adverse Events

In P018, similar proportions of subjects reported AEs in the DOR group (80.2%) and in the DRV+r group (78.3%) [Table 2.7.4: 20]. The majority of these events were mild to moderate in intensity and were considered by the investigator to be unrelated to study drug.

The proportions of subjects who reported an SAE or a drug-related AE were similar for the 2 treatment groups. Few subjects discontinued due to an AE or a drug-related AE in either group.

Table 2.7.4: 20
Analysis of Adverse Event Summary Weeks 0-48 (P018)

	DOR 100 mg QD		Darunavir/ritonavir 800/100 mg QD		Difference in % vs Darunavir/ritonavir 800/100 mg QD
	n	(%)	n	(%)	Estimate (95% CI)[†]
Subjects in population	383		383		
with one or more adverse events	307	(80.2)	300	(78.3)	1.8 (-3.9, 7.6)
with no adverse events	76	(19.8)	83	(21.7)	-1.8 (-7.6, 3.9)
with drug-related[‡] adverse events	117	(30.5)	123	(32.1)	-1.6 (-8.1, 5.0)
with serious adverse events	19	(5.0)	23	(6.0)	-1.0 (-4.4, 2.3)
with serious drug-related adverse events	1	(0.3)	1	(0.3)	0.0 (-1.2, 1.2)
who died	1	(0.3)	0	(0.0)	0.3 (-0.7, 1.5)
discontinued[§] due to an adverse event	6	(1.6)	12	(3.1)	-1.6 (-4.0, 0.6)
discontinued due to a drug-related adverse event	4	(1.0)	8	(2.1)	-1.0 (-3.1, 0.8)
discontinued due to a serious adverse event	1	(0.3)	2	(0.5)	-0.3 (-1.6, 1.0)
discontinued due to a serious drug-related adverse event	0	(0.0)	1	(0.3)	-0.3 (-1.5, 0.7)

[†] Based on Miettinen & Nurminen method.
[‡] Determined by the investigator to be related to the drug.
[§] Study medication withdrawn.
Estimated differences and confidence intervals are provided in accordance with the statistical analysis plan.
Note: DOR 100 mg QD and darunavir/ritonavir 800/100 mg QD were administered with TRUVADA™ or EPZICOM™/KIVEXA™.

Source: [P018V01MK1439: analysis-adsl] [P018V01MK1439: tabulations-aeplus]

The most frequently reported AEs (≥5% of subjects in either treatment group presented in descending order of DOR frequency) were diarrhea, headache, nausea, upper respiratory tract infection, fatigue, nasopharyngitis, back pain, dizziness, upper abdominal pain, and cough [Table 2.7.4: 21] [Ref. 5.3.5.1: P018V01MK1439: Table 12-5]. Diarrhea was more frequently observed for DRV+r (22.5%) compared with DOR (14.1%) (treatment difference -8.4% [-13.8, -2.9]). No other notable clinical differences were observed between the treatment groups. The proportions of subjects in the DOR and the DRV+r treatment groups reporting AEs under the SOCs of Nervous System Disorders (22.5%, and 19.1%, respectively), and Psychiatric Disorders (13.3% in both treatment groups) were similar, with no clinically relevant differences between treatment groups.

While it should be noted that a 95% CI excluding 0 should not be viewed as an indicator of statistical significance of between-group differences (due to lack of multiplicity adjustment), several specific AEs had a 95% CI for the treatment difference that excluded 0. Of these, some occurred more often in the DOR group (back pain, sleep disorder, cough, and sinus congestion) and some occurred more often in the DRV+r group (diarrhea, influenza-like illness, oral candidiasis, hypercholesterolemia, and lethargy). Evaluation of the data did not provide any information to consider them of clinically important. The majority of the events were mild and very few of moderate intensity.

Through Week 48, the majority of subjects who reported treatment-emergent AEs experienced AEs that were considered by the investigator to be of mild or moderate intensity. Fifty-three subjects (6.9%) experienced AEs of severe intensity (DOR: 26 subjects [6.8%]; DRV+r: 27 subjects [7.0%]) [Ref. 5.3.5.1: P018V01MK1439: Table 14.3-5]. The frequency of subjects with severe AEs was comparable between treatment groups.

There were no differences in the occurrence of AEs with respect to gender, age, or race.

A listing by treatment group and by subject of all AEs, including day of onset, intensity and outcome is found in the CSR for this trial [Ref. 5.3.5.1: P018V01MK1439: 16.2.7].

Table 2.7.4: 21
Analysis of Subjects With Adverse Events
(Incidence ≥4 Subjects in One or More Treatment Groups)
Weeks 0-48 (P018)

	DOR 100 mg QD		Darunavir/ritonavir 800/100 mg QD		Difference in % vs Darunavir/ritonavir 800/100 mg QD
	n	(%)	n	(%)	Estimate (95% CI)[†]
Subjects in population	383		383		
with one or more adverse events	307	(80.2)	300	(78.3)	1.8 (-3.9, 7.6)
with no adverse events	76	(19.8)	83	(21.7)	-1.8 (-7.6, 3.9)
Blood and lymphatic system disorders	**12**	**(3.1)**	**15**	**(3.9)**	**-0.8 (-3.6, 1.9)**
Anaemia	5	(1.3)	4	(1.0)	0.3 (-1.5, 2.1)
Lymphadenopathy	4	(1.0)	6	(1.6)	-0.5 (-2.5, 1.3)
Cardiac disorders	**5**	**(1.3)**	**4**	**(1.0)**	**0.3 (-1.5, 2.1)**
Ear and labyrinth disorders	**10**	**(2.6)**	**5**	**(1.3)**	**1.3 (-0.7, 3.6)**
Eye disorders	**4**	**(1.0)**	**6**	**(1.6)**	**-0.5 (-2.5, 1.3)**
Gastrointestinal disorders	**137**	**(35.8)**	**162**	**(42.3)**	**-6.5 (-13.4, 0.4)**
Abdominal discomfort	6	(1.6)	4	(1.0)	0.5 (-1.3, 2.5)
Abdominal distension	5	(1.3)	4	(1.0)	0.3 (-1.5, 2.1)
Abdominal pain	12	(3.1)	17	(4.4)	-1.3 (-4.2, 1.5)
Abdominal pain upper	19	(5.0)	10	(2.6)	2.3 (-0.4, 5.3)
Constipation	11	(2.9)	6	(1.6)	1.3 (-0.9, 3.7)
Diarrhoea	54	(14.1)	86	(22.5)	-8.4 (-13.8, -2.9)
Dyspepsia	9	(2.3)	7	(1.8)	0.5 (-1.7, 2.8)
Faeces soft	1	(0.3)	6	(1.6)	-1.3 (-3.1, 0.1)
Flatulence	7	(1.8)	11	(2.9)	-1.0 (-3.5, 1.2)
Haemorrhoids	4	(1.0)	6	(1.6)	-0.5 (-2.5, 1.3)
Nausea	41	(10.7)	46	(12.0)	-1.3 (-5.9, 3.2)
Toothache	7	(1.8)	10	(2.6)	-0.8 (-3.1, 1.4)
Vomiting	12	(3.1)	10	(2.6)	0.5 (-2.0, 3.1)
General disorders and administration site conditions	**62**	**(16.2)**	**57**	**(14.9)**	**1.3 (-3.9, 6.5)**
Asthenia	9	(2.3)	7	(1.8)	0.5 (-1.7, 2.8)
Chest pain	4	(1.0)	3	(0.8)	0.3 (-1.4, 2.0)
Fatigue	31	(8.1)	20	(5.2)	2.9 (-0.7, 6.6)
Influenza like illness	1	(0.3)	7	(1.8)	-1.6 (-3.5, -0.2)
Pyrexia	12	(3.1)	7	(1.8)	1.3 (-1.0, 3.8)
Infections and infestations	**193**	**(50.4)**	**184**	**(48.0)**	**2.3 (-4.7, 9.4)**
Bronchitis	11	(2.9)	18	(4.7)	-1.8 (-4.8, 0.9)
Conjunctivitis	9	(2.3)	5	(1.3)	1.0 (-1.0, 3.3)
Folliculitis	6	(1.6)	3	(0.8)	0.8 (-0.9, 2.7)
Fungal skin infection	4	(1.0)	3	(0.8)	0.3 (-1.4, 2.0)

Analysis of Subjects With Adverse Events
(Incidence ≥4 Subjects in One or More Treatment Groups)
Weeks 0-48 (P018)

	DOR 100 mg QD		Darunavir/ritonavir 800/100 mg QD		Difference in % vs Darunavir/ritonavir 800/100 mg QD
	n	(%)	n	(%)	Estimate (95% CI)[†]
Infections and infestations	**193**	**(50.4)**	**184**	**(48.0)**	**2.3 (-4.7, 9.4)**
Gastroenteritis	11	(2.9)	12	(3.1)	-0.3 (-2.9, 2.3)
Gonorrhoea	4	(1.0)	7	(1.8)	-0.8 (-2.8, 1.1)
Herpes zoster	7	(1.8)	4	(1.0)	0.8 (-1.1, 2.8)
Influenza	10	(2.6)	11	(2.9)	-0.3 (-2.8, 2.2)
Nasopharyngitis	30	(7.8)	39	(10.2)	-2.3 (-6.5, 1.7)
Oral candidiasis	2	(0.5)	9	(2.3)	-1.8 (-3.9, -0.2)
Oral herpes	5	(1.3)	4	(1.0)	0.3 (-1.5, 2.1)
Pharyngitis	7	(1.8)	10	(2.6)	-0.8 (-3.1, 1.4)
Pneumonia	5	(1.3)	3	(0.8)	0.5 (-1.1, 2.3)
Proctitis gonococcal	5	(1.3)	1	(0.3)	1.0 (-0.3, 2.8)
Respiratory tract infection	8	(2.1)	12	(3.1)	-1.0 (-3.6, 1.3)
Respiratory tract infection viral	8	(2.1)	4	(1.0)	1.0 (-0.8, 3.1)
Rhinitis	3	(0.8)	6	(1.6)	-0.8 (-2.7, 0.9)
Sinusitis	8	(2.1)	7	(1.8)	0.3 (-1.9, 2.5)
Syphilis	17	(4.4)	13	(3.4)	1.0 (-1.8, 4.0)
Tonsillitis	3	(0.8)	5	(1.3)	-0.5 (-2.3, 1.1)
Tracheobronchitis	1	(0.3)	5	(1.3)	-1.0 (-2.8, 0.3)
Upper respiratory tract infection	36	(9.4)	23	(6.0)	3.4 (-0.4, 7.3)
Urinary tract infection	4	(1.0)	4	(1.0)	0.0 (-1.7, 1.7)
Viral infection	4	(1.0)	0	(0.0)	1.0 (0.0, 2.7)
Injury, poisoning and procedural complications	**17**	**(4.4)**	**20**	**(5.2)**	**-0.8 (-4.0, 2.3)**
Investigations	**43**	**(11.2)**	**37**	**(9.7)**	**1.6 (-2.8, 6.0)**
Alanine aminotransferase increased	8	(2.1)	6	(1.6)	0.5 (-1.5, 2.7)
Aspartate aminotransferase increased	8	(2.1)	8	(2.1)	0.0 (-2.2, 2.2)
Blood creatine phosphokinase increased	9	(2.3)	7	(1.8)	0.5 (-1.7, 2.8)
Blood pressure increased	3	(0.8)	6	(1.6)	-0.8 (-2.7, 0.9)
Lipase increased	1	(0.3)	6	(1.6)	-1.3 (-3.1, 0.1)
Weight increased	4	(1.0)	3	(0.8)	0.3 (-1.4, 2.0)
Metabolism and nutrition disorders	**22**	**(5.7)**	**31**	**(8.1)**	**-2.3 (-6.1, 1.3)**
Decreased appetite	6	(1.6)	6	(1.6)	0.0 (-2.0, 2.0)
Hypercholesterolaemia	1	(0.3)	7	(1.8)	-1.6 (-3.5, -0.2)
Musculoskeletal and connective tissue disorders	**58**	**(15.1)**	**40**	**(10.4)**	**4.7 (-0.0, 9.5)**
Arthralgia	10	(2.6)	6	(1.6)	1.0 (-1.1, 3.4)
Back pain	21	(5.5)	8	(2.1)	3.4 (0.7, 6.4)
Musculoskeletal pain	6	(1.6)	3	(0.8)	0.8 (-0.9, 2.7)

Analysis of Subjects With Adverse Events
(Incidence ≥4 Subjects in One or More Treatment Groups)
Weeks 0-48 (P018)

	DOR 100 mg QD		Darunavir/ritonavir 800/100 mg QD		Difference in % vs Darunavir/ritonavir 800/100 mg QD
	n	(%)	n	(%)	Estimate (95% CI)[†]
Musculoskeletal and connective tissue disorders	**58**	**(15.1)**	**40**	**(10.4)**	**4.7 (-0.0, 9.5)**
Myalgia	8	(2.1)	4	(1.0)	1.0 (-0.8, 3.1)
Neck pain	1	(0.3)	4	(1.0)	-0.8 (-2.4, 0.5)
Pain in extremity	9	(2.3)	7	(1.8)	0.5 (-1.7, 2.8)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**11**	**(2.9)**	**10**	**(2.6)**	**0.3 (-2.2, 2.8)**
Anogenital warts	5	(1.3)	5	(1.3)	0.0 (-1.9, 1.9)
Nervous system disorders	**86**	**(22.5)**	**73**	**(19.1)**	**3.4 (-2.4, 9.2)**
Dizziness	19	(5.0)	15	(3.9)	1.0 (-2.0, 4.1)
Dysgeusia	4	(1.0)	1	(0.3)	0.8 (-0.5, 2.4)
Headache	53	(13.8)	41	(10.7)	3.1 (-1.5, 7.8)
Lethargy	0	(0.0)	6	(1.6)	-1.6 (-3.4, -0.6)
Migraine	4	(1.0)	2	(0.5)	0.5 (-1.0, 2.2)
Paraesthesia	6	(1.6)	1	(0.3)	1.3 (-0.1, 3.1)
Somnolence	3	(0.8)	6	(1.6)	-0.8 (-2.7, 0.9)
Psychiatric disorders	**51**	**(13.3)**	**51**	**(13.3)**	**0.0 (-4.9, 4.9)**
Abnormal dreams	5	(1.3)	3	(0.8)	0.5 (-1.1, 2.3)
Anxiety	4	(1.0)	8	(2.1)	-1.0 (-3.1, 0.8)
Depression	5	(1.3)	8	(2.1)	-0.8 (-2.9, 1.2)
Insomnia	14	(3.7)	18	(4.7)	-1.0 (-4.1, 1.9)
Irritability	4	(1.0)	0	(0.0)	1.0 (0.0, 2.7)
Nightmare	1	(0.3)	5	(1.3)	-1.0 (-2.8, 0.3)
Sleep disorder	10	(2.6)	1	(0.3)	2.3 (0.8, 4.5)
Stress	4	(1.0)	2	(0.5)	0.5 (-1.0, 2.2)
Renal and urinary disorders	**4**	**(1.0)**	**8**	**(2.1)**	**-1.0 (-3.1, 0.8)**
Reproductive system and breast disorders	**16**	**(4.2)**	**10**	**(2.6)**	**1.6 (-1.1, 4.4)**
Menorrhagia	4	(1.0)	0	(0.0)	1.0 (0.0, 2.7)
Respiratory, thoracic and mediastinal disorders	**51**	**(13.3)**	**36**	**(9.4)**	**3.9 (-0.6, 8.5)**
Cough	19	(5.0)	6	(1.6)	3.4 (0.9, 6.2)
Oropharyngeal pain	9	(2.3)	7	(1.8)	0.5 (-1.7, 2.8)
Rhinitis allergic	8	(2.1)	5	(1.3)	0.8 (-1.2, 2.9)
Rhinorrhoea	5	(1.3)	3	(0.8)	0.5 (-1.1, 2.3)
Sinus congestion	5	(1.3)	0	(0.0)	1.3 (0.3, 3.0)

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Analysis of Subjects With Adverse Events
(Incidence ≥4 Subjects in One or More Treatment Groups)
Weeks 0-48 (P018)

	DOR 100 mg QD		Darunavir/ritonavir 800/100 mg QD		Difference in % vs Darunavir/ritonavir 800/100 mg QD
	n	(%)	n	(%)	Estimate (95% CI)[†]
Skin and subcutaneous tissue disorders	**60**	**(15.7)**	**62**	**(16.2)**	**-0.5 (-5.7, 4.7)**
Acne	4	(1.0)	6	(1.6)	-0.5 (-2.5, 1.3)
Dermatitis contact	4	(1.0)	1	(0.3)	0.8 (-0.5, 2.4)
Eczema	3	(0.8)	6	(1.6)	-0.8 (-2.7, 0.9)
Pruritus	3	(0.8)	4	(1.0)	-0.3 (-2.0, 1.4)
Rash	4	(1.0)	6	(1.6)	-0.5 (-2.5, 1.3)
Rash erythematous	8	(2.1)	5	(1.3)	0.8 (-1.2, 2.9)
Rash macular	3	(0.8)	7	(1.8)	-1.0 (-3.0, 0.7)
Rash maculo-papular	3	(0.8)	4	(1.0)	-0.3 (-2.0, 1.4)
Rash papular	5	(1.3)	9	(2.3)	-1.0 (-3.3, 1.0)
Vascular disorders	**5**	**(1.3)**	**6**	**(1.6)**	**-0.3 (-2.2, 1.6)**
Hypertension	4	(1.0)	4	(1.0)	0.0 (-1.7, 1.7)

[†] Based on Miettinen & Nurminen method.
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.
Estimated differences and confidence intervals are provided in accordance with the statistical analysis plan.
Only includes AEs occurring or worsening after the first dose of study medication through 14 days after the last dose of study medication.
Note: DOR 100 mg QD and darunavir/ritonavir 800/100 mg QD were administered with TRUVADA™ or EPZICOM™/KIVEXA™.

Source: [P018V01MK1439: analysis-adsl] [P018V01MK1439: tabulations-aeplus]

Drug-Related Adverse Events (Overall)

In P018, drug-related AEs were reported with a similar proportion by subjects in the DOR treatment group (30.5%) compared with the DRV+r treatment group (32.1%) [Table 2.7.4: 22]. Drug-related AEs were most frequently associated with the SOC of gastrointestinal disorders with a lower observed proportion in the DOR treatment group compared with the DRV+r treatment group. Overall, the most frequently (incidence ≥2% in 1 or more of the treatment groups) reported drug-related AEs were diarrhea, nausea headache, fatigue, dizziness, and upper abdominal pain. Similar to the analysis of all AEs, drug-related diarrhea was reported for fewer subjects in the DOR group (5.5%) compared with the DVR+r group (12.8%). No other clinically relevant differences between treatment groups were observed.

The proportions of subjects with AEs that were considered by the investigator to be drug-related and moderate or severe in intensity were similar in both treatment groups (DOR 6.5%, vs. DRV+r 7.0%) [Ref. 5.3.5.1: P018V01MK1439: Table 14.3-9]. The most commonly reported drug-related AE of moderate or severe intensity by Week 48 (incidence ≥0%) was diarrhea (DOR: 1.6% vs DRV+r: 1.8%).

Table 2.7.4: 22
Subjects With Drug-Related Adverse Events
(Incidence ≥2% in One or More Treatment Groups)
Overall Drug Related
Weeks 0-48 (P018)

	Doravirine 100 mg QD		Darunavir/ritonavir 800/100 mg QD		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	383		383		766	
with one or more drug-related adverse events	117	(30.5)	123	(32.1)	240	(31.3)
with no drug-related adverse events	266	(69.5)	260	(67.9)	526	(68.7)
Gastrointestinal disorders	**66**	**(17.2)**	**85**	**(22.2)**	**151**	**(19.7)**
Abdominal pain upper	9	(2.3)	2	(0.5)	11	(1.4)
Diarrhoea	21	(5.5)	49	(12.8)	70	(9.1)
Nausea	25	(6.5)	29	(7.6)	54	(7.0)
General disorders and administration site conditions	**24**	**(6.3)**	**13**	**(3.4)**	**37**	**(4.8)**
Fatigue	18	(4.7)	8	(2.1)	26	(3.4)
Metabolism and nutrition disorders	**4**	**(1.0)**	**8**	**(2.1)**	**12**	**(1.6)**
Nervous system disorders	**36**	**(9.4)**	**19**	**(5.0)**	**55**	**(7.2)**
Dizziness	11	(2.9)	7	(1.8)	18	(2.3)
Headache	23	(6.0)	10	(2.6)	33	(4.3)
Psychiatric disorders	**18**	**(4.7)**	**13**	**(3.4)**	**31**	**(4.0)**
Skin and subcutaneous tissue disorders	**13**	**(3.4)**	**17**	**(4.4)**	**30**	**(3.9)**

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.

Only includes AEs occurring or worsening 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™.

Source: [P018V01MK1439: analysis-adsl] [P018V01MK1439: tabulations-aeplus]

2.3.2 Deaths

One death was reported in P018 by Week 48. A subject in the DOR treatment group experienced an AE recorded as "death." The last reported dose of the study therapy was administered on Day 222. The 41-year-old subject had a medical history of tuberculosis, seizures, hypertension, and HIV-1 infection (diagnosed approximately 1.5 years prior to first dose of study medication). The subject's HIV-1 ribonucleic acid (RNA) at screening was 70,280 copies/mL; it was 73 copies/mL on Study Day 173. On Study Day 222 (the date of the last reported dose), the subject reported dizziness while watching television, and subsequently collapsed and died at home. At the time of the death, the subject's non-serious AEs of mild muscle spasms, mild cough, and mild diarrhea were ongoing; the subject had no reported deterioration of health prior to death. The subject's death certificate listed the cause of death as "natural causes." No autopsy was performed. In the opinion of the investigator, the death was not related to study drug. A complete narrative for this case is found in the CSR for this trial [Ref. 5.3.5.1: P018V01MK1439: 16.2.7.2].

2.3.3 Other Serious Adverse Events

By Week 48, 42 (5.5%) of the 766 treated subjects in P018 reported AEs that met the criteria of SAE [Ref. 5.3.5.1: P018V01MK1439: Table 12-4]. The proportion of subjects with SAEs was similar in the DOR treatment group (5.0%) compared with the DRV+r treatment group (6.0%). No single SAE was experienced by more than 2 subjects in the study; the most common SAEs (>1 subject in either treatment group) were anal fistula (1 subject each in both groups), tuberculosis (2 subjects in the DVR+r group), and back pain (2 subjects in the DRV+r group).

Two subjects (1 in each treatment group) experienced SAEs that were considered by the investigator to be drug related SAEs [Ref. 5.3.5.1: P018V01MK1439: Table 14.3-11].

- One subject in the DOR treatment group experienced drug-related SAEs of nausea and vomiting. The subject experienced acute kidney injury on Day 1 prior to starting study drug. The subject developed SAEs of nausea and vomiting on Day 4 and was admitted to the hospital on Day 6. The subject was discontinued from the trial on Day 1 due to acute kidney injury. The drug-related SAEs of nausea and vomiting were concurrent, and both resolved without dose interruption or modification on Day 7[Ref. 5.3.5.1: P018V01MK1439: 16.2.7.1.1].
- One subject in the DRV+r treatment group experienced edema peripheral [Ref. 5.3.5.1: P018V01MK1439: Table 14-3.11], which resulted in the discontinuation of the subject from the trial after 2 months of treatment [Ref. 5.3.5.1: P018V01MK1439: 16.2.7.1.1].

A summary of SAEs through the data cutoff date is provided in [Ref. 5.3.5.1: P018V01MK1439: Table 14.3-12]. Results are comparable to those observed for the Week 48 data.

Listings of SAEs by subject by Week 48 and through the data cutoff date are in [Ref. 5.3.5.1: P018V01MK1439: 16.2.7.1.1] and [Ref. 5.3.5.1: P018V01MK1439: 16.2.7.1.2], respectively. Narratives for subjects with SAEs are in [Ref. 5.3.5.1: P018V01MK1439: 16.2.7.2].

2.3.4 Adverse Events Leading to Discontinuation

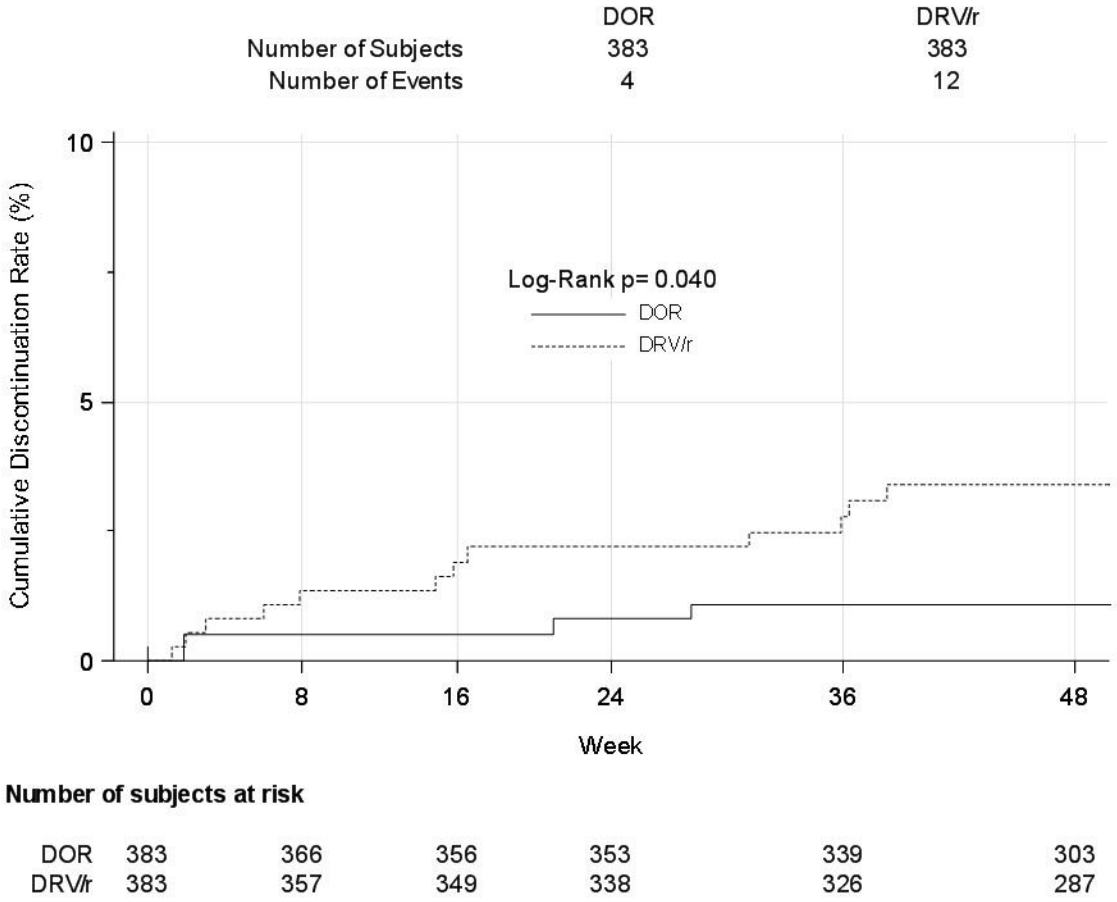
Through Week 48, a total of 18 subjects experienced AEs that resulted in discontinuation from the study: 6 subjects (1.6%) in the DOR group and 12 subjects (3.1%) in the DRV+r [Ref. 5.3.5.1: P018V01MK1439: Table 12-4].

Twelve of these 18 subjects discontinued due to drug-related AEs: 4 subjects (1.0%) in the DOR group and 8 subjects (2.1%) in the DRV+r group.

For 3 subjects (1 in the DOR group and 2 in the DRV+r group), discontinuation was due to an SAE (unrelated death in the DOR group; related peripheral edema and unrelated tuberculosis in the DRV+r group) [Ref. 5.3.5.1: P018V01MK1439: 16.2.7.1.5].

In P018, there was a smaller risk of discontinuation due to AE in the DOR treatment group (4 events) compared with the DRV+r treatment group (12 events) [Figure 2.7.4: 2]. Results of the log-rank test indicate that the time to discontinuation due to any AE through Week 48 was longer for DOR compared with DRV+r ($p = 0.040$, not adjusted for multiplicity) [Ref. 5.3.5.1: P018V01MK1439: Table 14.3-13]. Note that for this analysis, 2 subjects in the DOR treatment group who discontinued (a subject whose death was reported as the reason for discontinuation on the disposition form and a subject who discontinued after the Week 48 window) were censored from the analysis of time to discontinuation due to AE.

Figure 2.7.4: 2
Kaplan-Meier Plot for Time to Discontinuation Due to Adverse Event Weeks 0-48 (P018)



2.3.5 Conclusions

In P018, DOR 100 mg QD in combination with FTC/TDF or ABC/3TC for 48 weeks was generally well tolerated in 383 treatment-naïve HIV-1 infected subjects.

The results of this trial suggest that the 100 mg dose of DOR has a favorable safety profile when compared with DRV+r.

The risk of discontinuation due to AE was smaller in the DOR treatment group compared with the DRV+r treatment group.

The time to discontinuation due to any AE was longer for DOR compared with DRV+r (nominal p=0.040, log-rank test).

2.4 Adverse Events in P021 (Phase 3 Trial)

2.4.1 Common Adverse Events

Overall, in P021, a lower observed proportion of subjects experienced AEs in the DOR/3TC/TDF group (82.7%) compared with the EFV/FTC/TDF group (90.7%) (treatment difference -8.0% [-13.0, -3.1]) [Table 2.7.4: 23]. A substantially lower proportion of subjects reported drug-related AE(s) in the DOR/3TC/TDF treatment group (31.0%) compared with the EFV/FTC/TDF treatment group (62.9%) (treatment difference -31.9% [-38.6, -24.8]). There were also lower proportions of subjects with discontinuations due to AEs (3.0%, vs.6.6%) (treatment difference -3.6% [-6.9, -0.5]) and discontinuations due to drug related AEs (2.2%, vs. 5.8%) (treatment difference -3.6% [-6.7, -0.8]) in the DOR/3TC/TDF group compared with the EFV/FTC/TDF group.

Table 2.7.4: 23
Analysis of Adverse Event Summary Weeks 0-48 (P021)

	DOR/3TC/TDF QD		EFV/FTC/TDF QD		Difference in % vs EFV/FTC/TDF QD
	n	(%)	n	(%)	Estimate (95% CI)[†]
Subjects in population	364		364		
with one or more adverse events	301	(82.7)	330	(90.7)	-8.0 (-13.0, -3.1)
with no adverse events	63	(17.3)	34	(9.3)	8.0 (3.1, 13.0)
with drug-related[‡] adverse events	113	(31.0)	229	(62.9)	-31.9 (-38.6, -24.8)
with serious adverse events	13	(3.6)	21	(5.8)	-2.2 (-5.5, 0.9)
with serious drug-related adverse events	1	(0.3)	4	(1.1)	-0.8 (-2.5, 0.5)
who died	0	(0.0)	2	(0.5)	-0.5 (-2.0, 0.5)
discontinued[§] due to an adverse event	11	(3.0)	24	(6.6)	-3.6 (-6.9, -0.5)
discontinued due to a drug-related adverse event	8	(2.2)	21	(5.8)	-3.6 (-6.7, -0.8)
discontinued due to a serious adverse event	2	(0.5)	4	(1.1)	-0.5 (-2.3, 1.0)
discontinued due to a serious drug-related adverse event	1	(0.3)	3	(0.8)	-0.5 (-2.2, 0.8)

[†] Based on Miettinen & Nurminen method.
[‡] Determined by the investigator to be related to the drug.
[§] Study medication withdrawn.
Estimated differences and confidence intervals are provided in accordance with the statistical analysis plan.
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] [P021V01MK1439A: tabulations-aeplus]

The most frequently reported AEs in either treatment group were dizziness, headache, rash, diarrhea, nasopharyngitis, nausea and abnormal dreams [Table 2.7.4: 24]. Dizziness was reported substantially more frequently for the EFV/FTC/TDF group compared with the DOR/3TC.TDF group (37.1% vs 8.8%) (treatment difference -28.3% [-34.0, -22.5]).

While it should be noted that a 95% CI excluding 0 should not be viewed as an indicator of statistical significance of between-group differences (due to lack of multiplicity adjustment), several AEs had a 95% CI for the treatment difference that excluded 0. Each of these events (presented in descending order of EFV/FTC/TDF reporting frequency) (dizziness, rash, abnormal dreams, somnolence dermatitis allergic, vertigo) was reported for a higher

proportion of subjects in the EFV/FTC/TDF group compared with the DOR/3TC/TDF group. One event (hypertension) was reported more often in the DOR/3TC/TDF group (2.5%) than in the EFV/FTC/TDF group (0.8%).

Through Week 48, the majority of subjects who reported AEs experienced AEs that were considered by the investigator to be of mild or moderate intensity [Ref. 5.3.5.1: P021V01MK1439A: Table 14.3-5]. Only a small proportion of subjects (sixty-three [9.3%] experienced AEs of severe intensity (DOR/3TC/TDF: 28 subjects [7.7%]; EFV/FTC/TDF: 40 subjects [11.0%]). A listing by treatment group and by subject of all AEs, including day of onset, intensity and outcome, is found in [Ref. 5.3.5.1: P021V01MK1439A: 16.2.7].

Overall summaries of AEs by Week 48 are provided in [Ref. 5.3.5.1: P021V01MK1439A: Table 14 3-1] (Weeks 0-48) and beyond Week 48 are provided in [Ref. 5.3.5.1: P021V01MK1439A: Table 14.3-2] (All Data Available) by treatment group and in total.

Table 2.7.4: 24
Analysis of Subjects With Adverse Events
(Incidence ≥4 Subjects in One or More Treatment Groups)
Weeks 0-48 (P021)

	DOR/3TC/TDF QD		EFV/FTC/TDF QD		Difference in % vs EFV/FTC/TDF QD
	n	(%)	n	(%)	Estimate (95% CI)[†]
Subjects in population	364		364		
with one or more adverse events	301	(82.7)	330	(90.7)	-8.0 (-13.0, -3.1)
with no adverse events	63	(17.3)	34	(9.3)	8.0 (3.1, 13.0)
Blood and lymphatic system disorders	**15**	**(4.1)**	**12**	**(3.3)**	**0.8 (-2.0, 3.8)**
Lymphadenopathy	6	(1.6)	4	(1.1)	0.5 (-1.3, 2.6)
Cardiac disorders	**6**	**(1.6)**	**4**	**(1.1)**	**0.5 (-1.3, 2.6)**
Ear and labyrinth disorders	**6**	**(1.6)**	**16**	**(4.4)**	**-2.7 (-5.6, -0.3)**
Ear pain	1	(0.3)	4	(1.1)	-0.8 (-2.5, 0.5)
Vertigo	1	(0.3)	7	(1.9)	-1.6 (-3.7, -0.2)
Eye disorders	**10**	**(2.7)**	**11**	**(3.0)**	**-0.3 (-2.9, 2.3)**
Gastrointestinal disorders	**120**	**(33.0)**	**136**	**(37.4)**	**-4.4 (-11.3, 2.5)**
Abdominal pain	9	(2.5)	13	(3.6)	-1.1 (-3.8, 1.5)
Abdominal pain lower	1	(0.3)	5	(1.4)	-1.1 (-2.9, 0.3)
Abdominal pain upper	8	(2.2)	2	(0.5)	1.6 (-0.1, 3.8)
Aphthous ulcer	4	(1.1)	0	(0.0)	1.1 (0.0, 2.8)
Colitis	2	(0.5)	4	(1.1)	-0.5 (-2.3, 1.0)
Constipation	8	(2.2)	5	(1.4)	0.8 (-1.3, 3.1)
Diarrhoea	39	(10.7)	49	(13.5)	-2.7 (-7.6, 2.0)
Dyspepsia	6	(1.6)	8	(2.2)	-0.5 (-2.8, 1.6)
Food poisoning	5	(1.4)	3	(0.8)	0.5 (-1.2, 2.5)
Gastritis	4	(1.1)	2	(0.5)	0.5 (-1.0, 2.3)
Gastrooesophageal reflux disease	3	(0.8)	5	(1.4)	-0.5 (-2.5, 1.2)
Haemorrhoids	5	(1.4)	6	(1.6)	-0.3 (-2.3, 1.7)
Nausea	28	(7.7)	39	(10.7)	-3.0 (-7.3, 1.2)
Toothache	3	(0.8)	5	(1.4)	-0.5 (-2.5, 1.2)
Vomiting	15	(4.1)	27	(7.4)	-3.3 (-6.9, 0.1)
General disorders and administration site conditions	**56**	**(15.4)**	**53**	**(14.6)**	**0.8 (-4.4, 6.1)**
Asthenia	3	(0.8)	8	(2.2)	-1.4 (-3.6, 0.5)
Fatigue	21	(5.8)	22	(6.0)	-0.3 (-3.8, 3.3)
Influenza like illness	8	(2.2)	9	(2.5)	-0.3 (-2.7, 2.1)
Pyrexia	13	(3.6)	6	(1.6)	1.9 (-0.4, 4.6)
Hepatobiliary disorders	**4**	**(1.1)**	**3**	**(0.8)**	**0.3 (-1.4, 2.1)**
Immune system disorders	**4**	**(1.1)**	**6**	**(1.6)**	**-0.5 (-2.6, 1.3)**

Analysis of Subjects With Adverse Events
(Incidence ≥4 Subjects in One or More Treatment Groups)
Weeks 0-48 (P021)

	DOR/3TC/TDF QD		EFV/FTC/TDF QD		Difference in % vs EFV/FTC/TDF QD
	n	(%)	n	(%)	Estimate (95% CI)[†]
Infections and infestations	**183**	**(50.3)**	**174**	**(47.8)**	**2.5 (-4.8, 9.7)**
Acute sinusitis	4	(1.1)	3	(0.8)	0.3 (-1.4, 2.1)
Bronchitis	7	(1.9)	11	(3.0)	-1.1 (-3.6, 1.3)
Chlamydial infection	5	(1.4)	3	(0.8)	0.5 (-1.2, 2.5)
Conjunctivitis	5	(1.4)	2	(0.5)	0.8 (-0.8, 2.7)
Folliculitis	6	(1.6)	4	(1.1)	0.5 (-1.3, 2.6)
Gastroenteritis	11	(3.0)	9	(2.5)	0.5 (-2.0, 3.2)
Gonorrhoea	6	(1.6)	2	(0.5)	1.1 (-0.5, 3.1)
Herpes virus infection	1	(0.3)	4	(1.1)	-0.8 (-2.5, 0.5)
Herpes zoster	3	(0.8)	6	(1.6)	-0.8 (-2.8, 0.9)
Influenza	8	(2.2)	11	(3.0)	-0.8 (-3.4, 1.6)
Nasopharyngitis	39	(10.7)	31	(8.5)	2.2 (-2.1, 6.6)
Onychomycosis	4	(1.1)	2	(0.5)	0.5 (-1.0, 2.3)
Oral candidiasis	4	(1.1)	0	(0.0)	1.1 (0.0, 2.8)
Oral herpes	4	(1.1)	5	(1.4)	-0.3 (-2.2, 1.6)
Pharyngitis	20	(5.5)	15	(4.1)	1.4 (-1.8, 4.7)
Proctitis chlamydial	4	(1.1)	0	(0.0)	1.1 (0.0, 2.8)
Respiratory tract infection	4	(1.1)	5	(1.4)	-0.3 (-2.2, 1.6)
Respiratory tract infection viral	4	(1.1)	3	(0.8)	0.3 (-1.4, 2.1)
Sinusitis	4	(1.1)	11	(3.0)	-1.9 (-4.4, 0.2)
Subcutaneous abscess	6	(1.6)	1	(0.3)	1.4 (-0.1, 3.3)
Syphilis	8	(2.2)	8	(2.2)	0.0 (-2.3, 2.3)
Tonsillitis	14	(3.8)	8	(2.2)	1.6 (-0.9, 4.4)
Upper respiratory tract infection	33	(9.1)	23	(6.3)	2.7 (-1.2, 6.8)
Urethritis	6	(1.6)	1	(0.3)	1.4 (-0.1, 3.3)
Urinary tract infection	3	(0.8)	5	(1.4)	-0.5 (-2.5, 1.2)
Viral infection	6	(1.6)	1	(0.3)	1.4 (-0.1, 3.3)
Injury, poisoning and procedural complications	**21**	**(5.8)**	**34**	**(9.3)**	**-3.6 (-7.6, 0.3)**
Contusion	4	(1.1)	2	(0.5)	0.5 (-1.0, 2.3)
Ligament sprain	3	(0.8)	4	(1.1)	-0.3 (-2.1, 1.4)
Investigations	**29**	**(8.0)**	**43**	**(11.8)**	**-3.8 (-8.3, 0.5)**
Alanine aminotransferase increased	10	(2.7)	10	(2.7)	0.0 (-2.6, 2.6)
Aspartate aminotransferase increased	9	(2.5)	12	(3.3)	-0.8 (-3.5, 1.7)
Blood alkaline phosphatase increased	0	(0.0)	4	(1.1)	-1.1 (-2.8, -0.0)
Blood creatine phosphokinase increased	7	(1.9)	14	(3.8)	-1.9 (-4.7, 0.6)
Blood pressure increased	5	(1.4)	0	(0.0)	1.4 (0.3, 3.2)
Weight decreased	1	(0.3)	7	(1.9)	-1.6 (-3.7, -0.2)
Metabolism and nutrition disorders	**26**	**(7.1)**	**35**	**(9.6)**	**-2.5 (-6.6, 1.6)**
Decreased appetite	8	(2.2)	7	(1.9)	0.3 (-2.0, 2.6)

Analysis of Subjects With Adverse Events
(Incidence ≥4 Subjects in One or More Treatment Groups)
Weeks 0-48 (P021)

	DOR/3TC/TDF QD		EFV/FTC/TDF QD		Difference in % vs EFV/FTC/TDF QD
	n	(%)	n	(%)	Estimate (95% CI)[†]
Metabolism and nutrition disorders	**26**	**(7.1)**	**35**	**(9.6)**	**-2.5 (-6.6, 1.6)**
Hypercholesterolaemia	0	(0.0)	5	(1.4)	-1.4 (-3.2, -0.3)
Hypertriglyceridaemia	1	(0.3)	4	(1.1)	-0.8 (-2.5, 0.5)
Musculoskeletal and connective tissue disorders	**34**	**(9.3)**	**48**	**(13.2)**	**-3.8 (-8.5, 0.8)**
Arthralgia	11	(3.0)	8	(2.2)	0.8 (-1.6, 3.4)
Back pain	9	(2.5)	15	(4.1)	-1.6 (-4.5, 1.0)
Myalgia	4	(1.1)	8	(2.2)	-1.1 (-3.3, 0.9)
Pain in extremity	3	(0.8)	6	(1.6)	-0.8 (-2.8, 0.9)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**15**	**(4.1)**	**12**	**(3.3)**	**0.8 (-2.0, 3.8)**
Anogenital warts	9	(2.5)	8	(2.2)	0.3 (-2.1, 2.7)
Nervous system disorders	**95**	**(26.1)**	**177**	**(48.6)**	**-22.5 (-29.3, -15.6)**
Disturbance in attention	2	(0.5)	4	(1.1)	-0.5 (-2.3, 1.0)
Dizziness	32	(8.8)	135	(37.1)	-28.3 (-34.0, -22.5)
Headache	47	(12.9)	45	(12.4)	0.5 (-4.3, 5.4)
Somnolence	12	(3.3)	27	(7.4)	-4.1 (-7.6, -0.9)
Psychiatric disorders	**62**	**(17.0)**	**122**	**(33.5)**	**-16.5 (-22.7, -10.2)**
Abnormal dreams	17	(4.7)	42	(11.5)	-6.9 (-11.0, -3.0)
Anxiety	8	(2.2)	10	(2.7)	-0.5 (-3.1, 1.9)
Depressed mood	4	(1.1)	7	(1.9)	-0.8 (-3.0, 1.1)
Depression	8	(2.2)	12	(3.3)	-1.1 (-3.7, 1.4)
Insomnia	19	(5.2)	32	(8.8)	-3.6 (-7.4, 0.1)
Irritability	1	(0.3)	4	(1.1)	-0.8 (-2.5, 0.5)
Nightmare	12	(3.3)	17	(4.7)	-1.4 (-4.4, 1.6)
Sleep disorder	4	(1.1)	11	(3.0)	-1.9 (-4.4, 0.2)
Renal and urinary disorders	**8**	**(2.2)**	**7**	**(1.9)**	**0.3 (-2.0, 2.6)**
Reproductive system and breast disorders	**13**	**(3.6)**	**18**	**(4.9)**	**-1.4 (-4.5, 1.6)**
Respiratory, thoracic and mediastinal disorders	**49**	**(13.5)**	**33**	**(9.1)**	**4.4 (-0.2, 9.1)**
Cough	16	(4.4)	14	(3.8)	0.5 (-2.5, 3.6)
Epistaxis	4	(1.1)	1	(0.3)	0.8 (-0.5, 2.5)
Nasal congestion	5	(1.4)	7	(1.9)	-0.5 (-2.7, 1.5)
Oropharyngeal pain	11	(3.0)	6	(1.6)	1.4 (-0.9, 3.9)
Rhinitis allergic	5	(1.4)	1	(0.3)	1.1 (-0.3, 2.9)

Analysis of Subjects With Adverse Events
(Incidence ≥4 Subjects in One or More Treatment Groups)
Weeks 0-48 (P021)

	DOR/3TC/TDF QD		EFV/FTC/TDF QD		Difference in % vs EFV/FTC/TDF QD
	n	(%)	n	(%)	Estimate (95% CI)[†]
Respiratory, thoracic and mediastinal disorders	**49**	**(13.5)**	**33**	**(9.1)**	**4.4 (-0.2, 9.1)**
Rhinorrhoea	5	(1.4)	3	(0.8)	0.5 (-1.2, 2.5)
Sinus congestion	4	(1.1)	4	(1.1)	0.0 (-1.8, 1.8)
Skin and subcutaneous tissue disorders	**61**	**(16.8)**	**95**	**(26.1)**	**-9.3 (-15.3, -3.4)**
Alopecia	6	(1.6)	2	(0.5)	1.1 (-0.5, 3.1)
Dermal cyst	4	(1.1)	1	(0.3)	0.8 (-0.5, 2.5)
Dermatitis allergic	1	(0.3)	7	(1.9)	-1.6 (-3.7, -0.2)
Pruritus	5	(1.4)	6	(1.6)	-0.3 (-2.3, 1.7)
Rash	17	(4.7)	44	(12.1)	-7.4 (-11.6, -3.5)
Rash erythematous	0	(0.0)	4	(1.1)	-1.1 (-2.8, -0.0)
Rash generalised	0	(0.0)	6	(1.6)	-1.6 (-3.6, -0.6)
Rash maculo-papular	3	(0.8)	4	(1.1)	-0.3 (-2.1, 1.4)
Vascular disorders	**14**	**(3.8)**	**7**	**(1.9)**	**1.9 (-0.6, 4.7)**
Hypertension	9	(2.5)	3	(0.8)	1.6 (-0.2, 3.9)

[†] Based on Miettinen & Nurminen method.
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.
Estimated differences and confidence intervals are provided in accordance with the statistical analysis plan.
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] [P021V01MK1439A: tabulations-aeplus]

Drug-Related Adverse Events (Overall)

In P021, drug-related AEs were reported for a lower proportion of subjects in the DOR/3TC/TDF treatment group (31.0%) compared with the EFV/FTC/TDF treatment group (62.9%) [Table 2.7.4: 25]. Drug-related AEs were most frequently associated with the SOC of nervous system disorders. A lower proportion of subjects in the DOR/3TC/TDF treatment group (12.9%) compared to the EFV/FTC/TDF treatment group (37.9%) experienced drug-related AEs in this SOC.

The most commonly reported drug-related AEs (≥2% of subjects in either treatment group presented in descending order of DOR frequency) were dizziness, somnolence, headache, abnormal dreams, and rash. Notably, the AE of dizziness was disproportionally higher in the EFV/FTC/TDF group (31.9%) compared with the DOR/3TC/TDF group (6.6%). Rash was also reported at a higher rate for the EFV/FTC/TDF group (8.5%) compared with the DOR/3TC/TDF group (1.6%). The other reported drug-related AEs did not have meaningful clinical differences between treatment groups.

AEs considered by the investigator to be drug-related and moderate or severe in intensity were experienced by fewer subjects in the DOR/3TC/TDF treatment group (10.4%), compared to the EFV/FTC/TDF treatment group (25.0%) [Ref. 5.3.5.1: P021V01MK1439A: Table 14.3-11].

The most common drug-related AE by Week 48 (incidence ≥2% of subjects in either treatment group presented in descending order of DOR frequency) that were considered by the investigator to be moderate or severe in intensity were dizziness, abnormal dreams, and rash. Each of these AEs was reported for a higher proportion of subjects in the EFV/FTC/TDF treatment group compared with the DOR/3TC/TDF treatment group. Notably, dizziness and rash were reported at a higher rate in the EFV/FTC/TDF group (6.0% and 4.7%) compared with the DOR/3TC/TDF group (1.4% and <1%).

The proportions of subjects with any drug-related AE by preferred term, for all such AEs (with >0% incidence), are summarized in [Ref. 5.3.5.1: P021V01MK1439A: Table 14.3-10].

Table 2.7.4: 25
Subjects With Drug-Related Adverse Events
(Incidence ≥2% in One or More Treatment Groups)
Overall Drug Related
Weeks 0-48 (P021)

	DOR/3TC/TDF QD		EFV/FTC/TDF QD		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	364		364		728	
with one or more drug-related adverse events	113	(31.0)	229	(62.9)	342	(47.0)
with no drug-related adverse events	251	(69.0)	135	(37.1)	386	(53.0)
Ear and labyrinth disorders	1	(0.3)	10	(2.7)	11	(1.5)
Gastrointestinal disorders	33	(9.1)	59	(16.2)	92	(12.6)
Diarrhoea	12	(3.3)	20	(5.5)	32	(4.4)
Nausea	18	(4.9)	24	(6.6)	42	(5.8)
Vomiting	6	(1.6)	11	(3.0)	17	(2.3)
General disorders and administration site conditions	20	(5.5)	23	(6.3)	43	(5.9)
Fatigue	13	(3.6)	11	(3.0)	24	(3.3)
Investigations	4	(1.1)	12	(3.3)	16	(2.2)
Metabolism and nutrition disorders	8	(2.2)	12	(3.3)	20	(2.7)
Nervous system disorders	47	(12.9)	138	(37.9)	185	(25.4)
Dizziness	24	(6.6)	116	(31.9)	140	(19.2)
Headache	14	(3.8)	16	(4.4)	30	(4.1)
Somnolence	11	(3.0)	24	(6.6)	35	(4.8)
Psychiatric disorders	42	(11.5)	86	(23.6)	128	(17.6)
Abnormal dreams	17	(4.7)	34	(9.3)	51	(7.0)
Insomnia	15	(4.1)	18	(4.9)	33	(4.5)
Nightmare	9	(2.5)	15	(4.1)	24	(3.3)
Sleep disorder	2	(0.5)	8	(2.2)	10	(1.4)
Skin and subcutaneous tissue disorders	12	(3.3)	55	(15.1)	67	(9.2)
Rash	6	(1.6)	31	(8.5)	37	(5.1)

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.
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] [P021V01MK1439A: tabulations-aeplus]

2.4.2 Deaths

In P021, two deaths were reported for the EFV/FTC/TDF treatment group by Week 48. Both were considered by the investigator to be not drug-related.

- One subject in the EFV/FTC/TDF treatment group was found unconscious at home on Day 58 with a needle nearby and venipuncture site in the left upper limb. Subsequently, the subject was brought to the Emergency Department where vital signs were not recordable, and the subject did not respond to cardiopulmonary resuscitation. It was unknown if, or what the subject had ingested or injected. No autopsy report or death certificate was available; thus, the reported cause of death was not known. It was reported that the subject had not taken study medication on Day 58 and the reported last dose of study medication was on Day 57.
- One subject in the EFV/FTC/TDF treatment group committed suicide on Day 337. The study medication that had been dispensed the previous day was unopened. The subject had experienced traumatic events (friend's death and job loss) prior to the suicide and the investigator considered the suicide as not related to study therapy.

Two additional subject deaths were reported as post-treatment (1 in each treatment group) and were considered by the investigator to be not drug-related. These deaths have been displayed as post-treatment since the last recorded dose of study medication was >14 days from the date of death. However, this reflects the subjects' last study visit, and not necessarily the day they took the last dose of study drug.

- One subject in the DOR/3TC/TDF treatment group died on Day 87. The subject was not hospitalized and had last been seen by the investigator on Day 58 at the last scheduled study visit. An autopsy was not performed and the cause of death was reported to be unknown. The last recorded dose of study medication was on Day 58 at the subject's study visit. It is unknown but presumed the subject was taking study medication at the time of death.
- One subject in the EFV/FTC/TDF treatment group died on Day 384 of injuries sustained in a road accident. The last recorded dose of study medication was on Day 338 at the subject's last scheduled study visit. It is unknown but presumed the subject was taking study medication at the time of death.

Complete narratives for these cases are found in [Ref. 5.3.5.1: P021V01MK1439A: 16.2.7.2].

2.4.3 Other Serious Adverse Events

By Week 48, 34 (4.7%) of the 728 treated subjects in P021 experienced an SAE [Ref. 5.3.5.1: P021V01MK1439A: Table 14.3-1]. The proportion of subjects with SAEs was comparable for the DOR/3TV/TDF treatment group (3.6%) against the EFV/FTC/TDF treatment group (5.8%). No single SAE was experienced by more than 2 subjects in the study. The most commonly reported SAEs (>1 subject in either treatment group) were

anogenital warts (2 subjects in the DOR/3TC/TDF group), appendicitis, endometritis and pneumonia (each of these AEs were experienced by 1 subject in the DOR/3TC/TDF group and 1 subject in the EFV/FTC/TDF group).

Five subjects (1 in the DOR/3TC/TDF group and 4 in the EFV/FTC/TDF treatment group) experienced SAEs that were considered by the investigator to be drug related SAEs:

One subject in the DOR/3TC/TDF group experienced 3 drug-related SAEs: asthenia, insomnia, and nightmare. The subject was discontinued from the study on Day 272. The asthenia was resolving and by the data cutoff date, the insomnia had not yet resolved, and the nightmare had resolved with a duration of 3.14 weeks.

Four subjects in the EFV/FTC/TDF group experienced 1 drug-related SAE each as follows:

- Hypertriglyceridaemia (dose interrupted and SAE resolved in 1.54 months)
- Rash generalized (subject discontinued and SAE resolved in 1.14 weeks)
- Rash macular (subject discontinued and SAE resolved in 2.86 weeks)
- Rash maculo-papular (subject discontinued and SAE resolved in 2 weeks)

Listings of SAEs by subject by Week 48 and through the data cutoff date are in [Ref. 5.3.5.1: P021V01MK1439A: 16.2.7.1.1] and [Ref. 5.3.5.1: P021V01MK1439A: 16.2.7.1.2], respectively. Narratives for subjects with SAEs are in [Ref. 5.3.5.1: P021V01MK1439A: 16.2.7.2].

Narratives for these subjects are found in the CSR for this trial [Ref. 5.3.5.1: P021V01MK1439A: 16.2.7.2].

2.4.4 Adverse Events Leading to Discontinuation

By Week 48, 35 subjects in P021 experienced AEs that led to discontinuation. A lower proportion of subjects in the DOR/3TC/TDF treatment group (11 subjects, 3.0%) were discontinued from the study due to an AE, compared with the EFV/FTC/TDF treatment group (24 subjects, 6.6%) [Table 2.7.4: 23]. The most common AE leading to discontinuation was rash, which occurred only in the EFV/FTC/TDF group (12 subjects [Ref. 5.3.5.1: P021V01MK1439A: 16.2.7-6]). No single AE leading to discontinuation in the DOR/3TC/TDF group occurred in more than 1 subject.

A lower proportion of subjects discontinued from the study due to drug-related AEs in the DOR/3TC/TDF treatment group (8 subjects [2.2%]) compared with the EFV/FTC/TDF group (21 subjects [5.8%]) [Table 2.7.4: 23] by Week 48. The main reasons for discontinuation were:

- DOR/3TC/TDF group: 4 subjects discontinued from the study due to a drug-related CNS AE, 1 subject due to drug-related alopecia, 1 subject due to drug-related abdominal pain upper, and 1 subject with drug-related vomiting.

- EFV/FTC/TDF group: 12 subjects discontinued from the study due to a drug-related AE of rash and 9 subjects due to drug-related CNS-AE [Ref. 5.3.5.1: P021V01MK1439A: 16.2.7-6].

Six (2 in the DOR/3TC/TDF group and 4 in the EFV/FTC/TDF group) of the 35 subjects discontinued from the study due to an SAE(s) s [Ref. 5.3.5.1: P021V01MK1439A: 16.2.7-6]:

- DOR/3TC/TDF group: 1 subject with drug-related asthenia, insomnia, and nightmare and 1 subject with esophageal obstruction
- EFV/FTC/TDF group: 1 subject each with acute kidney injury, rash generalized, rash macular, and rash maculo-papular.

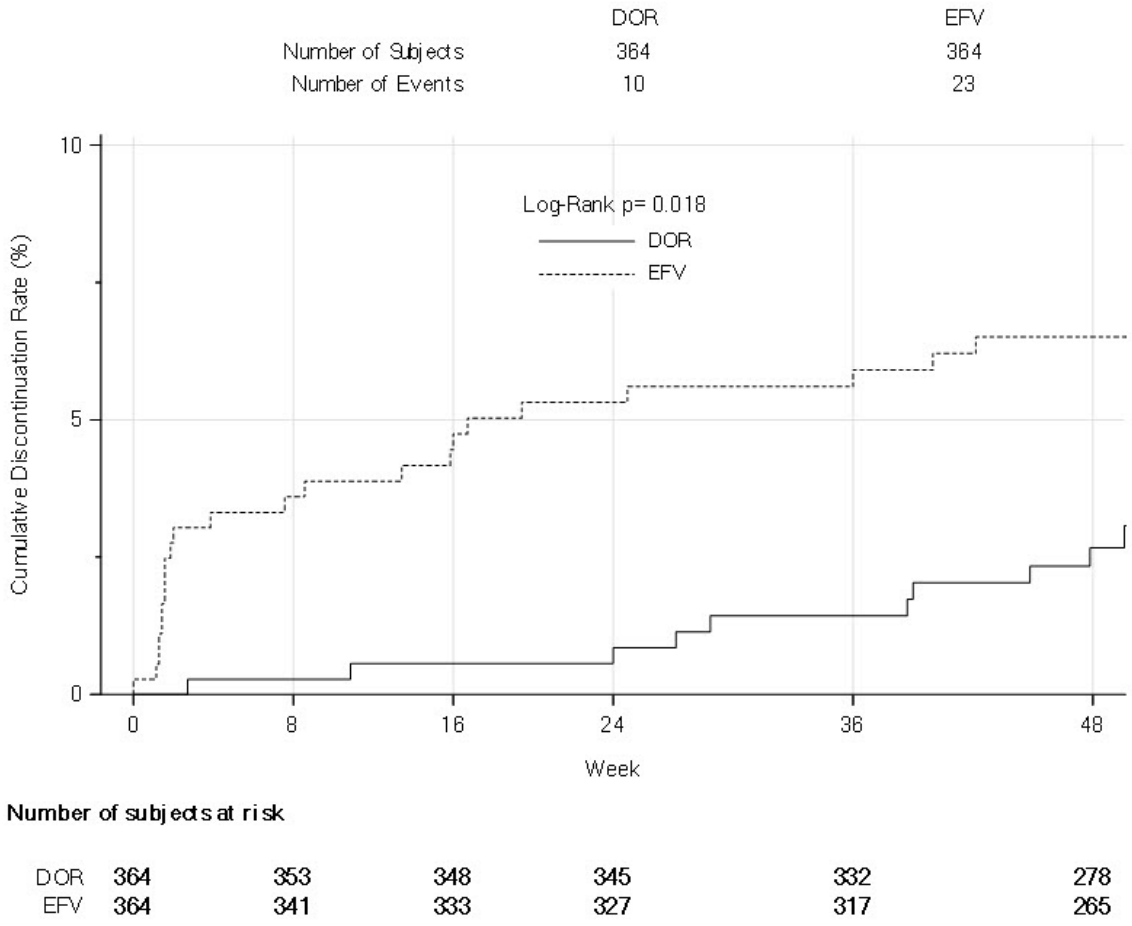
Overall, there was a lower risk of discontinuation due to AE in the DOR/3TC/TDF treatment group (10 events) compared with the EFV/FTC/TDF treatment group (23 events). Results of the log-rank test indicate that the time to discontinuation due to any AE was longer for DOR/3TC/TDF compared with EFV/FTC/TDF ($p = 0.018$, not adjusted for multiplicity), as seen in [Ref. 5.3.5.1: P021V01MK1439A: Table 14.3-15]. As seen in the Kaplan-Meir plot for time to discontinuation due to AE, subjects in the EFV treatment group experienced AEs that led to discontinuation from the study earlier in the trial (~Week 1 to 2 of the study) than the subjects in the DOR/3TC/TDF treatment group, and this difference was maintained thereafter.

Three subjects (0.8%) in the DOR/3TC/TDF treatment group compared with 6 subjects (1.6%) in the EFV/FTC/TDF treatment group discontinued study drug due to neuropsychiatric events.

The Kaplan-Meier plot for time to discontinuation due to AE is presented in [Figure 2.7.4: 3].

A listing of all subjects who discontinued due to AE by Week 48 is provided in [Ref. 5.3.5.1: P021V01MK1439A: 16.2.7-6] and a listing of subjects who discontinued due to AE through the data cutoff date is provided in [Ref. 5.3.5.1: P021V01MK1439A: 16.2.7-7].

Figure 2.7.4: 3
Kaplan-Meier Plot for Time to Discontinuation Due to Adverse Event Weeks 0-48 (P021)



DOR=DOR/3TC/TDF QD; EFV=EFV/FTC/TDF QD
Source: [P021V01MK1439A: analysis-adtte]

2.4.5 Adverse Events of Special Interest

2.4.5.1 Neuropsychiatric Events

The proportion of participants with AEs in prespecified neuropsychiatric categories by Week 48 were pre-defined safety endpoints in P021. A selected list of neuropsychiatric adverse event categories was examined, including the following:

- **Prespecified Tier-1 categories/primary endpoints**: Dizziness, sleep disorders/disturbances, altered sensorium (including disturbance in attention)
- **Prespecified Tier-2 categories/secondary endpoints**: Depression/suicide/self-injury, psychosis/psychotic disorders.

The Tier 1 safety endpoints were subject to inferential testing for statistical significance with p values and 95% CIs provided for between-group comparisons. The Tier 2 endpoints were assessed via point estimates with 95% CIs provided for between-group comparisons. A complete list of the preferred terms (based on MedDRA version 19.1) that were used to define these neuropsychiatric categories can be found in Appendix I of the supplemental SAP [Ref. 5.3.5.1: P021V01MK1439A: 16.1.9.1].

The proportion of subjects with neuropsychiatric events overall by Week 48 was lower in the DOR/3TC/TDF treatment group compared with the EFV/FTC/TDF treatment group (23.6% vs 56.9%, respectively; treatment difference of -33.2% [-39.8, -26.4]) [Table 2.7.4: 26]. The DOR/3TC/TDF treatment group was statistically significantly superior (ie more favorable safety results) to the EFV/FTC/TDF treatment group for each of the 3 categories of dizziness, sleep disorders/disturbances, and altered sensorium (including disturbance in attention) (2-sided $p \leq 0.001$, 2-sided $p \leq 0.001$ and 2-sided $p = 0.033$, respectively).

The number and percentage of subjects with neuropsychiatric events by specific term and a sensitivity analysis which included the Altered Sensorium category (DOR/3TC/TDF vs EFV/FTC/TDF) by Week 48 are provided in [Ref. 5.3.5.1: P021V01MK1439A: Table 12-5]. This sensitivity analysis showed similar results for the DOR/3TC/TDF group compared with the EFV/FTC/TDF group for this category (2-sided $p = 0.014$).

A tabulation of subjects with neuropsychiatric adverse events by Week 48 is presented in [Ref. 5.3.5.1: P021V01MK1439A: Table 14.3-3], and subjects with neuropsychiatric adverse events including disturbance in attention by Week 48 is presented in [Ref. 5.3.5.1: P021V01MK1439A: Table 14.3-4].

Table 2.7.4: 26
Analysis of Subjects with Neuropsychiatric Adverse Events by Week 48 (P021)

	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 prespecified 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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2.4.6 Conclusions

In P021, DOR/3TC/TDF administered for 48 weeks was generally well tolerated in 364 treatment-naïve subjects infected with HIV-1 and had a favorable safety profile compared to EFV/FTC/TDF.

DOR/3TC/TDF had a superior neuropsychiatric safety profile compared to that of EFV/FTC/TDF as assessed by the neuropsychiatric events of dizziness, sleep disorders and disturbances, and altered sensorium; that is, a statistically significantly lower proportion of DOR/3TC/TDF-treated subjects compared to EFV/FTC/TDF-treated subjects reported neuropsychiatric adverse events by Week 48 in the pre-specified categories of dizziness, sleep disorders and disturbances, and altered sensorium. The treatment difference between the treatment groups was also considered to be clinically meaningful.

The time to discontinuation due to any AE was longer for DOR/3TC/TDF compared with EFV/FTCTDF (non-multiplicity-adjusted p=0.018, log-rank test).

A lower proportion of subjects in the DOR/3TC/TDF group (3%) discontinued due to an AE by Week 48 compared with the EFV/FTC/TDF group (7%) [treatment difference -3.6%, -6.9, -0.5].

2.5 Adverse Events in the Integrated Safety Population Pool

The following section in this summary of safety provides the results of the integrated analysis of safety that was performed in two population pools. The main pool included subjects from the two Phase 3 trials (P018 and P021) and subjects initially randomized to the 100 mg dose group of DOR and EFV group in P007 (Main Safety Pool). A separate pooled analysis was conducted for discontinuation due to adverse events (AE) and neuropsychiatric AEs that included only subjects initially randomized to the DOR 100 mg dose group and EFV group from P007 and subjects from P021 (Special Safety Pool).

A description of the endpoints and timepoints assessed for the MSP and SSP is provided in [Sec. 1.1.3]. The trials and treatment groups included in each pool are depicted in [Figure 2.7.4: 1].

2.5.1 Adverse Events in the Main Safety Pool (P007, P018, and P021)

2.5.1.1 Common Adverse Events

By Week 48, the proportion of subjects reporting AEs, drug-related AEs, and SAEs in the MSP were similar for the Main Combined DOR treatment group and the Main DRV+r treatment group [Table 2.7.4: 27]. The proportion of subjects discontinuing study medication due to AEs and drug-related AEs was also similar for these treatment groups.

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. Similar proportions of subjects reported AEs in other categories in both treatment groups.

Table 2.7.4: 27
Adverse Event Summary
Main Safety Pool (P007 (DOR 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: DOR 100 mg administered with FTC/TDF in P007 and P018 or ABC/3TC in P018, or fixed dose combination of DOR/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: EFV 600 mg administered with FTC/TDF in P007, or fixed dose combination of EFV/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]

By Week 48 in the MSP, the most frequently reported AEs in the Main Combined DOR, the Main DVR+r, and Main Combined EFV treatment groups were under the SOCs of Infections and Infestations (51.0%, 48.0%, and 48.1%, respectively), Gastrointestinal Disorders (34.9%, 42.3%, and 37.9%, respectively), Nervous System Disorders (24.7%, 19.1%, and 47.2%, respectively), and Psychiatric Disorders (16.8%, 13.3%, and 36.0%, respectively) [Table 2.7.4: 28].

The most frequently reported AEs for all treatment groups (incidence ≥5% in one or more treatment groups) were headache, diarrhea, nausea, nasopharyngitis, upper respiratory tract infection, dizziness, and fatigue (presented in descending order of the Main Combined DOR frequency).

The AE of dizziness was more frequently observed among subjects treated with EFV (35.4%) than among those treated with DOR (7.1%). In addition, the AEs of abnormal dreams and rash were more frequently observed among subjects treated with EFV (12.3% and 11.0%) than among those treated with DOR (3.4% and 3.0%). The AE of diarrhea was more frequently observed among subjects treated with DRV+r (22.5%) than among those treated with DOR (12.4%).

Summaries of AEs for all data available through the data cutoff date are provided in [Table 5.3.5.3.3-trtmtnve48wk: 22]. Results are consistent with the AEs by Week 48 described above.

A summary with incidence >0% is provided in [Table 5.3.5.3.3-trtmtnve48wk: 23], and a summary with incidence >10% is provided in [Table 5.3.5.3.3-trtmtnve48wk: 25].

Table 2.7.4: 28
Subjects With Adverse Events
(Incidence ≥5% in One or More Treatment Groups)
Main Safety Pool (P007 (DOR 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)**

Subjects With Adverse Events
(Incidence ≥5% in One or More Treatment Groups)
Main Safety Pool (P007 (DOR 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: DOR 100 mg administered with FTC/TDF in P007 and P018 or ABC/3TC in P018, or fixed dose combination of DOR/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: EFV 600 mg administered with FTC/TDF in P007, or fixed dose combination of EFV/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]

Drug-Related Adverse Events (Overall)

In the MSP, drug-related AEs were reported for a lower proportion of subjects in the Main Combined DOR treatment group (30.9%) compared to the Main Combined EFV treatment group (61.4%) [Table 2.7.4: 29].

- The most frequently reported drug-related AEs for the Main Combined DOR treatment group (presented in descending order of the Main Combined DOR frequency) were nausea, dizziness, headache, diarrhea, abnormal dreams, and insomnia.
- Diarrhea was reported for a lower proportion of subjects in the Main Combined DOR group compared with the Main DRV+r treatment group.
- Dizziness, abnormal dreams, and rash were reported for a lower proportion of subjects in the Main Combined DOR group compared with the Main Combined EFV treatment group.
- All other drug-related AEs were reported in similar proportions of subjects in each of the 3 groups, with no meaningful clinical differences observed.
- Drug-related AEs of moderate or severe intensity were reported for 8.8% of subjects in the Main Combined DOR treatment group, 7.0% in the Main DRV+r treatment group, and 25.8% of subjects in the Main Combined EFV treatment group [Table 2.7.4: 30].

Table 2.7.4: 29
Subjects With Drug-Related Adverse Events
(Incidence ≥2% in One or More Treatment Groups)
Overall Drug Related
Main Safety Pool (P007 (DOR 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 drug-related adverse events	264	(30.9)	123	(32.1)	290	(61.4)
with no drug-related adverse events	591	(69.1)	260	(67.9)	182	(38.6)
Ear and labyrinth disorders	**1**	**(0.1)**	**0**	**(0.0)**	**11**	**(2.3)**
Gastrointestinal disorders	**111**	**(13.0)**	**85**	**(22.2)**	**78**	**(16.5)**
Diarrhoea	34	(4.0)	49	(12.8)	27	(5.7)
Nausea	51	(6.0)	29	(7.6)	30	(6.4)
Vomiting	14	(1.6)	5	(1.3)	13	(2.8)
General disorders and administration site conditions	**48**	**(5.6)**	**13**	**(3.4)**	**35**	**(7.4)**
Fatigue	35	(4.1)	8	(2.1)	16	(3.4)
Investigations	**11**	**(1.3)**	**5**	**(1.3)**	**14**	**(3.0)**
Metabolism and nutrition disorders	**12**	**(1.4)**	**8**	**(2.1)**	**15**	**(3.2)**
Nervous system disorders	**94**	**(11.0)**	**19**	**(5.0)**	**176**	**(37.3)**
Dizziness	42	(4.9)	7	(1.8)	145	(30.7)
Headache	40	(4.7)	10	(2.6)	22	(4.7)
Somnolence	12	(1.4)	1	(0.3)	25	(5.3)
Psychiatric disorders	**81**	**(9.5)**	**13**	**(3.4)**	**120**	**(25.4)**
Abnormal dreams	27	(3.2)	1	(0.3)	50	(10.6)
Insomnia	26	(3.0)	6	(1.6)	21	(4.4)
Nightmare	16	(1.9)	3	(0.8)	24	(5.1)
Sleep disorder	13	(1.5)	1	(0.3)	15	(3.2)
Skin and subcutaneous tissue disorders	**28**	**(3.3)**	**17**	**(4.4)**	**69**	**(14.6)**

Subjects With Drug-Related Adverse Events
(Incidence ≥2% in One or More Treatment Groups)
Overall Drug Related
Main Safety Pool (P007 (DOR 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	**28**	**(3.3)**	**17**	**(4.4)**	**69**	**(14.6)**
Rash	8	(0.9)	2	(0.5)	34	(7.2)

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: DOR 100 mg administered with FTC/TDF in P007 and P018 or ABC/3TC in P018, or fixed dose combination of DOR/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: EFV 600 mg administered with FTC/TDF in P007, or fixed dose combination of EFV/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]

Table 2.7.4: 30
Subjects With Drug-Related Adverse Events of Moderate or Severe Intensities
(Incidence ≥2% in One or More Treatment Groups)
Overall Drug Related
Main Safety Pool (P007 (DOR 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 drug-related adverse events	75	(8.8)	27	(7.0)	122	(25.8)
with no drug-related adverse events	780	(91.2)	356	(93.0)	350	(74.2)
Gastrointestinal disorders	**21**	**(2.5)**	**10**	**(2.6)**	**13**	**(2.8)**
Nervous system disorders	**15**	**(1.8)**	**6**	**(1.6)**	**46**	**(9.7)**
Dizziness	7	(0.8)	1	(0.3)	34	(7.2)
Psychiatric disorders	**27**	**(3.2)**	**5**	**(1.3)**	**38**	**(8.1)**
Abnormal dreams	3	(0.4)	0	(0.0)	14	(3.0)
Skin and subcutaneous tissue disorders	**8**	**(0.9)**	**5**	**(1.3)**	**38**	**(8.1)**
Rash	2	(0.2)	1	(0.3)	19	(4.0)

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: DOR 100 mg administered with FTC/TDF in P007 and P018 or ABC/3TC in P018, or fixed dose combination of DOR/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: EFV 600 mg administered with FTC/TDF in P007, or fixed dose combination of EFV/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]

Proportions of subjects with any drug-related AE, for all such AEs (with >0% incidence), are provided for the MSP in [Table 5.3.5.3.3-trtmtnve48wk: 26].

Proportions of subjects with any drug-related AE of moderate or severe intensity, for all such AEs (with >0% incidence), are provided for the MSP in [Table 5.3.5.3.3-trtmtnve48wk: 28].

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2.5.1.2 Deaths

Three deaths (<1% of the MSP) were reported in the MSP by Week 48. None of the deaths were considered to be related to study drug by the investigators. One subject (P018) was in the Main Combined DOR group (case of death: natural causes) and 2 subjects (P021) were in the Main Combined EFV group (in 1 case the cause of death was unknown, in the other the cause of death was suicide) [Table 2.7.4: 27]. The 3 subject deaths are also described in [Sec. 2.7.4.2.3.2] and [Sec. 2.7.4.2.4.2].

Two additional deaths (both in P021) were reported post-study, 1 in the Main Combined DOR treatment group (the cause of death was unknown), and 1 in the Main Combined EFV treatment group (the cause of death was injuries sustained in a road accident) [Sec. 2.7.4.2.4.2] [Table 5.3.5.3.3-trtmtnve48wk: 32]. Those deaths were also considered to be not related to study medication.

No deaths were reported for the Main DRV+r group.

Listings of subjects with AEs resulting in death by Week 48, through the data cutoff date, and through the data cutoff date including post-study are in [Table 5.3.5.3.3-trtmtnve48wk: 30], [Table 5.3.5.3.3-trtmtnve48wk: 31], and [Table 5.3.5.3.3-trtmtnve48wk: 32] respectively.

2.5.1.3 Other Serious Adverse Events

By Week 48, SAEs were reported for a low (92 subjects, 5.4%) proportion of the 1710 treated subjects in the MSP [Table 2.7.4: 31]. The proportion of subjects with SAEs was generally similar in the 3 Main treatment groups. SAEs reported for ≥2 subjects were: anogenital warts (Main Combined DOR: n=2), appendicitis (Main Combined DOR: n=2, and Main Combined EFV: n=1), pneumonia (Main Combined DOR: n=2 and Main Combined EFV group: n=1), tuberculosis (Main DRV+r: N=2), back pain (Main DRV+r: N=2), and suicidal ideation (Main Combined EFV: N=2). All other SAEs occurred in 1 subject each [Table 2.7.4: 31].

A summary of SAEs through the data cutoff date with incidence >0% is provided in [Table 5.3.5.3.3-trtmtnve48wk: 34]. Listings of SAEs by subject by Week 48 and through the data cutoff date are in [Table 5.3.5.3.3-trtmtnve48wk: 36] and [Table 5.3.5.3.3-trtmtnve48wk: 37] respectively. Narratives for subjects with SAEs are in provided in the individual CSRs [Ref. 5.3.5.1: P007V01MK1439: 16.2.7] [Ref. 5.3.5.1: P018V01MK1439: 16.2.7.2] [Ref. 5.3.5.1: P021V01MK1439A: 16.2.7.2].

Table 2.7.4: 31
Subjects With Serious Adverse Events
(Incidence >0% in One or More Treatment Groups)
Main Safety Pool (P007 (DOR 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 serious adverse events	39	(4.6)	23	(6.0)	30	(6.4)
with no serious adverse events	816	(95.4)	360	(94.0)	442	(93.6)
Blood and lymphatic system disorders	**1**	**(0.1)**	**0**	**(0.0)**	**0**	**(0.0)**
Normochromic normocytic anaemia	1	(0.1)	0	(0.0)	0	(0.0)
Cardiac disorders	**1**	**(0.1)**	**0**	**(0.0)**	**0**	**(0.0)**
Supraventricular tachycardia	1	(0.1)	0	(0.0)	0	(0.0)
Ear and labyrinth disorders	**1**	**(0.1)**	**1**	**(0.3)**	**0**	**(0.0)**
Deafness	1	(0.1)	0	(0.0)	0	(0.0)
Vertigo	0	(0.0)	1	(0.3)	0	(0.0)
Gastrointestinal disorders	**4**	**(0.5)**	**3**	**(0.8)**	**1**	**(0.2)**
Abdominal distension	0	(0.0)	1	(0.3)	0	(0.0)
Abdominal pain	0	(0.0)	1	(0.3)	0	(0.0)
Anal fistula	1	(0.1)	1	(0.3)	0	(0.0)
Colitis	1	(0.1)	0	(0.0)	1	(0.2)
Inguinal hernia	0	(0.0)	1	(0.3)	0	(0.0)
Nausea	1	(0.1)	0	(0.0)	0	(0.0)
Oesophageal obstruction	1	(0.1)	0	(0.0)	0	(0.0)
Vomiting	1	(0.1)	0	(0.0)	0	(0.0)
General disorders and administration site conditions	**2**	**(0.2)**	**2**	**(0.5)**	**1**	**(0.2)**
Asthenia	1	(0.1)	0	(0.0)	0	(0.0)
Death	1	(0.1)	0	(0.0)	1	(0.2)
Non-cardiac chest pain	0	(0.0)	1	(0.3)	0	(0.0)
Oedema peripheral	0	(0.0)	1	(0.3)	0	(0.0)
Hepatobiliary disorders	**3**	**(0.4)**	**0**	**(0.0)**	**0**	**(0.0)**
Bile duct stone	1	(0.1)	0	(0.0)	0	(0.0)
Cholecystitis	1	(0.1)	0	(0.0)	0	(0.0)
Cholecystitis acute	1	(0.1)	0	(0.0)	0	(0.0)
Infections and infestations	**13**	**(1.5)**	**8**	**(2.1)**	**9**	**(1.9)**
Abdominal abscess	1	(0.1)	0	(0.0)	1	(0.2)
Acute hepatitis C	1	(0.1)	0	(0.0)	0	(0.0)
Appendicitis	2	(0.2)	0	(0.0)	1	(0.2)
Atypical pneumonia	0	(0.0)	1	(0.3)	0	(0.0)
Bronchitis	0	(0.0)	1	(0.3)	0	(0.0)

Subjects With Serious Adverse Events
(Incidence >0% in One or More Treatment Groups)
Main Safety Pool (P007 (DOR 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	(%)
Infections and infestations	**13**	**(1.5)**	**8**	**(2.1)**	**9**	**(1.9)**
Clostridium difficile infection	0	(0.0)	0	(0.0)	1	(0.2)
Diverticulitis	0	(0.0)	0	(0.0)	1	(0.2)
Endometritis	1	(0.1)	0	(0.0)	1	(0.2)
Gastroenteritis	1	(0.1)	0	(0.0)	0	(0.0)
Gastrointestinal viral infection	0	(0.0)	0	(0.0)	1	(0.2)
Influenza	0	(0.0)	1	(0.3)	0	(0.0)
Meningitis tuberculous	0	(0.0)	1	(0.3)	0	(0.0)
Nasopharyngitis	1	(0.1)	0	(0.0)	0	(0.0)
Oophoritis	0	(0.0)	0	(0.0)	1	(0.2)
Oral bacterial infection	0	(0.0)	0	(0.0)	1	(0.2)
Parotitis	1	(0.1)	0	(0.0)	0	(0.0)
Perirectal abscess	1	(0.1)	0	(0.0)	0	(0.0)
Pharyngitis	0	(0.0)	1	(0.3)	0	(0.0)
Pilonidal cyst	0	(0.0)	0	(0.0)	1	(0.2)
Pneumonia	2	(0.2)	0	(0.0)	1	(0.2)
Pneumonia bacterial	0	(0.0)	0	(0.0)	1	(0.2)
Post procedural infection	0	(0.0)	1	(0.3)	0	(0.0)
Sepsis	0	(0.0)	0	(0.0)	1	(0.2)
Sinusitis	0	(0.0)	0	(0.0)	1	(0.2)
Subcutaneous abscess	1	(0.1)	0	(0.0)	0	(0.0)
Tuberculosis	0	(0.0)	2	(0.5)	0	(0.0)
Tuberculosis of central nervous system	0	(0.0)	1	(0.3)	0	(0.0)
Viral infection	1	(0.1)	0	(0.0)	0	(0.0)
Injury, poisoning and procedural complications	**4**	**(0.5)**	**2**	**(0.5)**	**4**	**(0.8)**
Alcohol poisoning	0	(0.0)	0	(0.0)	1	(0.2)
Femur fracture	1	(0.1)	0	(0.0)	0	(0.0)
Foreign body	0	(0.0)	0	(0.0)	1	(0.2)
Jaw fracture	1	(0.1)	0	(0.0)	0	(0.0)
Post procedural haemorrhage	1	(0.1)	1	(0.3)	0	(0.0)
Subdural haematoma	0	(0.0)	1	(0.3)	1	(0.2)
Tendon rupture	0	(0.0)	0	(0.0)	1	(0.2)
Traumatic haemothorax	1	(0.1)	0	(0.0)	0	(0.0)
Metabolism and nutrition disorders	**1**	**(0.1)**	**1**	**(0.3)**	**1**	**(0.2)**
Hypertriglyceridaemia	0	(0.0)	0	(0.0)	1	(0.2)
Hyponatraemia	0	(0.0)	1	(0.3)	0	(0.0)
Hypovolaemia	1	(0.1)	0	(0.0)	0	(0.0)

Subjects With Serious Adverse Events
(Incidence >0% in One or More Treatment Groups)
Main Safety Pool (P007 (DOR 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	(%)
Musculoskeletal and connective tissue disorders	**2**	**(0.2)**	**3**	**(0.8)**	**0**	**(0.0)**
Back pain	0	(0.0)	2	(0.5)	0	(0.0)
Intervertebral disc protrusion	1	(0.1)	0	(0.0)	0	(0.0)
Muscular weakness	1	(0.1)	0	(0.0)	0	(0.0)
Rhabdomyolysis	0	(0.0)	1	(0.3)	0	(0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**7**	**(0.8)**	**3**	**(0.8)**	**1**	**(0.2)**
Anal squamous cell carcinoma	1	(0.1)	1	(0.3)	0	(0.0)
Anogenital warts	2	(0.2)	0	(0.0)	0	(0.0)
B-cell unclassifiable lymphoma high grade	1	(0.1)	0	(0.0)	0	(0.0)
Basal cell carcinoma	0	(0.0)	0	(0.0)	1	(0.2)
Hodgkin's disease	1	(0.1)	0	(0.0)	0	(0.0)
Kaposi's sarcoma	1	(0.1)	0	(0.0)	0	(0.0)
Pancreatic carcinoma	0	(0.0)	1	(0.3)	0	(0.0)
Squamous cell carcinoma	1	(0.1)	0	(0.0)	0	(0.0)
Squamous cell carcinoma of skin	0	(0.0)	1	(0.3)	0	(0.0)
Squamous cell carcinoma of the tongue	1	(0.1)	0	(0.0)	0	(0.0)
Nervous system disorders	**2**	**(0.2)**	**3**	**(0.8)**	**2**	**(0.4)**
Aphasia	0	(0.0)	1	(0.3)	0	(0.0)
Cerebrovascular accident	1	(0.1)	0	(0.0)	0	(0.0)
Dizziness	0	(0.0)	0	(0.0)	1	(0.2)
Facial paralysis	0	(0.0)	1	(0.3)	0	(0.0)
Headache	1	(0.1)	0	(0.0)	0	(0.0)
Hemiparesis	1	(0.1)	0	(0.0)	0	(0.0)
Hypoaesthesia	1	(0.1)	0	(0.0)	0	(0.0)
Syncope	0	(0.0)	1	(0.3)	1	(0.2)
Pregnancy, puerperium and perinatal conditions	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.2)**
Abortion spontaneous	0	(0.0)	0	(0.0)	1	(0.2)
Psychiatric disorders	**4**	**(0.5)**	**2**	**(0.5)**	**5**	**(1.1)**
Completed suicide	0	(0.0)	0	(0.0)	1	(0.2)
Depression	0	(0.0)	1	(0.3)	1	(0.2)
Drug abuse	1	(0.1)	0	(0.0)	0	(0.0)
Insomnia	1	(0.1)	0	(0.0)	0	(0.0)
Nightmare	1	(0.1)	0	(0.0)	0	(0.0)
Psychotic disorder	1	(0.1)	0	(0.0)	0	(0.0)

Subjects With Serious Adverse Events
(Incidence >0% in One or More Treatment Groups)
Main Safety Pool (P007 (DOR 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	(%)
Psychiatric disorders	**4**	**(0.5)**	**2**	**(0.5)**	**5**	**(1.1)**
Schizoaffective disorder depressive type	0	(0.0)	1	(0.3)	0	(0.0)
Substance-induced mood disorder	1	(0.1)	0	(0.0)	0	(0.0)
Suicidal ideation	0	(0.0)	0	(0.0)	2	(0.4)
Suicide attempt	0	(0.0)	0	(0.0)	1	(0.2)
Renal and urinary disorders	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.2)**
Acute kidney injury	0	(0.0)	0	(0.0)	1	(0.2)
Respiratory, thoracic and mediastinal disorders	**0**	**(0.0)**	**2**	**(0.5)**	**1**	**(0.2)**
Asthma	0	(0.0)	0	(0.0)	1	(0.2)
Bronchospasm	0	(0.0)	1	(0.3)	0	(0.0)
Chronic obstructive pulmonary disease	0	(0.0)	1	(0.3)	0	(0.0)
Stridor	0	(0.0)	1	(0.3)	0	(0.0)
Skin and subcutaneous tissue disorders	**0**	**(0.0)**	**0**	**(0.0)**	**3**	**(0.6)**
Rash generalised	0	(0.0)	0	(0.0)	1	(0.2)
Rash macular	0	(0.0)	0	(0.0)	1	(0.2)
Rash maculo-papular	0	(0.0)	0	(0.0)	1	(0.2)
Social circumstances	**1**	**(0.1)**	**0**	**(0.0)**	**0**	**(0.0)**
Drug abuser	1	(0.1)	0	(0.0)	0	(0.0)
Vascular disorders	**0**	**(0.0)**	**0**	**(0.0)**	**2**	**(0.4)**
Deep vein thrombosis	0	(0.0)	0	(0.0)	1	(0.2)
Malignant hypertension	0	(0.0)	0	(0.0)	1	(0.2)

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: DOR 100 mg administered with FTC/TDF in P007 and P018 or ABC/3TC in P018, or fixed dose combination of DOR/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: EFV 600 mg administered with FTC/TDF in P007, or fixed dose combination of EFV/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]

Serious Drug-Related Adverse Events

By Week 48, only 9 (0.5%) of the 1710 subjects in the MSP reported drug-related SAEs [Table 2.7.4: 32]. The proportions of subjects with drug-related SAEs were generally similar for the 3 Main treatment groups (0.2% [2 subjects] for the Main Combined DOR treatment group, 0.3% [1 subject] for the Main DRV+r treatment group, and 1.3% [6 subjects] for the Main Combined EFV treatment group 1.3%). Each of the individual serious drug-related AE terms occurred in 1 subject each.

The 2 subjects from the Main Combined DOR treatment group (1 subject with nausea and vomiting in P018 and 1 subject with asthenia, insomnia, and nightmare in P021 are described

in [Sec. 2.7.4.2.3.3] and [Sec. 2.7.4.2.4.3], respectively. The 1 subject in the Main DVR+r treatment group with a drug-related SAE (peripheral edema) is described in [Sec. 2.7.4.2.3.3].

In the Main Combined EFV treatment group, 6 subjects experienced 1 drug-related SAE as follows: dizziness, suicidal ideation, hypertriglyceridemia, rash generalized, rash macular, and rash maculo-papular by Week 48. The suicidal ideation resolved with sequelae, and the other SAEs resolved. For the hypertriglyceridemia, the dose was interrupted. All 3 subjects with rash (generalized, macular,maculo-papular) discontinued due to these drug-related SAEs.

Narratives for these cases are found in the individual CSRs [Ref. 5.3.5.1: P007V01MK1439: 16.2.7] [Ref. 5.3.5.1: P018V01MK1439: 16.2.7.2] [Ref. 5.3.5.1: P021V01MK1439A: 16.2.7.2].

As noted above, listings of SAEs by subject (whether or not the SAEs were considered drug-related) by Week 48 and through the data cutoff date are in [Table 5.3.5.3.3-trtmtnve48wk: 36] and [Table 5.3.5.3.3-trtmtnve48wk: 37], respectively.

Table 2.7.4: 32
Subjects With Serious Drug-Related Adverse Events
(Incidence >0% in One or More Treatment Groups)
Overall Drug Related
Main Safety Pool (P007 (DOR 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 serious drug-related adverse events	2	(0.2)	1	(0.3)	6	(1.3)
with no serious drug-related adverse events	853	(99.8)	382	(99.7)	466	(98.7)
Gastrointestinal disorders	**1**	**(0.1)**	**0**	**(0.0)**	**0**	**(0.0)**
Nausea	1	(0.1)	0	(0.0)	0	(0.0)
Vomiting	1	(0.1)	0	(0.0)	0	(0.0)
General disorders and administration site conditions	**1**	**(0.1)**	**1**	**(0.3)**	**0**	**(0.0)**
Asthenia	1	(0.1)	0	(0.0)	0	(0.0)
Oedema peripheral	0	(0.0)	1	(0.3)	0	(0.0)
Metabolism and nutrition disorders	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.2)**
Hypertriglyceridaemia	0	(0.0)	0	(0.0)	1	(0.2)
Nervous system disorders	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.2)**
Dizziness	0	(0.0)	0	(0.0)	1	(0.2)
Psychiatric disorders	**1**	**(0.1)**	**0**	**(0.0)**	**1**	**(0.2)**
Insomnia	1	(0.1)	0	(0.0)	0	(0.0)
Nightmare	1	(0.1)	0	(0.0)	0	(0.0)
Suicidal ideation	0	(0.0)	0	(0.0)	1	(0.2)
Skin and subcutaneous tissue disorders	**0**	**(0.0)**	**0**	**(0.0)**	**3**	**(0.6)**
Rash generalised	0	(0.0)	0	(0.0)	1	(0.2)
Rash macular	0	(0.0)	0	(0.0)	1	(0.2)

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Subjects With Serious Drug-Related Adverse Events
(Incidence >0% in One or More Treatment Groups)
Overall Drug Related
Main Safety Pool (P007 (DOR 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	**0**	**(0.0)**	**0**	**(0.0)**	**3**	**(0.6)**
Rash maculo-papular	0	(0.0)	0	(0.0)	1	(0.2)

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: DOR 100 mg administered with FTC/TDF in P007 and P018 or ABC/3TC in P018, or fixed dose combination of DOR/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: EFV 600 mg administered with FTC/TDF in P007, or fixed dose combination of EFV/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]

2.5.1.4 Adverse Events Leading to Discontinuation

By Week 48, a similar proportion of subjects in the MSP discontinued study medication due to an AE in the Main Combined DOR treatment group (2.5%) compared to the Main DRV+r treatment group (3.1%). A higher proportion of subjects in the Main Combined EFV treatment group (6.6%) discontinued study medication due to an AE compared to subjects in the Main Combined DOR treatment group [Table 5.3.5.3.3-trtmtnve48wk: 38].

By SOC, a higher observed proportion of subjects in the Main Combined EFV treatment group discontinued study medication due to AEs related to Psychiatric Disorders (1.9%), Nervous System Disorders (1.7%), or Skin and Subcutaneous Disorders (2.5%), compared to subjects in the Main Combined DOR group (0.5%, 0.1%, and 0.4%, respectively).

The number and percentage of subjects with specific AEs that led to discontinuation of study medication, summarized by SOC and preferred term through the data cut-off date, are provided in [Table 5.3.5.3.3-trtmtnve48wk: 39]. A listing of all subjects who discontinued due to AE by Week 48 is provided in [Table 5.3.5.3.3-trtmtnve48wk: 40]; a listing of subjects who discontinued due to AE through the data cutoff date is provided in [Table 5.3.5.3.3-trtmtnve48wk: 41].

2.5.1.5 Analysis of Adverse Events by Organ System or Syndrome

A review of AEs by organ system/ syndrome in the MSP is presented for the important clinical event of rash immune reconstitution syndrome (IRIS), and AIDS defining conditions. The occurrence of the ECI of overdose without an associated AE is described in [Sec. 2.7.4.5.6].

Listings of AEs by subject in P007, P018, and P021 can be found in [Ref. 5.3.5.1: P007V01MK1439: 16.2.7] [Ref. 5.3.5.1: P018V01MK1439: 16.2.7] [Ref. 5.3.5.1: P021V01MK1439A: 16.2.7]. The number and percentage of subjects with specific AEs summarized by SOC and preferred term by Week 48 in the MSP are in [Table 5.3.5.3.3-trtmtnve48wk: 23].

Rash

Although rash was not defined as an ECI for any of the trials included in this application, it is considered to be an important clinical event because rash is commonly associated with use of EFV and other members of the NNRTI class. To evaluate this event, an analysis of all preferred terms related to rash (rash, exfoliative rash, erythematous rash, follicular rash, genital rash, generalized rash, macular rash, maculo-papular rash, papular rash, pruritic rash, pustular rash, vesicular rash, and viral rash) was performed for the MSP.

A lower proportion of subjects experienced ≥1 AE with a PT related to rash in the Main Combined DOR (7.1%) treatment group compared with the Main Combined EFV treatment group (15.7%) [Table 2.7.4: 33]. The proportions of subjects with the PT of "rash" were notably lower for the Main Combined DOR (3.0%) treatment group compared with the Main Combined EFV treatment group (11.0%).

In the Main Combined DOR treatment group, 7.1% of subjects experienced AEs with a preferred term related to rash. Most of these were mild (6%) or moderate (1.3%) in intensity; only 1 was considered to be severe (0.1%) [Table 5.3.5.3.3-trtmtnve48wk: 43]. Nineteen subjects (2.2%) had their rash events considered to be related to study drug by the investigator. Two subjects (0.2%) were discontinued from the study due to the event of rash.

In the Main DRV+r treatment group 8.4% of subjects experienced AEs with a PT related to rash. Most of these were mild (6.8%) or moderate (1.3%). Ten subjects (2.6%) had their rash events considered to be related to study drug by the investigator. One subject (0.2%) discontinued from the study due to the event of rash.

In the Main Combined EFV treatment group, a higher proportion of subjects (15.7%) experienced AEs with a PT related to rash, compared to the Main Combined DOR. Most of these were mild (9.3%) or moderate (5.5%) in intensity. Four subjects (2.9%) had events of severe intensity. Forty eight subjects (10.2%) had rash events considered to be related to study drug by the investigator. Ten subjects (2.1%) were discontinued from the study due to the event of rash.

A listing of subjects with these AEs is found in [Table 5.3.5.3.3-trtmtnve48wk: 43].

Table 2.7.4: 33
Subjects With Adverse Events
(Incidence >0% in One or More Treatment Groups)
Rash
Main Safety Pool (P007 (DOR 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	61	(7.1)	32	(8.4)	74	(15.7)
with no adverse events	794	(92.9)	351	(91.6)	398	(84.3)
Infections and infestations	**3**	**(0.4)**	**1**	**(0.3)**	**1**	**(0.2)**
Rash pustular	2	(0.2)	1	(0.3)	0	(0.0)
Viral rash	1	(0.1)	0	(0.0)	1	(0.2)
Reproductive system and breast disorders	**1**	**(0.1)**	**0**	**(0.0)**	**0**	**(0.0)**
Genital rash	1	(0.1)	0	(0.0)	0	(0.0)
Skin and subcutaneous tissue disorders	**57**	**(6.7)**	**32**	**(8.4)**	**73**	**(15.5)**
Exfoliative rash	0	(0.0)	0	(0.0)	1	(0.2)
Rash	26	(3.0)	6	(1.6)	52	(11.0)
Rash erythematous	8	(0.9)	5	(1.3)	4	(0.8)
Rash follicular	2	(0.2)	2	(0.5)	0	(0.0)
Rash generalised	4	(0.5)	0	(0.0)	7	(1.5)
Rash macular	3	(0.4)	7	(1.8)	3	(0.6)
Rash maculo-papular	6	(0.7)	4	(1.0)	4	(0.8)
Rash papular	7	(0.8)	9	(2.3)	1	(0.2)
Rash pruritic	2	(0.2)	0	(0.0)	2	(0.4)
Rash vesicular	1	(0.1)	0	(0.0)	0	(0.0)

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: DOR 100 mg administered with FTC/TDF in P007 and P018 or ABC/3TC in P018, or fixed dose combination of DOR/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: EFV 600 mg administered with FTC/TDF in P007, or fixed dose combination of EFV/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]

Immune Reconstitution Syndrome

In the MSP, 14 subjects (<1% of the MSP) experienced at least 1 AE identified by the investigator as probably related to IRIS [Table 2.7.4: 34]. A similar proportion of subjects were observed in all three treatment groups (Main Combined DOR 0.5%, Main DRV+r 1.8%, and Main Combined EFV 0.8%)[Table 2.7.4: 34].

Across the treatment groups, most of these AEs were considered to be unrelated to study medication and most resolved with no action taken with regard to study medication.

Three subjects had AEs associated with IRIS that met the criteria to be considered SAE: tuberculosis (1 subject in the Main Combined DOR group), tuberculosis of central nervous system (1 subject in the Main Combined DOR group), and meningitis tuberculosis (1 subject in the Main Combined DOR group). Each of these events were not considered to be true cases of IRIS by the investigator.

A listing of subjects with these events by Week 48 is found in [Table 5.3.5.3.3-trtmtnve48wk: 45].

Table 2.7.4: 34
Subjects With Adverse Events
(Incidence >0% in One or More Treatment Groups)
Immune Reconstitution Syndrome
P018 and P021 Combined
Weeks 0-48

	DOR Regimen (P018, P021)		DRV+r (P018)		EFV/FTC/TDF (P021)	
	n	(%)	n	(%)	n	(%)
Subjects in population	747		383		364	
with one or more adverse events	4	(0.5)	7	(1.8)	3	(0.8)
with no adverse events	743	(99.5)	376	(98.2)	361	(99.2)
Blood and lymphatic system disorders	**0**	**(0.0)**	**1**	**(0.3)**	**0**	**(0.0)**
Lymphadenopathy	0	(0.0)	1	(0.3)	0	(0.0)
Gastrointestinal disorders	**0**	**(0.0)**	**1**	**(0.3)**	**0**	**(0.0)**
Gastrointestinal disorder	0	(0.0)	1	(0.3)	0	(0.0)
General disorders and administration site conditions	**0**	**(0.0)**	**1**	**(0.3)**	**0**	**(0.0)**
Pyrexia	0	(0.0)	1	(0.3)	0	(0.0)
Hepatobiliary disorders	**1**	**(0.1)**	**0**	**(0.0)**	**0**	**(0.0)**
Hepatitis	1	(0.1)	0	(0.0)	0	(0.0)
Infections and infestations	**1**	**(0.1)**	**5**	**(1.3)**	**3**	**(0.8)**
Acute sinusitis	0	(0.0)	0	(0.0)	1	(0.3)
Folliculitis	0	(0.0)	1	(0.3)	0	(0.0)
Gastroenteritis	0	(0.0)	0	(0.0)	1	(0.3)
Hepatitis B	0	(0.0)	1	(0.3)	0	(0.0)
Herpes simplex	1	(0.1)	0	(0.0)	0	(0.0)
Herpes zoster	0	(0.0)	0	(0.0)	1	(0.3)
Meningitis tuberculous	0	(0.0)	1	(0.3)	0	(0.0)
Molluscum contagiosum	0	(0.0)	1	(0.3)	0	(0.0)
Oral herpes	1	(0.1)	0	(0.0)	0	(0.0)
Tuberculosis	0	(0.0)	1	(0.3)	0	(0.0)
Tuberculosis of central nervous system	0	(0.0)	1	(0.3)	0	(0.0)
Investigations	**1**	**(0.1)**	**0**	**(0.0)**	**0**	**(0.0)**
Alanine aminotransferase increased	1	(0.1)	0	(0.0)	0	(0.0)
Aspartate aminotransferase increased	1	(0.1)	0	(0.0)	0	(0.0)
Skin and subcutaneous tissue disorders	**1**	**(0.1)**	**1**	**(0.3)**	**0**	**(0.0)**
Eczema	0	(0.0)	1	(0.3)	0	(0.0)

Subjects With Adverse Events
(Incidence >0% in One or More Treatment Groups)
Immune Reconstitution Syndrome
P018 and P021 Combined
Weeks 0-48

	DOR Regimen (P018, P021)		DRV+r (P018)		EFV/FTC/TDF (P021)	
	n	(%)	n	(%)	n	(%)
Skin and subcutaneous tissue disorders	**1**	**(0.1)**	**1**	**(0.3)**	**0**	**(0.0)**
Eosinophilic pustular folliculitis	1	(0.1)	0	(0.0)	0	(0.0)

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.
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]

AIDS-Defining Conditions

Seven subjects (<1% of the MSP) in the MSP experienced ≥1 AE identified as related to an AIDS-defining conditions [Table 2.7.4: 35]. None of the AEs were considered to be drug-related.

Of the 2 subjects in the Main DOR group, 1 subject had a high grade B-cell unclassifiable lymphoma and 1 subject had Kaposi's sarcoma. Of the 4 subjects in the Main DRV+r group, 3 had tuberculosis and 1 had both meningitis tuberculosis and tuberculosis of the central nervous system. One subject in the Main Combined EFV group had cytomegalovirus infection [Table 2.7.4: 35]. With the exception of the cases of tuberculosis and the cytomegalovirus infection, all of these events were classified as SAEs. A listing of subjects with 1 or more AIDS-defining conditions is provided in [Table 5.3.5.3.3-trtmtnve48wk: 47].

Table 2.7.4: 35
Subjects With Adverse Events
(Incidence >0% in One or More Treatment Groups)
AIDS Defining Condition
Main Safety Pool (P007 (DOR 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	2	(0.2)	4	(1.0)	1	(0.2)
with no adverse events	853	(99.8)	379	(99.0)	471	(99.8)
Infections and infestations	**0**	**(0.0)**	**4**	**(1.0)**	**1**	**(0.2)**
Cytomegalovirus infection	0	(0.0)	0	(0.0)	1	(0.2)
Meningitis tuberculous	0	(0.0)	1	(0.3)	0	(0.0)
Tuberculosis	0	(0.0)	3	(0.8)	0	(0.0)
Tuberculosis of central nervous system	0	(0.0)	1	(0.3)	0	(0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**2**	**(0.2)**	**0**	**(0.0)**	**0**	**(0.0)**
B-cell unclassifiable lymphoma high grade	1	(0.1)	0	(0.0)	0	(0.0)
Kaposi's sarcoma	1	(0.1)	0	(0.0)	0	(0.0)

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: DOR 100 mg administered with FTC/TDF in P007 and P018 or ABC/3TC in P018, or fixed dose combination of DOR/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: EFV 600 mg administered with FTC/TDF in P007, or fixed dose combination of EFV/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]

2.5.1.6 Conclusions

In the MSP, 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 of treatment.

DOR 100 mg compared to DRV+r 800/100 mg, each in combination with FTC/TDF or ABC/3TC, demonstrated a similar safety profile.

DOR had similar proportion of subjects who discontinued study medication due to an AE compared to DRV+r

DOR/3TC/TDF had lower proportion of subjects who discontinued study medication due to an AE compared to EFV/FTC/TDF.

DOR/3TC/TDF had a lower proportion of subjects that experience AEs of rash compared with EFV/FTC/TDF.

DOR/3TC/TDF compared to EFV/FTC/TDF demonstrated a superior safety profile with respect to the neuropsychiatric event categories of dizziness, sleep disorders and disturbances, and altered sensorium.

The results of these pooled analyses indicate that DOR and DOR/3TC/TDF have a favorable safety profile.

2.5.2 Adverse Events in the Special Safety Pool (P007 and P021) to Address Pre-specified Safety Endpoints/Safety Hypotheses

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

A description of the endpoints and timepoints assessed for the SSP is provided in [Sec. 1.1.3]. The trials and treatment groups included in the SSP are depicted in [Figure 2.7.4: 1].

2.5.2.1 Adverse Events of Special Interest

2.5.2.1.1 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 (2.8%) compared with the Special Combined EFV treatment group (6.1%) (treatment difference of -3.4% [-6.2, -0.8]), (2-sided p-value=0.012) [Table 2.7.4: 36].

Table 2.7.4: 36
Analysis of Proportion of Subjects Discontinuing from the Study Due to Adverse Event
Special Safety Pool (P007 (DOR 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

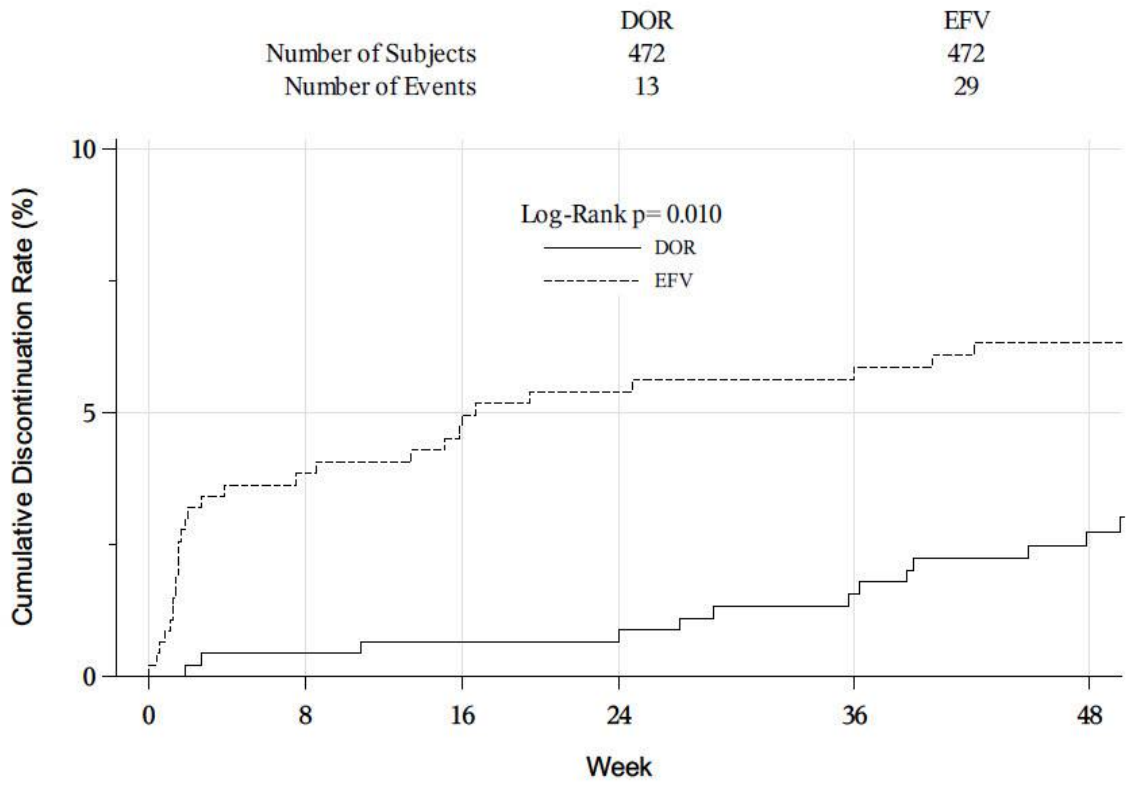
[†] Based on Miettinen & Nurminen method with weights proportional to the size of each protocol (P007, P021).
Special Combined DOR: DOR 100 mg administered with FTC/TDF in P007, or fixed dose combination of DOR/lamivudine/tenofovir disoproxil fumarate 100/300/300 mg in P021.
Special Combined EFV: EFV 600 mg administered with FTC/TDF in P007, or fixed dose combination of EFV/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 Kaplan-Meier plot for time to discontinuation due to an AE is presented in [Figure 2.7.4: 4]. The cumulative discontinuation rate over time is lower in the DOR group. Results of the log-rank test identified a treatment difference (log-rank p = 0.010, unadjusted for multiplicity) by Week 48 in time to discontinuation due to AE [Figure 2.7.4: 4].

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Figure 2.7.4: 4
Kaplan-Meier Plot for Time to Discontinuation Due to Adverse Event
Special Safety Pool (P007 (DOR 100 mg q.d. Group) and P021 Combined)
Weeks 0-48



Number of subjects at risk

DOR	472	457	451	446	429	373
EFV	472	442	428	421	411	358

DOR=Special Combined DOR; EFV=Special Combined EFV
Source: [ISS: analysis-adtte]

2.5.2.1.2 Neuropsychiatric Events

The frequency of pre-specified neuropsychiatric events by Week 8 and by Week 48 were summarized in the SSP in the categories of dizziness, sleep disorders and disturbances, altered sensorium, depression and suicide/self-injury, and psychosis and psychotic disorders. A pre-selected list of terms from the SOC Nervous System and Psychiatric Disorders were summarized in these categories.

The number and percentage of subjects with neuropsychiatric events by specific term and SOC are presented in [Table 5.3.5.3.3-trtmtnve48wk: 52] (Week 8) and in [Table 5.3.5.3.3-trtmtnve48wk: 53] (Week 48). A listing of subjects with neuropsychiatric AEs by Week 48 is presented in [Table 5.3.5.3.3-trtmtnve48wk: 54].

Most neuropsychiatric events in this analysis had been reported by Week 8, with only 4.7% more subjects in the Special Combined DOR treatment group and 5.3% more subjects in the Special Combined EFV treatment group reporting neuropsychiatric AEs between Week 8 and Week 48 [Table 2.7.4: 37] and [Table 2.7.4: 38]. The greatest increase in reported neuropsychiatric AEs was observed in the category of depression and suicide/self-injury in both the Special Combined DOR treatment group (increase of 2.5%) and the Special Combined EFV group (increase of 4.2%). At both timepoints, all neuropsychiatric event categories were reported more frequently in the Special Combined EFV treatment group.

By Week 48, of the 944 treated subjects, 382 (40.6%) had $\geq$1 neuropsychiatric AEs. In the Special Combined DOR treatment group, a lower proportion of subjects (25%) had 1 or more neuropsychiatric events compared to the Special Combined EFV treatment group (55.9%) with a treatment difference of -30.9% (-36.8, -24.9). Dizziness (8.9% for the Special Combined DOR treatment group vs 35.4% for the Special Combined EFV treatment group), and sleep disorders and disturbances (14.0% for the Special Combined DOR treatment group vs 27.3% for the Special Combined 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.

Three subjects (0.8%) in the DOR/3TC/TDF treatment group compared with 6 subjects (1.6%) in the EFV/FTC/TDF treatment group discontinued study drug due to neuropsychiatric events.

Table 2.7.4: 37
Analysis of Subjects with Neuropsychiatric Adverse Events by Week 8
Special Safety Pool (P007 (DOR 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: DOR 100 mg administered with FTC/TDF in P007, or fixed dose combination of DOR/lamivudine/tenofovir disoproxil fumarate 100/300/300 mg in P021.

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

Source: [ISS: analysis-adsl; adcns]

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Table 2.7.4: 38
Analysis of Subjects with Neuropsychiatric Adverse Events by Week 48
Special Safety Pool (P007 (DOR 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: DOR 100 mg administered with FTC/TDF in P007, or fixed dose combination of DOR/lamivudine/tenofovir disoproxil fumarate 100/300/300 mg in P021.

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

Source: [ISS: analysis-adsl; adcns]

2.5.2.2 Conclusions

In the SSP, DOR 100 mg and DOR/3TC/TDF administered QD for 48 weeks were generally well tolerated in 472 treatment-naïve subjects infected with HIV-1 in P007 and P021. The results of this pooled analysis indicate that both DOR and DOR/3TC/TDF have a favorable safety profile.

The proportion of subjects who discontinued from the study due to an AE was statistically significantly lower in the Special Combined DOR treatment groups compared with the Special Combined EFV treatment group, driven primarily by neuropsychiatric adverse events.

A slightly lower proportion of subjects in the DOR/3TC/TDF treatment group compared with subjects in the EFV/FTC/TDF treatment group discontinued study drug due to neuropsychiatric events.

DOR/3TC/TDF demonstrated a superior safety profile compared with EFV/FTC/TDF with respect to the neuropsychiatric event categories of dizziness, sleep disorders and disturbances, and altered sensorium.

2.6 Adverse Events From Other Ongoing Trials

The clinical trials included in this Section (P024, P028, and P030) were ongoing as of the cut-off dates for the results reported in this Summary of Clinical Safety, with no milestones reached for planned analysis. A description of the study design of these clinical trials is provided in [Sec. 1.1.1]. The reported data here are preliminary. Narratives for subjects who experienced any of the following events are being provided for P024. None of the subjects in P028 and P030 met any of these reporting categories; thus, no narratives are provided at this time for these 2 trials.

As noted in [Sec. 1.1.1], subjects in P024 were randomized in a 2:1 ratio to either an immediate switch to MK-1439A on Study Day 1 (Immediate Switch Group) or a delayed switch to MK-1439A at Study Week 24 (Delayed Switch Group). At the time of the database cut-off for this submission, 446 subjects in the Immediate Switch Group had been treated with DOR/3TC/TDF and 176 subjects in the Delayed Switch Group completed 24 weeks of baseline regimen and switched to DOR/3TC/TDF [Table 2.7.4: 1].

Deaths

As of the cutoff dates, no subjects have died in P024. One subject screened for study P024 died during the screening period, due to an acute myocardial infarction. The reported event was considered not related to the investigational therapy, as the subject had not received the investigational product.

Narratives for subjects with AEs resulting in death are in [Ref. 5.3.5.3: 04QBN4].

Other Serious Adverse Events

As of the cut-off date, 30 subjects in P024 experienced other SAEs during the treatment period (10 subjects in the delayed switch group and 20 subjects in the immediate switch group on DOR). Of the 10 subjects in the delayed switch group, 5 were receiving the baseline regimen at the onset of the SAE(s) and 5 were receiving DOR at the onset of the SAE(s). The SAEs experienced by 3 subjects in the immediate switch group were considered by the investigator to be related to study medication; each of these SAEs led to discontinuation and are discussed below. One additional subject in P024 experienced a SAE during the screening period. Narratives for subjects with SAEs are in [Ref. 5.3.5.3: 04QBN4].

Discontinuation due to Adverse Events

As of the cut-off date, 8 subjects in P024 (2 subjects in the delayed switch group and 6 subjects in the immediate switch group) have discontinued due to AEs. Both of the subjects in the delayed switch group were receiving DOR at the onset of the AEs that led to discontinuation. Of these 8 subjects, 6 subjects (2 subjects in the delayed switch group and 4 subjects in the immediate switch group) in P024 experienced AEs leading to discontinuation that were considered by the investigator to be related to study medication. The drug-related AEs that led to discontinuation were ALT increased (1 subject in the delayed switch group and 1 subject in the immediate switch group), decreased appetite (1 subject in the immediate switch group), hepatitis (1 subject in the delayed switch group),

fatigue and sleep disorder (both reported by the same subject in the immediate switch group), and myalgia, generalized edema, rash macular, and renal pain (all reported by the same subject in the immediate switch group). Narratives for subjects who discontinued due to AEs are in [Ref. 5.3.5.3: 04QBN4].

Discontinuation due to Serious Adverse Events

As of the cut-off dates, 5 subjects in P024 (all in the immediate switch group) have discontinued due to SAEs. Of these subjects, 3 subjects in the immediate switch group in P024 had SAEs leading to discontinuation that were considered by the investigator to be related to study medication. Drug-related SAEs that led to discontinuation were pancreatitis (1 subject), depression (1 subject), and lipase increased and amylase increased (both reported by the same subject). Narratives for subjects who discontinued due to SAEs are in [Ref. 5.3.5.3: 04QBN4].

2.7 Narratives

Narratives for subjects with AEs resulting in death, SAEs, and AEs leading to discontinuation of study medication for all subjects in the individual trials (P007, P018, and P021) can be found in [Ref. 5.3.5.1: P007V01MK1439: 16.2.7.2] [Ref. 5.3.5.1: P018V01MK1439: 16.2.7.2] [Ref. 5.3.5.1: P021V01MK1439A: 16.2.7.2]. Narratives for subjects with AEs resulting in death, SAEs, and AEs leading to discontinuation of study medication in the ongoing clinical trial P024 are included in this document.

2.8 Overall Clinical Adverse Event Conclusions

DOR and DOR/3TC/TDF administered once-daily for 48 weeks were both generally well tolerated in the treatment of 855 treatment-naïve subjects (P007 100 mg arm [108 subjects] P018 [383 subjects] and P021 [364 subjects]) infected with HIV-1.

DOR and DOR/3TC/TDF both demonstrated a favorable safety profile:

- There were few deaths, non-fatal SAEs, or AEs leading to discontinuation; very few of these events were assessed as being related to treatment.
- Few AEs occurred at an incidence of >10%. The majority of AEs were mild in intensity; very few were severe.
- Overall, the most commonly reported AEs were headache (13.3%), nasopharyngitis (9.5%) and nausea (9.5%).
- The most commonly reported drug-related AEs were nausea (6.0%), dizziness (4.9%), headache (4.7%) and diarrhea (4.0%).
- DOR and DOR/3TC/TDF safety profiles did not clinically differ according to the different treatment exposures.

The general safety profiles of DOR and DOR/3TC/TDF are comparable to those of DRV+r and with demonstrated superiority to EFV with respect to the neuropsychiatric event categories of dizziness, sleep disorders and disturbances, and altered sensorium. The time to discontinuation due to any AE was longer for DOR and DOR/3TC/TDF compared with EFV.

3 CLINICAL LABORATORY EVALUATIONS

3.1 Clinical Laboratory Evaluations in the Phase 1 Trials

Laboratory evaluations including chemistry/hematology and urinalysis panels were conducted at various timepoints during the course of each Phase 1 clinical pharmacology trial. The results for some laboratory parameters were outside the normal ranges. However, the majority of these values were considered to be minor variations and/or indicative of the underlying disease state (ie, HIV-1-infection, hepatic or renal impairment). Any laboratory parameter values considered to be clinically significant were reported as AEs. No pooled analyses for laboratory safety data for the clinical pharmacology trials were performed, except for the laboratory-emergent and laboratory-related AEs that are presented in the CPSOS in the SOC of Investigations [Sec. 5.3.5.3.1.5-trtmtnve48wk]. All descriptive summaries of laboratory safety data, if applicable to the protocol, were included in the individual CSRs. No trends for clinically meaningful changes in laboratory parameters values were identified within any of the trials.

One SAE of increased hepatic enzymes was reported for an HIV-1 infected subject in P005 at the post-study visit. The SAE was considered not related to trial drug by the investigator. The narrative can be found in the trial CSR [Ref. 5.3.4.1: P005V01: 16.2.7.3].

3.2 Clinical Laboratory Evaluations in P007 (Phase 2b Dose-Ranging Trial)

3.2.1 Pre-Defined Limit of Change Evaluations

Predefined limits of change (PDLC) for clinical laboratory values in study P007 were based on the Division of AIDS 'Table for Grading the Severity of Adult and Pediatric AEs, version 2.0.' The analysis of the PDLC included subjects whose laboratory grade worsened during the trial. Point estimates and 95% CIs are provided for the difference between treatment groups.

Compared with the EFV group at Week 96, the proportion of subjects meeting PDLC criteria was lower in the combined DOR group for fasting low-density lipoprotein cholesterol (LDL-C) (Grade 2), cholesterol (Grade 1 and Grade 2), and alkaline phosphatase (Grade 1) [Table 2.7.4: 39].

The proportion of subjects meeting PDLC criteria was higher in the combined DOR group for serum creatinine (Grade 2) compared with EFV. Grade 3 or 4 creatinine elevations were uncommon in both groups. No subject in either treatment group met the criteria for drug-induced liver injury (DILI) [Ref. 5.3.5.1: P007V01MK1439: Table 14.3-9]. None of these laboratory findings were considered to be clinically meaningful

More Grade 1 bilirubin elevations were observed for the combined DOR group compared with the EFV group (6.1% versus 2.8%, respectively). Notably, this pattern was not observed for bilirubin values greater than Grade 1 nor for AST, ALT, or alkaline phosphatase elevations, which tended to be lower for the DOR groups compared with EFV.

For all other selected laboratory parameters in Part I/II combined, there were no notable differences between treatment groups.

Table 2.7.4: 39
Subjects With Laboratory Findings That Met Predefined Criteria (PDLC)
(Incidence ≥4 events in One or More Treatment Groups)
Part I/II Combined (Doravirine All Doses vs. Efavirenz; Weeks 0-96)
All Subjects as Treated (P007)

Laboratory Test (Unit)	PDLC Criterion	Grade	Treatment	N	n/m(%)	Difference [Doravirine minus Efavirenz][†] (95% CI)
Blood Chemistry Tests						
fasting(non-random) serum LDL-C (mg/dL)	130 - <160	Grade 1	Doravirine 25 mg	40	3/39 (7.7)	-6.0 (-15.9, 7.7)
			Doravirine 50 mg	43	1/40 (2.5)	-11.2 (-19.8, 0.1)
			Doravirine 100 mg	108	8/102 (7.8)	-5.9 (-14.9, 2.8)
			Doravirine 200 mg	41	5/38 (13.2)	-0.6 (-11.8, 14.7)
			Doravirine Combined	232	17/219 (7.8)	-6.0 (-14.5, 0.9)
			Efavirenz 600 mg	108	14/102 (13.7)	
	160 - <190	Grade 2	Doravirine 25 mg	40	1/39 (2.6)	-7.2 (-15.2, 4.0)
			Doravirine 50 mg	43	0/40 (0.0)	-9.8 (-17.1, -0.7)
			Doravirine 100 mg	108	2/102 (2.0)	-7.8 (-15.4, -1.6)
			Doravirine 200 mg	41	0/38 (0.0)	-9.8 (-17.1, -0.3)
			Doravirine Combined	232	3/219 (1.4)	-8.4 (-15.9, -3.6)
			Efavirenz 600 mg	108	10/102 (9.8)	
fasting(non-random) serum cholesterol (mg/dL)	200 - <240	Grade 1	Doravirine 25 mg	40	3/39 (7.7)	-12.7 (-23.3, 1.4)
			Doravirine 50 mg	43	1/42 (2.4)	-18.0 (-27.4, -6.7)
			Doravirine 100 mg	108	10/104 (9.6)	-10.8 (-20.8, -1.1)
			Doravirine 200 mg	41	7/39 (17.9)	-2.4 (-15.3, 13.8)

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Subjects With Laboratory Findings That Met Predefined Criteria (PDLC)
(Incidence ≥4 events in One or More Treatment Groups)
Part I/II Combined (Doravirine All Doses vs. Efavirenz; Weeks 0-96)
All Subjects as Treated

Laboratory Test (Unit)	PDLC Criterion	Grade	Treatment	N	n/m(%)	Difference [Doravirine minus Efavirenz][†] (95% CI)
fasting(non-random) serum cholesterol (mg/dL)	200 - <240	Grade 1	Doravirine Combined	232	21/224 (9.4)	-11.0 (-20.4, -3.0)
			Efavirenz 600 mg	108	21/103 (20.4)	
	240 - <300	Grade 2	Doravirine 25 mg	40	0/39 (0.0)	-9.7 (-17.0, -0.4)
			Doravirine 50 mg	43	2/42 (4.8)	-4.9 (-13.3, 6.9)
			Doravirine 100 mg	108	0/104 (0.0)	-9.7 (-17.0, -5.4)
			Doravirine 200 mg	41	0/39 (0.0)	-9.7 (-17.0, -0.4)
			Doravirine Combined	232	2/224 (0.9)	-8.8 (-16.1, -4.1)
			Efavirenz 600 mg	108	10/103 (9.7)	
fasting(non-random) serum triglyceride (mg/dL)	150 - 300	Grade 1	Doravirine 25 mg	40	8/39 (20.5)	0.1 (-13.3, 16.7)
			Doravirine 50 mg	43	3/42 (7.1)	-13.2 (-23.7, 0.2)
			Doravirine 100 mg	108	20/104 (19.2)	-1.2 (-12.2, 9.8)
			Doravirine 200 mg	41	4/39 (10.3)	-10.1 (-21.4, 4.7)
			Doravirine Combined	232	35/224 (15.6)	-4.8 (-14.5, 3.8)
			Efavirenz 600 mg	108	21/103 (20.4)	
	>300 - 500	Grade 2	Doravirine 25 mg	40	1/39 (2.6)	-6.2 (-13.8, 5.0)
			Doravirine 50 mg	43	0/42 (0.0)	-8.7 (-15.8, -0.1)
			Doravirine 100 mg	108	8/104 (7.7)	-1.0 (-9.1, 6.9)
			Doravirine 200 mg	41	5/39 (12.8)	4.1 (-6.1, 18.7)

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Subjects With Laboratory Findings That Met Predefined Criteria (PDLC)
(Incidence ≥4 events in One or More Treatment Groups)
Part I/II Combined (Doravirine All Doses vs. Efavirenz; Weeks 0-96)
All Subjects as Treated

Laboratory Test (Unit)	PDLC Criterion	Grade	Treatment	N	n/m(%)	Difference [Doravirine minus Efavirenz][†] (95% CI)
fasting(non-random) serum triglyceride (mg/dL)	>300 - 500	Grade 2	Doravirine Combined	232	14/224 (6.3)	-2.5 (-10.0, 3.2)
			Efavirenz 600 mg	108	9/103 (8.7)	
fasting(non-random) serum glucose test (mg/dL)	110 - 125	Grade 1	Doravirine 25 mg	40	4/39 (10.3)	-0.3 (-10.2, 13.9)
			Doravirine 50 mg	43	5/42 (11.9)	1.3 (-8.9, 15.3)
			Doravirine 100 mg	108	9/105 (8.6)	-2.0 (-10.5, 6.3)
			Doravirine 200 mg	41	2/39 (5.1)	-5.4 (-14.1, 7.1)
			Doravirine Combined	232	20/225 (8.9)	-1.7 (-9.7, 4.7)
			Efavirenz 600 mg	108	11/104 (10.6)	
	>125 - 250	Grade 2	Doravirine 25 mg	40	1/39 (2.6)	-1.3 (-7.5, 9.6)
			Doravirine 50 mg	43	1/42 (2.4)	-1.5 (-7.6, 8.8)
			Doravirine 100 mg	108	4/105 (3.8)	-0.0 (-6.2, 6.1)
			Doravirine 200 mg	41	2/39 (5.1)	1.3 (-5.6, 13.4)
			Doravirine Combined	232	8/225 (3.6)	-0.3 (-6.2, 3.8)
			Efavirenz 600 mg	108	4/104 (3.8)	
total serum bilirubin (mg/dL)	1.1 - <1.6 x ULN	Grade 1	Doravirine 25 mg	40	2/40 (5.0)	2.2 (-4.0, 14.0)
			Doravirine 50 mg	43	1/42 (2.4)	-0.4 (-6.0, 9.8)
			Doravirine 100 mg	108	8/107 (7.5)	4.7 (-1.4, 11.7)

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Subjects With Laboratory Findings That Met Predefined Criteria (PDLC)
(Incidence ≥4 events in One or More Treatment Groups)
Part I/II Combined (Doravirine All Doses vs. Efavirenz; Weeks 0-96)
All Subjects as Treated

Laboratory Test (Unit)	PDLC Criterion	Grade	Treatment	N	n/m(%)	Difference [Doravirine minus Efavirenz][†] (95% CI)
total serum bilirubin (mg/dL)	1.1 - <1.6 x ULN	Grade 1	Doravirine 200 mg	41	3/40 (7.5)	4.7 (-2.2, 17.4)
			Doravirine Combined	232	14/229 (6.1)	3.3 (-2.2, 7.8)
			Efavirenz 600 mg	108	3/108 (2.8)	
serum creatinine (mg/dL)	>1.3 - 1.8 x ULN or Increase of >0.3 mg/dL above baseline	Grade 2	Doravirine 25 mg	40	8/40 (20.0)	19.1 (9.2, 34.0)
			Doravirine 50 mg	43	2/42 (4.8)	3.8 (-1.2, 15.0)
			Doravirine 100 mg	108	5/107 (4.7)	3.7 (-0.9, 9.7)
			Doravirine 200 mg	41	4/40 (10.0)	9.1 (2.3, 22.3)
			Doravirine Combined	232	19/229 (8.3)	7.4 (2.7, 11.9)
			Efavirenz 600 mg	108	1/108 (0.9)	
serum aspartate aminotransferase (IU/L)	1.25 - <2.5 x ULN	Grade 1	Doravirine 25 mg	40	6/40 (15.0)	2.0 (-9.2, 17.2)
			Doravirine 50 mg	43	2/42 (4.8)	-8.2 (-17.0, 3.8)
			Doravirine 100 mg	108	12/107 (11.2)	-1.7 (-10.8, 7.3)
			Doravirine 200 mg	41	2/40 (5.0)	-8.0 (-16.8, 4.5)
			Doravirine Combined	232	22/229 (9.6)	-3.4 (-11.7, 3.5)
			Efavirenz 600 mg	108	14/108 (13.0)	
	2.5 - <5.0 x ULN	Grade 2	Doravirine 25 mg	40	0/40 (0.0)	-3.7 (-9.2, 5.2)
			Doravirine 50 mg	43	2/42 (4.8)	1.1 (-5.5, 12.4)

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Subjects With Laboratory Findings That Met Predefined Criteria (PDLC)
(Incidence ≥4 events in One or More Treatment Groups)
Part I/II Combined (Doravirine All Doses vs. Efavirenz; Weeks 0-96)
All Subjects as Treated

Laboratory Test (Unit)	PDLC Criterion	Grade	Treatment	N	n/m(%)	Difference [Doravirine minus Efavirenz][†] (95% CI)
serum aspartate aminotransferase (IU/L)	2.5 - <5.0 x ULN	Grade 2	Doravirine 100 mg	108	2/107 (1.9)	-1.8 (-7.5, 3.3)
			Doravirine 200 mg	41	2/40 (5.0)	1.3 (-5.3, 13.1)
			Doravirine Combined	232	6/229 (2.6)	-1.1 (-6.7, 2.7)
			Efavirenz 600 mg	108	4/108 (3.7)	
	>2.5 - 5.0 x Baseline		Doravirine 25 mg	40	5/40 (12.5)	-0.5 (-11.1, 14.2)
			Doravirine 50 mg	43	0/42 (0.0)	-13.0 (-20.6, -4.2)
			Doravirine 100 mg	108	8/107 (7.5)	-5.5 (-14.1, 2.8)
			Doravirine 200 mg	41	2/40 (5.0)	-8.0 (-16.8, 4.5)
			Doravirine Combined	232	15/229 (6.6)	-6.4 (-14.5, 0.0)
			Efavirenz 600 mg	108	14/108 (13.0)	
	>5.0 x Baseline		Doravirine 25 mg	40	2/40 (5.0)	0.4 (-6.6, 12.3)
			Doravirine 50 mg	43	3/42 (7.1)	2.5 (-5.0, 14.8)
			Doravirine 100 mg	108	3/107 (2.8)	-1.8 (-8.0, 3.9)
			Doravirine 200 mg	41	1/40 (2.5)	-2.1 (-8.5, 8.6)
			Doravirine Combined	232	9/229 (3.9)	-0.7 (-6.8, 3.6)
			Efavirenz 600 mg	108	5/108 (4.6)	
serum alanine aminotransferase (IU/L)	1.25 - <2.5 x ULN	Grade 1	Doravirine 25 mg	40	4/40 (10.0)	-5.7 (-16.2, 8.5)
			Doravirine 50 mg	43	5/42 (11.9)	-3.8 (-14.7, 10.5)

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Subjects With Laboratory Findings That Met Predefined Criteria (PDLC)
(Incidence ≥4 events in One or More Treatment Groups)
Part I/II Combined (Doravirine All Doses vs. Efavirenz; Weeks 0-96)
All Subjects as Treated

Laboratory Test (Unit)	PDLC Criterion	Grade	Treatment	N	n/m(%)	Difference [Doravirine minus Efavirenz][†] (95% CI)
serum alanine aminotransferase (IU/L)	1.25 - <2.5 x ULN	Grade 1	Doravirine 100 mg	108	12/107 (11.2)	-4.5 (-14.0, 4.8)
			Doravirine 200 mg	41	3/40 (7.5)	-8.2 (-18.1, 5.3)
			Doravirine Combined	232	24/229 (10.5)	-5.3 (-14.0, 2.1)
			Efavirenz 600 mg	108	17/108 (15.7)	
	>2.5 - 5.0 x Baseline		Doravirine 25 mg	40	4/40 (10.0)	-8.5 (-19.3, 5.9)
			Doravirine 50 mg	43	4/42 (9.5)	-9.0 (-19.6, 4.9)
			Doravirine 100 mg	108	15/107 (14.0)	-4.5 (-14.6, 5.5)
			Doravirine 200 mg	41	3/40 (7.5)	-11.0 (-21.2, 2.7)
			Doravirine Combined	232	26/229 (11.4)	-7.2 (-16.3, 0.7)
			Efavirenz 600 mg	108	20/108 (18.5)	
	>5.0 x Baseline		Doravirine 25 mg	40	4/40 (10.0)	3.5 (-5.3, 17.1)
			Doravirine 50 mg	43	2/42 (4.8)	-1.7 (-9.2, 9.8)
			Doravirine 100 mg	108	2/107 (1.9)	-4.6 (-11.2, 0.9)
			Doravirine 200 mg	41	1/40 (2.5)	-4.0 (-10.9, 6.8)
			Doravirine Combined	232	9/229 (3.9)	-2.6 (-9.2, 2.2)
			Efavirenz 600 mg	108	7/108 (6.5)	
serum alkaline phosphatase (IU/L)	1.25 - <2.5 x ULN	Grade 1	Doravirine 25 mg	40	2/40 (5.0)	-3.3 (-11.3, 8.8)
			Doravirine 50 mg	43	1/42 (2.4)	-6.0 (-13.3, 4.6)

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Subjects With Laboratory Findings That Met Predefined Criteria (PDLC)
(Incidence ≥4 events in One or More Treatment Groups)
Part I/II Combined (Doravirine All Doses vs. Efavirenz; Weeks 0-96)
All Subjects as Treated

Laboratory Test (Unit)	PDLC Criterion	Grade	Treatment	N	n/m(%)	Difference [Doravirine minus Efavirenz][†] (95% CI)
serum alkaline phosphatase (IU/L)	1.25 - <2.5 x ULN	Grade 1	Doravirine 100 mg	108	2/107 (1.9)	-6.5 (-13.5, -0.7)
			Doravirine 200 mg	41	1/40 (2.5)	-5.8 (-13.2, 5.1)
			Doravirine Combined	232	6/229 (2.6)	-5.7 (-12.7, -0.9)
			Efavirenz 600 mg	108	9/108 (8.3)	
serum lipase test (IU/L)	1.1 - <1.5 x ULN	Grade 1	Doravirine 25 mg	40	2/40 (5.0)	-6.1 (-14.7, 6.2)
			Doravirine 50 mg	43	2/42 (4.8)	-6.3 (-14.8, 5.5)
			Doravirine 100 mg	108	12/107 (11.2)	0.1 (-8.7, 8.9)
			Doravirine 200 mg	41	3/40 (7.5)	-3.6 (-12.8, 9.6)
			Doravirine Combined	232	19/229 (8.3)	-2.8 (-10.7, 3.5)
			Efavirenz 600 mg	108	12/108 (11.1)	
	1.5 - <3.0 x ULN	Grade 2	Doravirine 25 mg	40	6/40 (15.0)	6.7 (-3.8, 21.5)
			Doravirine 50 mg	43	2/42 (4.8)	-3.6 (-11.5, 8.1)
			Doravirine 100 mg	108	6/107 (5.6)	-2.7 (-10.2, 4.5)
			Doravirine 200 mg	41	4/40 (10.0)	1.7 (-7.6, 15.4)
			Doravirine Combined	232	18/229 (7.9)	-0.5 (-7.8, 5.3)
			Efavirenz 600 mg	108	9/108 (8.3)	
	3.0 - <5.0 x ULN	Grade 3	Doravirine 25 mg	40	0/40 (0.0)	-5.6 (-11.6, 3.4)
			Doravirine 50 mg	43	1/42 (2.4)	-3.2 (-9.8, 7.2)

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Subjects With Laboratory Findings That Met Predefined Criteria (PDLC)
(Incidence ≥4 events in One or More Treatment Groups)
Part I/II Combined (Doravirine All Doses vs. Efavirenz; Weeks 0-96)
All Subjects as Treated

Laboratory Test (Unit)	PDLC Criterion	Grade	Treatment	N	n/m(%)	Difference [Doravirine minus Efavirenz][†] (95% CI)
serum lipase test (IU/L)	3.0 - <5.0 x ULN	Grade 3	Doravirine 100 mg	108	4/107 (3.7)	-1.8 (-8.4, 4.4)
			Doravirine 200 mg	41	0/40 (0.0)	-5.6 (-11.6, 3.4)
			Doravirine Combined	232	5/229 (2.2)	-3.4 (-9.6, 0.7)
			Efavirenz 600 mg	108	6/108 (5.6)	

[†] A negative value favors doravirine over efavirenz. The 95% CIs were calculated using Miettinen and Nurminen's method.

For inclusion in this analysis, both a baseline and at least one on-treatment laboratory value had to be present. Only subjects with a worsened grade from baseline were included. A subject was listed with a Grade X event if his/her highest grade during treatment was X. A subject was included in the event of '>X-fold Baseline' if his/her highest laboratory value during treatment fell in this category and was more extreme than the upper limit of normal (ULN). Grading is based on DAIDS toxicity criteria.

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

n/m = number of subjects with PDLC/number of subjects with baseline and at least one on-treatment value of the laboratory test.

DAIDS=Division of AIDS.

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

Source: [P007V01MK1439: analysis-adsl; adlb]

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3.2.2 Abnormal Laboratory Values of Potential Clinical Relevance (Grade 3 and Grade 4)

All subjects for whom an abnormal laboratory value of potential clinical relevance in P007 was identified were reviewed. No relationship to study drug was established due to many confounding factors associated with each individual subject's medical history. No subject was discontinued from the trial for liver function tests categorized as DAIDS Grade 3 or 4.

Liver function tests (serum AST, serum ALT) with values categorized as potentially life-threatening (Grade 4) or severe (Grade 3) are discussed below. Other laboratory parameters with values categorized as Grade 3 or Grade 4 (absolute neutrophil count, platelet count, and serum lipase values) are presented in the study report [Ref. 5.3.5.1: P007V01MK1439: 12.3.2.3] [Ref. 5.3.5.1: P007V01MK1439: Table 14.3-28].

By Week 48, DAIDS Grade 3 laboratory abnormalities occurring at an incidence of ≥4 subjects in either treatment group were observed for serum AST (DOR Combined: n= 4 [1.7%]; EFV: n= 1 [0.9%]), and serum lipase (DOR Combined: n=4 [1.7%]; EFV: n=2 [1.9%]).

Serum AST and ALT

Overall, by Week 96 in P007, Grade 4 (≥10.0 × upper limit of normal [ULN]) serum ALT values were reported for 1/229 (0.4%) subjects in the combined DOR group and 1/108 (0.9%) subjects in the EFV group. Grade 4 AST values were reported for 1/229 (0.4%) subjects in the combined DOR group and 1/108 (0.9%) subjects in the EFV group.

Grade 3 serum ALT values were reported for 1/229 (0.4%) subjects in the combined DOR group (1/107 subjects in the DOR 100 mg group) and for 2/108 (1.9%) subjects in the EFV group.

Grade 3 (5.0 to <10.0 × ULN) serum AST values were reported for 4/229 (1.7%) subjects in the combined DOR groups (2/40 subjects in the DOR 25 mg group, 1/42 subjects in the DOR 50 mg group, and 1/107 subjects in the DOR 100 mg group) and for 1/108 (0.9%) subjects in the EFV group.

Patient profiles for subjects with liver function values categorized as DAIDS Grade 3 or 4 are in [Ref. 5.3.5.1: P007V01MK1439: 16.2.7.5].

Serum Lipase

By Week 96, Grade 4 (≥5.0 × ULN) serum lipase values were reported for 1.7% of subjects (4/229) in the combined DOR group (1/40 subjects in the DOR 25 mg group, 2/107 subjects in the DOR 100 mg group, and 1/40 subjects in the DOR 200 mg group) and for 1.9% of subjects (2/108) in the EFV group. Grade 3 (3.0 to <5.0 × ULN) values were reported for 2.2% of subjects (5/229) in the combined DOR groups (1/42 subjects in the DOR 50 mg group and 4/107 subjects in the DOR 100 mg group) and for 5.6% of subjects (6/108) in the

EFV group. These laboratory abnormalities were not associated with clinical symptoms of pancreatitis and resolved for all subjects while on study therapy

3.2.3 Laboratory Changes from Baseline

Summary changes from baseline in laboratory parameters in Part I/II combined through Week 96 are provided in [Ref. 5.3.5.1: P007V01MK1439: Table 14.3-21]. There were no notable changes from baseline in laboratory parameters between treatment groups in Part I/II combined through Week 96.

3.3 Clinical Laboratory Evaluations in P018 (Phase 3 Trial)

3.3.1 Pre-Defined Limit of Change Evaluations

Predefined limits of change (PDLC) for clinical laboratory values in study P018 were based on the Division of AIDS 'Table for Grading the Severity of Adult and Pediatric AEs, version 2.0.' The analysis of the PDLC included subjects whose laboratory grade worsened during the trial. Point estimates and 95% CIs are provided for the difference between treatment groups.

By Week 48, the proportions of subjects meeting PDLC criteria were lower for the DOR 100 mg group compared with the DRV+r group for fasting LDL-C (Grade 2 and Grade 3), fasting cholesterol (Grade 2), fasting triglycerides (Grade 1), and AST (Grade 3) [Table 2.7.4: 40].

Overall, a higher proportion of subjects with Grade 1 and/or Grade 2 values for total bilirubin were observed for the DOR group (6.6%) compared with the DRV+r group (1.4%). 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. All 6 subjects with Grade 2 bilirubin elevations had bilirubin at or above ULN at screening and/or baseline [Ref. 5.3.5.1: P018V01MK1439: 16.2.8.1]. None of the bilirubin elevations was associated with other liver function test abnormalities [Ref. 5.3.5.1: P018V01MK1439: 16.2.8.1] or with a clinically significant AE. None of the bilirubin elevations (of any grade) resulted in subject discontinuation from the trial [Ref. 5.3.5.1: P018V01MK1439: 16.2.7.1.5].

Numbers and percentages of subjects with laboratory values that met the predefined limits of change by Week 48, as well as through the data cutoff date, are provided in [Ref. 5.3.5.1: P018V01MK1439: Table 14.3-18] and [Ref. 5.3.5.1: P018V01MK1439: Table 14.3-19], respectively.

3.3.2 Abnormal Laboratory Values of Potential Clinical Relevance (Grade 3 and Grade 4)

All subjects for whom abnormal laboratory values of potential clinical relevance were identified at some point during the conduct of P018 were reviewed. No relationship to study drug was established due to many confounding factors associated with each individual subject's medical history. No subject in the DOR treatment group was discontinued from the

trial for liver function tests categorized as Grade 3 or 4 [Ref. 5.3.5.1: P018V01MK1439: 16.2.7.1.5].

By Week 48, Grade 4 laboratory abnormalities occurring for ≥4 subjects in either treatment group in P018 were observed for lipase (DOR: n=4 [1.1%]; DRV+r: n=3 [0.8%]) and creatinine kinase (DOR: n=6 [1.6%]; DRV+r: n=7 [1.9%]) [Table 2.7.4: 40]. No subjects discontinued from the study for any of these laboratories abnormalities.

Table 2.7.4: 40
Analysis of Subjects With Laboratory Findings That Met Predetermined Criteria (Incidence ≥ 4 Subjects in One or More Treatment Groups) Worsening Grade Weeks 0-48 (P018)

Criterion[†]	DOR 100 mg QD		Darunavir/ritonavir 800/100 mg QD		Difference [DOR - Darunavir] [‡]
	n/m	(%)	n/m	(%)	% (95% CI)
HEMATOLOGY					
Neutrophils (10^9/L)					
Grade 1: 0.800 - 1.000	6/379	(1.6)	3/378	(0.8)	0.8 (-0.9, 2.7)
Grade 2: 0.600 - 0.799	1/379	(0.3)	4/378	(1.1)	-0.8 (-2.5, 0.5)
Hemoglobin (g/dL)					
Grade 1: Male: 10.0 - 10.9 Female: 9.5 - 10.4	7/380	(1.8)	8/378	(2.1)	-0.3 (-2.5, 1.9)
Grade 2: Male: 9.0 - <10.0 Female: 8.5 - <9.5	3/380	(0.8)	6/378	(1.6)	-0.8 (-2.7, 0.9)
Platelets (10^9/L)					
Grade 1: 100 - <124.999	3/379	(0.8)	4/376	(1.1)	-0.3 (-2.0, 1.4)
CHEMISTRY					
Fasting LDL Cholesterol (mg/dL)					
Grade 1: 130 - <160	23/332	(6.9)	34/320	(10.6)	-3.7 (-8.2, 0.7)
Grade 2: 160 - <190	1/332	(0.3)	23/320	(7.2)	-6.9 (-10.3, -4.4)
Grade 3: >=190	1/332	(0.3)	9/320	(2.8)	-2.5 (-5.0, -0.8)
Fasting Cholesterol (mg/dL)					
Grade 1: 200 - <240	33/335	(9.9)	48/327	(14.7)	-4.8 (-9.9, 0.2)
Grade 2: 240 - <300	4/335	(1.2)	32/327	(9.8)	-8.6 (-12.4, -5.4)
Fasting Triglyceride (mg/dL)					
Grade 1: 150 - 300	41/335	(12.2)	71/327	(21.7)	-9.5 (-15.2, -3.8)
Grade 2: >300 - 500	9/335	(2.7)	13/327	(4.0)	-1.3 (-4.3, 1.5)
Fasting Glucose (mg/dL)					
Grade 1: 110 - 125	23/335	(6.9)	26/327	(8.0)	-1.1 (-5.2, 3.0)
Grade 2: >125 - 250	7/335	(2.1)	9/327	(2.8)	-0.7 (-3.3, 1.8)
Grade 3: >250 - 500	4/335	(1.2)	1/327	(0.3)	0.9 (-0.6, 2.8)
Total Bilirubin (mg/dL)					
Grade 1: 1.1 - <1.6 x ULN	19/380	(5.0)	4/378	(1.1)	3.9 (1.6, 6.7)
Grade 2: 1.6 - <2.6 x ULN	6/380	(1.6)	1/378	(0.3)	1.3 (-0.1, 3.2)
>2.5 - 5.0 x Baseline	5/380	(1.3)	1/378	(0.3)	1.1 (-0.3, 2.8)
Creatinine (mg/dL)					
Grade 2: >1.3 - 1.8 x ULN or Increase of >0.3 mg/dL above baseline	10/380	(2.6)	16/378	(4.2)	-1.6 (-4.4, 1.1)
Grade 3: >1.8 - <3.5 x ULN or Increase of 1.5 to <2.0 x above baseline	5/380	(1.3)	10/378	(2.6)	-1.3 (-3.6, 0.7)

Analysis of Subjects With Laboratory Findings That Met Predetermined Criteria (Incidence ≥ 4 Subjects in One or More Treatment Groups) Worsening Grade Weeks 0-48 (P018)

Criterion[†]	DOR 100 mg QD		Darunavir/ritonavir 800/100 mg QD		Difference [DOR - Darunavir] [‡]
	n/m	(%)	n/m	(%)	% (95% CI)
Aspartate Aminotransferase (IU/L)					
Grade 1: 1.25 - <2.5 x ULN	30/380	(7.9)	26/378	(6.9)	1.0 (-2.8, 4.8)
Grade 2: 2.5 - <5.0 x ULN	17/380	(4.5)	12/378	(3.2)	1.3 (-1.5, 4.2)
Grade 3: 5.0 - <10.0 x ULN	2/380	(0.5)	6/378	(1.6)	-1.1 (-3.0, 0.5)
>2.5 - 5.0 x Baseline	21/380	(5.5)	15/378	(4.0)	1.6 (-1.5, 4.8)
>5.0 x Baseline	11/380	(2.9)	12/378	(3.2)	-0.3 (-2.9, 2.3)
Alanine Aminotransferase (IU/L)					
Grade 1: 1.25 - <2.5 x ULN	33/369	(8.9)	27/375	(7.2)	1.7 (-2.2, 5.8)
Grade 2: 2.5 - <5.0 x ULN	10/369	(2.7)	7/375	(1.9)	0.8 (-1.4, 3.3)
Grade 3: 5.0 - <10.0 x ULN	4/369	(1.1)	6/375	(1.6)	-0.5 (-2.5, 1.3)
>2.5 - 5.0 x Baseline	27/369	(7.3)	15/375	(4.0)	3.3 (-0.0, 6.8)
>5.0 x Baseline	8/369	(2.2)	13/375	(3.5)	-1.3 (-3.9, 1.2)
Alkaline Phosphatase (IU/L)					
Grade 1: 1.25 - <2.5 x ULN	3/380	(0.8)	8/378	(2.1)	-1.3 (-3.4, 0.4)
Lipase (IU/L)					
Grade 1: 1.1 - <1.5 x ULN	20/380	(5.3)	23/378	(6.1)	-0.8 (-4.3, 2.6)
Grade 2: 1.5 - <3.0 x ULN	14/380	(3.7)	20/378	(5.3)	-1.6 (-4.7, 1.4)
Grade 3: 3.0 - <5.0 x ULN	6/380	(1.6)	6/378	(1.6)	-0.0 (-2.0, 2.0)
Grade 4: >=5.0 x ULN	4/380	(1.1)	3/378	(0.8)	0.3 (-1.4, 2.0)
Creatine Kinase (IU/L)					
Grade 1: 3.0 - <6.0 x ULN	22/380	(5.8)	22/378	(5.8)	-0.0 (-3.5, 3.4)
Grade 2: 6.0 - <10.0 x ULN	9/380	(2.4)	12/378	(3.2)	-0.8 (-3.4, 1.7)
Grade 3: 10.0 - <20.0 x ULN	7/380	(1.8)	7/378	(1.9)	-0.0 (-2.2, 2.1)
Grade 4: >= 20.0 x ULN	6/380	(1.6)	7/378	(1.9)	-0.3 (-2.4, 1.8)
Amylase (IU/L)					
Grade 1: 1.1 - <1.5 x ULN	16/380	(4.2)	16/378	(4.2)	-0.0 (-3.0, 3.0)
Grade 2: 1.5 - <3.0 x ULN	8/380	(2.1)	9/378	(2.4)	-0.3 (-2.6, 2.0)

[†] For graded criteria:subjects are counted once per test in the highest grade reported.

For inclusion in this analysis, both a baseline and at least one on-treatment laboratory value had to be present. Only subjects with a worsened grade from baseline were included. A subject was listed with a Grade X event if his/her highest grade during treatment was X.

[‡] The 95% CIs for the treatment differences in percent with PDLC were calculated using Miettinen and Nurminen method.

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 postbaseline test results that met the predetermined criterion.

m = Number of subjects with at least one postbaseline test result.

LLN = Lower limit of normal range. ULN = Upper limit of normal range.

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

Source: [P018V01MK1439: analysis-adlb]

3.3.3 Laboratory Changes from Baseline

Other than the changes in fasting lipid parameters discussed in [Sec. 2.7.4.3.3.3.1], there were no apparent differences between the treatment groups in P018, and no apparent trends indicative of DOR-related effects on clinical laboratory parameters.

Summary statistics for baseline, on-treatment, and change from baseline values for laboratory safety parameters were tabulated at each time point by treatment group, and the mean changes from baseline in clinical laboratory parameters were generally small in magnitude [Ref. 5.3.5.1: P018V01MK1439: Table 14.3-17].

3.3.3.1 Laboratory Changes from Baseline in Fasting Lipids

Assessing the superiority of DOR to DRV+r by mean change from baseline in fasting serum LDL-C at Week 48 and mean change from baseline in non-HDL-C at Week 48 was a pre-specified hypothesis for P018. Superiority of DOR over DRV+r was assessed for the above mentioned pre-specified hypothesis using ANCOVA models to compare the treatment groups, adjusted for baseline fasting lipid level. Initial assessment was conducted for all subjects in both treatment groups, regardless of use of lipid lowering agents before or during the trial. A sensitivity analysis was also conducted, as explained below, excluding from the analysis subjects on lipid-lowering agents at baseline.

DOR was superior to DRV+r with respect to changes from baseline in fasting LDL-C as demonstrated by the mean change from baseline for both treatment groups [-4.51 for DOR and 9.92 for the DRV+r group; difference of -14.61 mg/dL (-18.15, -11.06)]. The p-value for the treatment difference was <0.0001, indicating that the difference was statistically significant [Table 2.7.4: 41].

Similarly, the mean change from baseline in fasting non- high-density lipoprotein cholesterol (HDL-C) (mg/dL) was -5.30 mg/dL and 13.75 mg/dL for the DOR and DRV+r groups, respectively, with a statistically significant (p<0.001) treatment difference of -19.34 mg/dL (-23.33, -15.35)

Additionally, changes from baseline to Week 48 for fasting total cholesterol, fasting triglycerides, and fasting HDL-C were evaluated. The 95% CIs for the between-group differences for fasting total cholesterol (treatment difference -19.5 mg/dL) and fasting triglycerides (treatment difference -27.87 mg/dL) did not include “0”, suggest a benefit of DOR treatment over DRV+r for these 2 parameters.

Table 2.7.4: 41
Change From Baseline in Fasting Lipids at Week 48 (P018)

Treatment	N	Baseline Mean	Change from Baseline at Week 48		Difference Estimates (DOR - Darunavir)	
			Mean Change (SD)	95% CI†	Difference‡ 95% CI	p-Value
Fasting LDL Cholesterol (mg/dL)						
DOR 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)						
DOR 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)						
DOR 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)						
DOR 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)						
DOR 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 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: DOR 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]

The between-group difference in proportion of subjects who modified lipid-lowering therapy by Week 48 was also analyzed using Miettinen and Nurminen's method [Ref. 5.4: 00QHZT]. Few subjects in the DOR (N=8, 2.1%) and DRV+r (N=4, 1.0%) treatment groups modified their lipid-lowering therapy during the first 48 weeks of the study [Table 2.7.4: 42].

Table 2.7.4: 42
Proportion of Subjects who Modified Lipid-Lowering Therapy During the Study Weeks 0-48 (P018)

Treatment	Percent of Subjects Modified Lipid-Lowering Therapy During the Study		Difference Estimates† (DOR - Darunavir)	
	n/N	% (95% CI)	Difference	95% CI
DOR 100 mg QD	8/383	2.1 (0.9, 4.1)	1.0	(-0.8, 3.1)
Darunavir/ritonavir 800/100 mg QD	4/383	1.0 (0.3, 2.7)		

† The 95% CIs were calculated using Miettinen and Nurminen's method.
Note: DOR 100 mg QD and darunavir/ritonavir 800/100 mg QD were administered with TRUVADA™ or EPZICOM™/KIVEXA™.
N = Number of subjects in each treatment group.
n = Number of subjects modified lipid-lowering therapy.

Source: [P018V01MK1439: analysis-adsl; adlpd]

A sensitivity analysis was also conducted in order to corroborate the pre-specified hypothesis of assessing superiority of DOR to DRV+r by mean change from baseline in fasting serum LDL-C and in non-HDL-C at Week 48 in P018. In order to eliminate possible confounders, subjects on lipid-lowering agents at baseline were excluded from the analyses, and subjects who initiated lipid-lowering therapy post-baseline had their last fasted on-treatment valued carried forward for the Week 48 analysis (DOR n=6; DRV+r n=4). Twelve (3.7%) subjects in the DOR treatment group and 14 (4.4%) subjects in the DRV+r treatment group were excluded from the analyses. The results from the sensitivity analyses [Table 2.7.4: 43] are similar to the results from the initial analysis conducted, which included subjects regardless of lipid-lowering agents being used at baseline.

Table 2.7.4: 43
Sensitivity Analysis of Change From Baseline in Fasting Lipids at Week 48 Excluding Subjects on Lipid-Lowering Therapy at Baseline (P018)

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	317	91.36	-4.64 (20.78)	(-6.94, -2.35)	-14.40 (-18.01, -10.80)	<0.0001
Darunavir/ritonavir 800/100 mg QD	305	92.31	9.50 (27.27)	(6.43, 12.58)		
Fasting Non-HDL Cholesterol (mg/dL)						
Doravirine 100 mg QD	320	113.56	-5.42 (23.38)	(-8.00, -2.85)	-19.39 (-23.37, -15.40)	<0.0001
Darunavir/ritonavir 800/100 mg QD	311	114.53	13.73 (29.77)	(10.41, 17.05)		
Fasting Cholesterol (mg/dL)						
Doravirine 100 mg QD	320	157.15	-1.40 (25.59)	(-4.22, 1.41)	-19.58 (-23.94, -15.23)	nps*
Darunavir/ritonavir 800/100 mg QD	311	157.79	18.01 (33.06)	(14.32, 21.70)		
Fasting Triglyceride (mg/dL)						
Doravirine 100 mg QD	320	110.98	-3.06 (69.46)	(-10.70, 4.58)	-28.55 (-39.27, -17.84)	nps*
Darunavir/ritonavir 800/100 mg QD	311	113.75	24.55 (77.02)	(15.96, 33.14)		
Fasting HDL Cholesterol (mg/dL)						
Doravirine 100 mg QD	320	43.59	4.02 (10.73)	(2.84, 5.20)	-0.18 (-1.82, 1.46)	nps*
Darunavir/ritonavir 800/100 mg QD	311	43.25	4.28 (11.07)	(3.04, 5.51)		

Subjects on lipid-lowering agents at baseline were excluded from these analyses (DOR n = 12 and DRV+r n = 14). Subjects initiating a lipid-lowering therapy post-baseline had their last fasted on-treatment value carried forward for the Week 48 analysis (DOR n = 6 and DRV+r n = 4).

[†] 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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3.4 Clinical Laboratory Evaluations in P021 (Phase 3 Trial)

3.4.1 Pre-Defined Limit of Change Evaluations

Predefined limits of change (PDLC) for clinical laboratory values in study P021 were based on the Division of AIDS 'Table for Grading the Severity of Adult and Pediatric AEs, version 2.0.' The analysis of the PDLC included subjects whose laboratory grade worsened during the trial. Point estimates and 95% CIs are provided for the difference between treatment groups.

The proportions of subjects with laboratory findings meeting PDLC criteria at Week 48 were lower for the DOR/3TC/TDF treatment group compared with the EFV/FTC/TDF treatment group for the following laboratory values: fasting LDL-C (Grade 2), fasting cholesterol (Grade 1 and Grade 2), fasting triglycerides (Grade 1 and Grade 3), ALT (Grade 1), and alkaline phosphatase (Grade 1) [Table 2.7.4: 44]. A higher proportion of subjects in the DOR/3TC/TDF treatment group met PDLC criteria in the category of bilirubin for Grade 1 and Grade 2 events only.

The majority of bilirubin elevations in subjects on DOR/3TC/TDF were Grade 1, and both Grade 1 and Grade 2 elevations were single and transient with no pattern relative to dosing. The absence of bilirubin elevations in the EFV/FTC/TDF group is likely due to the induction of UGT1A1and MRPs that reduces bilirubin levels [Ref. 5.4: 04QVMV]. Similar findings of no elevations in total bilirubin with EFV have been observed in other clinical trials [Ref. 5.4: 04QVMS]. None of the bilirubin elevations in the DOR/3TC/TDF arm was associated with other liver function test abnormalities or with a clinically significant AE. No subjects discontinued the trial due to these laboratory abnormalities.

3.4.2 Abnormal Laboratory Values of Potential Clinical Relevance (Grade 3 and Grade 4)

All subjects in P021 for whom abnormal laboratory values of potential clinical relevance were identified were reviewed. No relationship to study drug was established due to confounding factors associated with each individual subject's medical history. No subject was discontinued from the trial for liver function tests categorized as Grade 3 or 4.

By Week 48, Grade 4 laboratory abnormalities occurring in ≥4 subjects in either treatment group were observed for creatinine kinase in the DOR/3TC/TDF treatment group (N=2 [0.6%]); and the EFV/FTC/TDF treatment group (N=4 [1.1%]).

Table 2.7.4: 44
Analysis of Subjects With Laboratory Findings That Met Predetermined Criteria (Incidence ≥ 4 Subjects in One or More Treatment Groups) Worsening Grade; Weeks 0-48 (P021)

Criterion†	DOR/3TC/TDF QD n/m	(%)	EFV/FTC/TDF QD n/m	(%)	Difference [DOR/3TC/TDF - EFV/FTC/TDF] ‡ % (95% CI)
HEMATOLOGY					
Hemoglobin (g/dL)					
Grade 1: Male: 10.0 - 10.9 Female: 9.5 - 10.4	9/362	(2.5)	5/359	(1.4)	1.1 (-1.0, 3.4)
CHEMISTRY					
Fasting LDL Cholesterol (mg/dL)					
Grade 1: 130 - <160	15/332	(4.5)	22/309	(7.1)	-2.6 (-6.5, 1.0)
Grade 2: 160 - <190	3/332	(0.9)	15/309	(4.9)	-4.0 (-7.1, -1.5)
Grade 3: >=190	1/332	(0.3)	5/309	(1.6)	-1.3 (-3.5, 0.2)
Fasting Cholesterol (mg/dL)					
Grade 1: 200 - <240	21/336	(6.3)	44/318	(13.8)	-7.6 (-12.4, -3.1)
Grade 2: 240 - <300	2/336	(0.6)	24/318	(7.5)	-7.0 (-10.5, -4.3)
Fasting Triglyceride (mg/dL)					
Grade 1: 150 - 300	32/336	(9.5)	51/318	(16.0)	-6.5 (-11.8, -1.4)
Grade 2: >300 - 500	13/336	(3.9)	19/318	(6.0)	-2.1 (-5.7, 1.3)
Grade 3: >500 - 1000	2/336	(0.6)	8/318	(2.5)	-1.9 (-4.4, -0.0)
Fasting Glucose (mg/dL)					
Grade 1: 110 - 125	12/336	(3.6)	13/318	(4.1)	-0.5 (-3.7, 2.6)
Grade 2: >125 - 250	6/336	(1.8)	5/318	(1.6)	0.2 (-2.1, 2.5)
Total Bilirubin (mg/dL)					
Grade 1: 1.1 - <1.6 x ULN	13/363	(3.6)	0/359	(0.0)	3.6 (2.1, 6.0)
Grade 2: 1.6 - <2.6 x ULN	9/363	(2.5)	0/359	(0.0)	2.5 (1.3, 4.6)
Creatinine (mg/dL)					
Grade 2: >1.3 - 1.8 x ULN or Increase of >0.3 mg/dL above baseline	8/363	(2.2)	5/359	(1.4)	0.8 (-1.3, 3.1)
Grade 3: >1.8 - <3.5 x ULN or Increase of 1.5 to <2.0 x above baseline	7/363	(1.9)	3/359	(0.8)	1.1 (-0.7, 3.2)

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Analysis of Subjects With Laboratory Findings That Met Predetermined Criteria (Incidence ≥ 4 Subjects in One or More Treatment Groups) Worsening Grade; Weeks 0-48

Criterion†	DOR/3TC/TDF QD n/m	(%)	EFV/FTC/TDF QD n/m	(%)	Difference [DOR/3TC/TDF - EFV/FTC/TDF] ‡ % (95% CI)
Aspartate Aminotransferase (IU/L)					
Grade 1: 1.25 - <2.5 x ULN	29/363	(8.0)	36/359	(10.0)	-2.0 (-6.3, 2.2)
Grade 2: 2.5 - <5.0 x ULN	6/363	(1.7)	8/359	(2.2)	-0.6 (-2.9, 1.6)
Grade 3: 5.0 - <10.0 x ULN	1/363	(0.3)	5/359	(1.4)	-1.1 (-3.0, 0.3)
>2.5 - 5.0 x Baseline	16/363	(4.4)	34/359	(9.5)	-5.1 (-9.0, -1.4)
>5.0 x Baseline	6/363	(1.7)	8/359	(2.2)	-0.6 (-2.9, 1.6)
Alanine Aminotransferase (IU/L)					
Grade 1: 1.25 - <2.5 x ULN	31/363	(8.5)	47/359	(13.1)	-4.6 (-9.2, -0.0)
Grade 2: 2.5 - <5.0 x ULN	12/363	(3.3)	13/359	(3.6)	-0.3 (-3.2, 2.5)
Grade 3: 5.0 - <10.0 x ULN	2/363	(0.6)	5/359	(1.4)	-0.8 (-2.7, 0.8)
>2.5 - 5.0 x Baseline	21/363	(5.8)	44/359	(12.3)	-6.5 (-10.8, -2.3)
>5.0 x Baseline	12/363	(3.3)	21/359	(5.8)	-2.5 (-5.8, 0.5)
Alkaline Phosphatase (IU/L)					
Grade 1: 1.25 - <2.5 x ULN	13/363	(3.6)	28/359	(7.8)	-4.2 (-7.8, -0.9)
>2.5 - 5.0 x Baseline	6/363	(1.7)	6/359	(1.7)	-0.0 (-2.1, 2.1)
Lipase (IU/L)					
Grade 1: 1.1 - <1.5 x ULN	18/363	(5.0)	18/359	(5.0)	-0.1 (-3.4, 3.2)
Grade 2: 1.5 - <3.0 x ULN	19/363	(5.2)	15/359	(4.2)	1.1 (-2.1, 4.3)
Grade 3: 3.0 - <5.0 x ULN	3/363	(0.8)	5/359	(1.4)	-0.6 (-2.5, 1.2)
Creatine Kinase (IU/L)					
Grade 1: 3.0 - <6.0 x ULN	17/363	(4.7)	17/359	(4.7)	-0.1 (-3.3, 3.2)
Grade 2: 6.0 - <10.0 x ULN	9/363	(2.5)	7/359	(1.9)	0.5 (-1.8, 2.9)
Grade 3: 10.0 - <20.0 x ULN	6/363	(1.7)	7/359	(1.9)	-0.3 (-2.5, 1.9)
Grade 4: >= 20.0 x ULN	2/363	(0.6)	4/359	(1.1)	-0.6 (-2.3, 1.0)
Amylase (IU/L)					
Grade 1: 1.1 - <1.5 x ULN	9/363	(2.5)	14/359	(3.9)	-1.4 (-4.2, 1.2)
Grade 2: 1.5 - <3.0 x ULN	2/363	(0.6)	5/359	(1.4)	-0.8 (-2.7, 0.8)

† For graded criteria:subjects are counted once per test in the highest grade reported.

For inclusion in this analysis, both a baseline and at least one on-treatment laboratory value had to be present. Only subjects with a worsened grade from baseline were included. A subject was listed with a Grade X event if his/her highest grade during treatment was X.

‡ The 95% CIs for the treatment differences in percent with PDLC were calculated using Miettinen and Nurminen method.

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 postbaseline test results that met the predetermined criterion.

m = Number of subjects with at least one postbaseline test result.

LLN = Lower limit of normal range. ULN = Upper limit of normal range.

Source: [P021V01MK1439A: analysis-adlb]

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Numbers and percentages of subjects with laboratory values that met the predefined limits of change by Week 48, as well as through the data cutoff date, are provided in [Ref. 5.3.5.1: P021V01MK1439A: Table 14-3.37] and [Ref. 5.3.5.1: P021V01MK1439A: Table 14-3.21], respectively.

3.4.3 Laboratory Changes from Baseline

Other than the changes in fasting lipid parameters described in [Sec. 2.7.4.3.4.3.1], no apparent differences between treatment groups and no apparent trends indicative of DOR-related effects on clinical laboratory parameters were observed in P021 [Ref. 5.3.5.1: P021V01MK1439A: Table 14.3-19].

3.4.3.1 Laboratory Changes from Baseline in Fasting Lipids

Assessing superiority of DOR/3TC/TDF to EFV/FTC/TDF by mean change from baseline in fasting LDL-C at Week 48, and mean change from baseline in non-HDL-C at Week 48 was a pre-specified hypothesis in P021. Superiority of DOR/3TC/TDF over EFV/FTC/TDF was assessed for the above mentioned pre-specified hypotheses using ANCOVA models to compare the treatment groups, adjusted for baseline fasting lipid level. Initial assessment was conducted for all subjects in both treatment groups, regardless of use of lipid lowering agents before or during the trial. A sensitivity analysis was also conducted, as explained below, excluding from the analysis subjects on lipid-lowering agents at baseline.

DOR/3TC/TDF had a significantly mean decrease compared from baseline than EFV/FTC/TDF on fasting LDL-C (mg/dL) and fasting non-HDL-C (mg/dL). The mean change from baseline in fasting LDL-C was -1.58 mg/dL and 8.74 mg/dL for the DOR/3TC/TDF and EFV/FTC/TDF groups, respectively, with a treatment difference of -10.01mg/dL (-13.53, -6.49) and p-value of <0.0001, indicating that the difference was statistically significant [Table 2.7.4: 45].

Similarly, the mean change from baseline in fasting non-HDL-C was -3.83 mg/dL and 13.26 mg/dL for the DOR/3TC/TDF and EFV/FTC/TDF groups, respectively, with a treatment difference of -17.02 mg/dL (-20.89, -13.16) and p-value of <0.0001 indicating that the difference was statistically significant.

Changes from baseline to Week 48 for fasting total cholesterol, fasting triglycerides, and fasting HDL-C were also evaluated. The 95% CIs for the between-group differences for fasting total cholesterol (treatment difference -23.44 mg/dL), fasting triglycerides (treatment difference -35.96 mg/dL), and fasting HDL cholesterol (treatment difference -6.47 mg/dL) did not include “0”, suggesting a benefit of DOR treatment over EFV/FTC/TDF for these three variables.

Table 2.7.4: 45
Change From Baseline in Fasting Lipids at Week 48 (P021)

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]

The between-group difference in the proportion of subjects who modified lipid-lowering therapy by Week 48 was also analyzed using Miettinen and Nurminen's method [Ref. 5.4: 00QHZT]. Few subjects in the DOR/3TC/TDF (N=8, 2.2%) and EFV/FTC/TDF (N=9, 2.5%) treatment groups modified their lipid lowering therapy during the first 48 weeks of the study [Table 2.7.4: 46].

Table 2.7.4: 46
Proportion of Subjects who Modified Lipid-Lowering Therapy During the Study Weeks 0-48 (P021)

Treatment	Percent of Subjects Modified Lipid-Lowering Therapy During the Study		Difference Estimates[†] (DOR/3TC/TDF - EFV/FTC/TDF)	
	n/N	% (95% CI)	Difference	95% CI
DOR/3TC/TDF QD	8/364	2.2 (1.0, 4.3)	-0.3	(-2.7, 2.1)
EFV/FTC/TDF QD	9/364	2.5 (1.1, 4.6)		

[†] The 95% CIs were calculated using Miettinen and Nurminen's method.
N = Number of subjects in each treatment group.
n = Number of subjects modified lipid-lowering therapy.

Source: [P021V01MK1439A: analysis-adsl; adlpd]

A sensitivity analysis was also conducted in order to corroborate the pre-specified hypothesis of assessing superiority of DOR/3TC/TDF to EFV/FTC/TDF by mean change from baseline in fasting serum LDL-C and non-HDL-C at Week 48. In order to eliminate possible confounders, subjects on lipid-lowering agents at baseline were excluded from the analyses, and subjects who initiated lipid-lowering therapy post-baseline had their last fasted on-treatment valued carried forward for the Week 48 analysis ((DOR/3TC/TDF n=3; EFV/FTC/TDF n=8). Fifteen subjects in the DOR/3TC/TDF treatment group (4.1%) and 10 subjects in the EFV/FTC/TDF treatment group (2.7%) excluded from the analyses. The results from the sensitivity analyses [Table 2.7.4: 47] are similar to the results from the initial analysis conducted, which included subjects regardless of lipid-lowering agents being used at baseline.

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Table 2.7.4: 47
Sensitivity Analysis of Change From Baseline in Fasting Lipids at Week 48 Excluding Subjects on Lipid-Lowering Therapy at Baseline (P021)

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	317	91.68	-2.06 (21.65)	(-4.45, 0.33)	-10.24 (-13.78, -6.70)	<0.0001
EFV/FTC/TDF QD	298	91.27	8.29 (25.57)	(5.37, 11.20)		
Fasting Non-HDL Cholesterol (mg/dL)						
DOR/3TC/TDF QD	320	114.70	-4.09 (22.13)	(-6.52, -1.66)	-16.94 (-20.83, -13.05)	<0.0001
EFV/FTC/TDF QD	307	115.26	12.74 (28.77)	(9.51, 15.97)		
Fasting Cholesterol (mg/dL)						
DOR/3TC/TDF QD	320	156.84	-2.25 (25.31)	(-5.03, 0.54)	-23.37 (-27.54, -19.20)	nps*
EFV/FTC/TDF QD	307	156.83	21.12 (30.69)	(17.68, 24.57)		
Fasting Triglyceride (mg/dL)						
DOR/3TC/TDF QD	320	118.69	-12.01 (66.98)	(-19.38, -4.65)	-35.32 (-46.65, -24.00)	nps*
EFV/FTC/TDF QD	307	122.57	21.57 (93.88)	(11.02, 32.11)		
Fasting HDL Cholesterol (mg/dL)						
DOR/3TC/TDF QD	320	42.14	1.84 (9.67)	(0.78, 2.91)	-6.41 (-7.94, -4.87)	nps*
EFV/FTC/TDF QD	307	41.57	8.38 (10.66)	(7.18, 9.58)		

Subjects on lipid-lowering agents at baseline were excluded from these analyses (DOR/3TC/TDF n = 15 and EFV/FTC/TDF n = 10). Subjects initiating a lipid-lowering therapy post-baseline had their last fasted on-treatment value carried forward for the Week 48 analysis (DOR/3TC/TDF n = 3 and EFV/FTC/TDF n = 8).

[†] 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]

3.5 Clinical Laboratory Evaluations in the Integrated Safety Population Pool

3.5.1 Phase 2-3 Trials – Main Safety Pool (P007, P018, and P021)

The following section in this summary of safety provides the results of the integrated analysis of safety that was performed in the MSP, which includes data from trials P007, P018, and P021. A description of the endpoints and timepoints assessed for the MSP is provided in [Sec. 1.1.3].

3.5.1.1 Pre-Defined Limit of Change Evaluations

In the MSP, the proportions of subjects with clinical laboratory results meeting PDLC criteria at Week 48 for selected laboratory parameters were generally 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.

Numbers and percentages of subjects with laboratory values that met the predefined limits of change through the data cutoff date are provided in [Table 5.3.5.3.3-trtmtnve48wk: 59].

Numbers and percentages of subjects with laboratory values that met predefined limits of change that were Grade 3 or greater by Week 48 are provided in [Table 5.3.5.3.3-trtmtnve48wk: 58].

Numbers and percentages of subjects with laboratory values that met predefined limits of change from baseline by Week 48 are summarized in [Table 5.3.5.3.3-trtmtnve48wk: 60] and [Table 5.3.5.3.3-trtmtnve48wk: 61] for subjects who were hepatitis B and/or C positive and who were hepatitis B and/or C negative, respectively.

Abnormal Laboratory Values of Potential Clinical Relevance (Grade 3 and Grade 4)

By Week 48, Grade 4 laboratory abnormalities occurring in ≥4 subjects in any treatment group were similar for all 3 groups in the MSP. None of these potential laboratory abnormal values resulted in discontinuation of study drug and none was a reason for more serious event such as pancreatitis. The abnormal laboratories observed were creatine kinase (Main Combined DOR: N=8 [1.1%]; Main DRV+r: N=7, [1.9%]; Main Combined EFV: N=4 [1.1%]), lipase (Main Combined DOR: N=6 [0.7%]; Main DRV+r: N=3 [0.8%]; Main Combined EFV: N=4 [0.9%]), and neutrophils (Main Combined DOR: N=4 [0.5%]; Main DRV+r: N=2 [0.4%]; Main Combined EFV: N=2 [0.4%]).

Table 2.7.4: 48
Subjects With Laboratory Findings That Met Predetermined Criteria
Main Safety Pool (P007 (Doravirine 100 mg q.d. Group) and P018 and P021 Combined)
Worsening Grade; Weeks 0-48

Criterion†	Main Combined DOR		Main DRV+r		Main Combined EFV	
	n/m	(%)	n/m	(%)	n/m	(%)
HEMATOLOGY						
Neutrophils (10^9/L)						
Grade 1: 0.800 - 1.000	10/848	(1.2)	3/378	(0.8)	4/467	(0.9)
Grade 2: 0.600 - 0.799	3/848	(0.4)	4/378	(1.1)	3/467	(0.6)
Grade 3: 0.400 - 0.599	0/848	(0.0)	1/378	(0.3)	2/467	(0.4)
Grade 4: <0.400	4/848	(0.5)	2/378	(0.5)	2/467	(0.4)
Hemoglobin (g/dL)						
Grade 1: Male: 10.0 - 10.9 Female: 9.5 - 10.4	17/849	(2.0)	8/378	(2.1)	6/467	(1.3)
Grade 2: Male: 9.0 - <10.0 Female: 8.5 - <9.5	6/849	(0.7)	6/378	(1.6)	2/467	(0.4)
Grade 3: Male: 7.0 - <9.0 Female: 6.5 - <8.5	2/849	(0.2)	0/378	(0.0)	1/467	(0.2)
Grade 4: Male: <7.0 Female: <6.5	0/849	(0.0)	0/378	(0.0)	0/467	(0.0)
Platelets (10^9/L)						
Grade 1: 100 - <124.999	6/845	(0.7)	4/376	(1.1)	2/465	(0.4)
Grade 2: 50 - <100	4/845	(0.5)	2/376	(0.5)	1/465	(0.2)
Grade 3: 25 - <50	0/845	(0.0)	0/376	(0.0)	0/465	(0.0)
Grade 4: <25	1/845	(0.1)	0/376	(0.0)	0/465	(0.0)
CHEMISTRY						
Fasting LDL Cholesterol (mg/dL)						
Grade 1: 130 - <160	41/765	(5.4)	34/320	(10.6)	37/408	(9.1)
Grade 2: 160 - <190	6/765	(0.8)	23/320	(7.2)	19/408	(4.7)
Grade 3: ≥190	2/765	(0.3)	9/320	(2.8)	7/408	(1.7)
Fasting Cholesterol (mg/dL)						
Grade 1: 200 - <240	59/774	(7.6)	48/327	(14.7)	64/418	(15.3)
Grade 2: 240 - <300	6/774	(0.8)	32/327	(9.8)	31/418	(7.4)
Grade 3: ≥300	2/774	(0.3)	1/327	(0.3)	3/418	(0.7)
Fasting Triglyceride (mg/dL)						
Grade 1: 150 - 300	88/774	(11.4)	71/327	(21.7)	71/418	(17.0)
Grade 2: >300 - 500	31/774	(4.0)	13/327	(4.0)	26/418	(6.2)
Grade 3: >500 - 1000	4/774	(0.5)	2/327	(0.6)	10/418	(2.4)
Grade 4: >1000	0/774	(0.0)	2/327	(0.6)	0/418	(0.0)

Subjects With Laboratory Findings That Met Predetermined Criteria
Main Safety Pool (P007 (Doravirine 100 mg q.d. Group) and P018 and P021 Combined)
Worsening Grade; Weeks 0-48

Criterion[†]	Main Combined DOR		Main DRV+r		Main Combined EFV	
	n/m	(%)	n/m	(%)	n/m	(%)
Fasting Glucose (mg/dL)						
Grade 1: 110 - 125	44/775	(5.7)	26/327	(8.0)	22/418	(5.3)
Grade 2: >125 - 250	15/775	(1.9)	9/327	(2.8)	7/418	(1.7)
Grade 3: >250 - 500	4/775	(0.5)	1/327	(0.3)	2/418	(0.5)
Grade 4: >500	0/775	(0.0)	0/327	(0.0)	0/418	(0.0)
Total Bilirubin (mg/dL)						
Grade 1: 1.1 - <1.6 x ULN	38/850	(4.5)	4/378	(1.1)	1/467	(0.2)
Grade 2: 1.6 - <2.6 x ULN	15/850	(1.8)	1/378	(0.3)	0/467	(0.0)
Grade 3: 2.6 - <5.0 x ULN	1/850	(0.1)	0/378	(0.0)	0/467	(0.0)
Grade 4: ≥5.0 x ULN	1/850	(0.1)	0/378	(0.0)	1/467	(0.2)
>2.5 - 5.0 x Baseline	9/850	(1.1)	1/378	(0.3)	1/467	(0.2)
>5.0 - 10.0 x Baseline	2/850	(0.2)	0/378	(0.0)	0/467	(0.0)
>10.0 x Baseline	1/850	(0.1)	0/378	(0.0)	1/467	(0.2)
Direct Bilirubin (mg/dL)						
>2.5 - 5.0 x Baseline	1/850	(0.1)	1/378	(0.3)	0/467	(0.0)
>5.0 - 10.0 x Baseline	0/850	(0.0)	0/378	(0.0)	0/467	(0.0)
>10.0 x Baseline	3/850	(0.4)	0/378	(0.0)	1/467	(0.2)
Indirect Bilirubin (mg/dL)						
>2.5 - 5.0 x Baseline	4/850	(0.5)	0/378	(0.0)	0/467	(0.0)
>5.0 - 10.0 x Baseline	1/850	(0.1)	0/378	(0.0)	0/467	(0.0)
>10.0 x Baseline	1/850	(0.1)	0/378	(0.0)	1/467	(0.2)
Creatinine (mg/dL)						
Grade 1: 1.1 - 1.3 x ULN	1/850	(0.1)	0/378	(0.0)	0/467	(0.0)
Grade 2: >1.3 - 1.8 x ULN or Increase of >0.3 mg/dL above baseline	19/850	(2.2)	16/378	(4.2)	5/467	(1.1)
Grade 3: >1.8 - <3.5 x ULN or Increase of 1.5 to <2.0 x above baseline	12/850	(1.4)	10/378	(2.6)	3/467	(0.6)
Grade 4: ≥3.5 x ULN or Increase of ≥2.0 x above baseline	1/850	(0.1)	0/378	(0.0)	1/467	(0.2)
Aspartate Aminotransferase (IU/L)						
Grade 1: 1.25 - <2.5 x ULN	69/850	(8.1)	26/378	(6.9)	49/467	(10.5)

Subjects With Laboratory Findings That Met Predetermined Criteria
Main Safety Pool (P007 (Doravirine 100 mg q.d. Group) and P018 and P021 Combined)
Worsening Grade; Weeks 0-48

Criterion[†]	Main Combined DOR		Main DRV+r		Main Combined EFV	
	n/m	(%)	n/m	(%)	n/m	(%)
Aspartate Aminotransferase (IU/L)						
Grade 2: 2.5 - <5.0 x ULN	24/850	(2.8)	12/378	(3.2)	12/467	(2.6)
Grade 3: 5.0 - <10.0 x ULN	4/850	(0.5)	6/378	(1.6)	5/467	(1.1)
Grade 4: ≥10.0 x ULN	1/850	(0.1)	0/378	(0.0)	3/467	(0.6)
>2.5 - 5.0 x Baseline	41/850	(4.8)	15/378	(4.0)	43/467	(9.2)
>5.0 x Baseline	19/850	(2.2)	12/378	(3.2)	12/467	(2.6)
Alanine Aminotransferase (IU/L)						
Grade 1: 1.25 - <2.5 x ULN	72/839	(8.6)	27/375	(7.2)	60/467	(12.8)
Grade 2: 2.5 - <5.0 x ULN	23/839	(2.7)	7/375	(1.9)	13/467	(2.8)
Grade 3: 5.0 - <10.0 x ULN	7/839	(0.8)	6/375	(1.6)	7/467	(1.5)
Grade 4: ≥10.0 x ULN	1/839	(0.1)	3/375	(0.8)	1/467	(0.2)
>2.5 - 5.0 x Baseline	53/839	(6.3)	15/375	(4.0)	56/467	(12.0)
>5.0 x Baseline	22/839	(2.6)	13/375	(3.5)	26/467	(5.6)
Alkaline Phosphatase (IU/L)						
Grade 1: 1.25 - <2.5 x ULN	18/850	(2.1)	8/378	(2.1)	35/467	(7.5)
Grade 2: 2.5 - <5.0 x ULN	1/850	(0.1)	2/378	(0.5)	2/467	(0.4)
Grade 3: 5.0 - <10.0 x ULN	0/850	(0.0)	0/378	(0.0)	1/467	(0.2)
Grade 4: ≥10.0 x ULN	0/850	(0.0)	0/378	(0.0)	0/467	(0.0)
>2.5 - 5.0 x Baseline	8/850	(0.9)	1/378	(0.3)	8/467	(1.7)
>5.0 x Baseline	0/850	(0.0)	2/378	(0.5)	1/467	(0.2)
Lipase (IU/L)						
Grade 1: 1.1 - <1.5 x ULN	50/850	(5.9)	23/378	(6.1)	28/467	(6.0)
Grade 2: 1.5 - <3.0 x ULN	38/850	(4.5)	20/378	(5.3)	23/467	(4.9)
Grade 3: 3.0 - <5.0 x ULN	13/850	(1.5)	6/378	(1.6)	10/467	(2.1)
Grade 4: ≥5.0 x ULN	6/850	(0.7)	3/378	(0.8)	4/467	(0.9)
Creatine Kinase (IU/L)						
Grade 1: 3.0 - <6.0 x ULN	39/743	(5.2)	22/378	(5.8)	17/359	(4.7)
Grade 2: 6.0 - <10.0 x ULN	18/743	(2.4)	12/378	(3.2)	7/359	(1.9)
Grade 3: 10.0 - <20.0 x ULN	13/743	(1.7)	7/378	(1.9)	7/359	(1.9)
Grade 4: ≥ 20.0 x ULN	8/743	(1.1)	7/378	(1.9)	4/359	(1.1)

Subjects With Laboratory Findings That Met Predetermined Criteria
Main Safety Pool (P007 (Doravirine 100 mg q.d. Group) and P018 and P021 Combined)
Worsening Grade; Weeks 0-48

Criterion[†]	Main Combined DOR		Main DRV+r		Main Combined EFV	
	n/m	(%)	n/m	(%)	n/m	(%)
Amylase (IU/L)						
Grade 1: 1.1 - <1.5 x ULN	25/743	(3.4)	16/378	(4.2)	14/359	(3.9)
Grade 2: 1.5 - <3.0 x ULN	10/743	(1.3)	9/378	(2.4)	5/359	(1.4)
Grade 3: 3.0 - <5.0 x ULN	0/743	(0.0)	2/378	(0.5)	0/359	(0.0)
Grade 4: ≥ 5.0 x ULN	0/743	(0.0)	0/378	(0.0)	0/359	(0.0)

[†]For graded criteria: subjects are counted once per test in the highest grade reported.

For baseline criteria: subjects are counted in the '>X-fold Baseline' if the highest test value during treatment fell in this category.

For inclusion in this analysis, both a baseline and at least one on-treatment laboratory value had to be present. Only subjects with a worsened grade from baseline were included. A subject was listed with a Grade X event if his/her highest grade during treatment was X.

n = Number of subjects with postbaseline test results that met the predetermined criterion.

m = Number of subjects with at least one postbaseline test result.

LLN = Lower limit of normal range. ULN = Upper limit of normal range.

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 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.

Source: [ISS: analysis-adlb]

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3.5.1.2 Laboratory Changes from Baseline

Except for the changes in fasting lipid parameters discussed below no apparent differences between treatment groups and no apparent trends indicative of DOR related effects on clinical laboratory parameters were observed in the MSP [Table 5.3.5.3.3-trtmtnve48wk: 64].

Change from baseline in fasting LDL-C, fasting non–HDL-C, fasting total cholesterol, fasting triglycerides, and fasting HDL-C were evaluated in the MSP. DOR was associated with decreases from baseline in mean values for fasting LDL C, fasting non-HDL-C, fasting total cholesterol, and fasting triglycerides compared with increases in these values for both DRV+r and EFV [Table 2.7.4: 49]. Similar mean increases in fasting HDL-C values were observed for the 3 treatment groups.

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Table 2.7.4: 49
Change From Baseline in Fasting Lipids at Week 48
Main Safety Pool (P007 (DOR 100 mg q.d. Group) and P018 and P021 Combined)
Weeks 0-48

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)								
757	92.45	-3.69 (21.17)	318	91.76	9.92 (27.31)	403	91.76	9.14 (25.80)
Fasting Non-HDL Cholesterol (mg/dL)								
765	115.04	-4.74 (22.67)	325	114.44	13.75 (31.08)	413	115.41	13.36 (28.88)
Fasting Cholesterol (mg/dL)								
765	157.75	-2.21 (25.28)	325	157.71	17.90 (33.95)	413	156.99	21.22 (30.54)
Fasting Triglyceride (mg/dL)								
765	115.09	-6.12 (68.03)	325	117.02	21.97 (92.59)	413	120.12	20.86 (89.52)
Fasting HDL Cholesterol (mg/dL)								
765	42.72	2.53 (9.82)	325	43.27	4.15 (11.01)	413	41.58	7.86 (10.64)

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: DOR 100 mg administered with FTC/TDF in P007 and P018 or ABC/3TC in P018, or fixed dose combination of DOR/ 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: EFV 600 mg administered with FTC/TDF in P007, or fixed dose combination of EFV/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]

C Confidential

3.6 Overall Clinical Laboratory Evaluation Conclusions

For both DOR and DOR/3TC/TDF no subject presented abnormal laboratory values of potential clinical relevance that would be the cause to be discontinued from the trial.

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 trials (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<0.0001*])
- Non-HDL-C: P018 (-5.30 vs 13.75 mg/dL [-19.34; *p<0.0001*]); P021 (-3.83 vs 13.26 mg/dL [-17.02; *p<0.0001*])

4 VITAL SIGNS, PHYSICAL FINDINGS, AND OTHER OBSERVATIONS RELATED TO SAFETY

4.1 Vital Signs, Physical Findings, and Other Observations in the Phase 1 Trials

Vital signs were monitored within each Phase 1 trial; however, these data were not pooled across trials. All descriptive summaries of vital sign data, if applicable to the protocol, were included in the individual CSRs. While some vital sign values were outside the normal range in the Phase 1 trials, there were no consistent changes or remarkable safety concerns associated with DOR or DOR/3TC/TDF treatment in any population. Any clinically meaningful changes in vital signs were captured as AEs and presented in the CPSOS [Sec. 5.3.5.3.1.5-trtmtnve48wk].

In a thorough QT/QTc trial with DOR (P017), a single 1200 mg dose of DOR did not have a clinically meaningful effect on the QT interval corrected for heart rate by the population method (QTcP). No clinically significant changes were observed between treatment and screening/baseline values in any of the electrocardiogram parameters evaluated. No subject had a prolonged QTcP interval (>450 msec for males; >470 msec for females) at any time during the trial and all subjects had a QTcP change from baseline of ≤30 msec at all treatments at all-time points. No clinically meaningful changes in PR or QRS intervals were observed [Sec. 2.7.2.2.4.2] [Ref. 5.3.4.1: P017: 11].

While a thorough QT/QTc trial was not conducted with DOR/3TC/TDF, no QTc prolongation concerns are described within the prescribing information for TDF or 3TC. As described in [Sec. 2.7.1], the PK of the agents are similar when administered as single entities or as part of DOR/3TC/TDF, and, therefore, the safety profiles for the individual components are applicable to the FDC.

4.2 Vital Signs, Physical Findings, and Other Observations in P007 (Phase 2b Dose-Ranging Trial)

In P007, there were no clinically meaningful changes from baseline in vital signs in any of the treatment groups through Week 96 [Ref. 5.3.5.1: P007V01MK1439: Table 14.3-29].

4.3 Vital Signs, Physical Findings, and Other Observations in P018 (Phase 3 Trial)

In P018, no clinically relevant change from baseline was seen through Week 48 in either the DOR treatment group or the DRV+r treatment group for systolic and diastolic blood pressure, pulse rate, or respiratory rate [Ref. 5.3.5.1: P018V01MK1439: Table 14.3-20]. Mean changes from baseline were minimal over time for systolic blood pressure and diastolic blood pressure. Similarly, there was little variation in mean changes from baseline in pulse rate. There were also no clinically meaningful changes from baseline in physical findings in any of the treatment groups through Week 48.

4.4 Vital Signs, Physical Findings, and Other Observations in P021 (Phase 3 Trial)

In P021, no clinically relevant change from baseline was seen through Week 48 in either the DOR/3TC/TDF treatment group or the EFV/FTC/TDF treatment group for systolic and diastolic blood pressure, pulse rate, or respiratory rate [Ref. 5.3.5.1: P021V01MK1439A: Table 14-3.22]. Similar small increases in weight from baseline to Week 48 were seen in the DOR/3TC/TDF treatment group and EFV/FTC/TDF treatment group.

4.5 Vital Signs, Physical Findings, and Other Observations in the Integrated Safety Population Pool

4.5.1 Phase 2-3 Trials – Main Safety Pool (Protocols 007, 018, and 021)

In the MSP, there were no clinically meaningful changes from baseline in vital signs or physical findings in any of the treatment groups through Week 48 [Table 5.3.5.3.3-trtmtnve48wk: 66].

4.6 Conclusions

No clinically meaningful differences in vital signs measurements or physical findings were observed in P007, P018, and P021.

5 SAFETY IN SPECIAL GROUPS AND SITUATIONS

The safety of DOR and DOR/3TC/TDF was assessed in special groups and situations in the MSP and likely to be encountered in the clinical practice of treating HIV-1 infected patients. The MSP represents 1710 treated subjects [Sec. 2.7.4.1.1.3]. This section discusses the influence of intrinsic factors, such as demographic characteristics and comorbid conditions encountered in the HIV-1 population (such as gender, race, age, hepatitis B and/or C infection status, and baseline $CD4^+$ T-cell count), and extrinsic factors or concomitant medications that are commonly used in the HIV-1 infected population on the safety profile of DOR and DOR/3TC/TDF. These factors/settings may affect the safety profile of DOR and

DOR/3TC/TDF directly or indirectly through changes in drug exposure. The impact of these factors on the safety profile of DOR and DOR/3TC/TDF was assessed by comparing AEs and laboratory parameters in the presence or absence of a particular factor.

5.1 Intrinsic Factors

Clinical and laboratory AEs were reviewed for subject subgroups in the MSP based on age, gender, and race, ethnicity, as well as hepatitis B and/or C infection status, and baseline $CD4^+$ T-cell count.

Overall, AEs and laboratory abnormality profiles were generally similar in subject subgroups based on gender, race/ethnicity, age (<65 or >65 years; of note, that there were no subjects >75 years of age and only 11 subjects who were >65 years of age) [Table 2.7.4: 9].

In all cases, differences between treatment groups were generally small across subgroups defined by baseline factors. The incidence of AEs by SOC was generally similar for men and women overall, in the MSP for all three treatment groups (Main Combined DOR, Main DRV+r and the Main Combined EFV) [Table 5.3.5.3.3-trtmtnve48wk: 67], [Table 5.3.5.3.3-trtmtnve48wk: 68] although the gender data should be interpreted with caution due to the small numbers of women enrolled compared with men. Similar findings were generally noted when AEs were evaluated by race, with a higher proportion of Cardiovascular Disorders reported for Asians in both the Main Combined DOR group and the Main Combined EFV group. There were no Asian subjects who discontinued from the study due to drug-related AE among the Cardiovascular Disorders SOC [Table 5.3.5.3.3-trtmtnve48wk: 71], [Table 5.3.5.3.3-trtmtnve48wk: 72].

For all other intrinsic factors evaluated for the MSP, the incidence of treatment-emergent AEs were generally similar among the three treatment groups by ethnicity [Table 5.3.5.3.3-trtmtnve48wk: 73], [Table 5.3.5.3.3-trtmtnve48wk: 74], baseline hepatitis status [Table 5.3.5.3.3-trtmtnve48wk: 75], [Table 5.3.5.3.3-trtmtnve48wk: 76], and baseline $CD4^+$ T-cell count [Table 5.3.5.3.3-trtmtnve48wk: 77], [Table 5.3.5.3.3-trtmtnve48wk: 78].

With respect to age, subjects were categorized as being within the age ranges of 18 to 64 years or ≥65 years; only 11 subjects (Main Combined DOR: N=5, Main DRV+r: N=4, and Main Combined EFV: N=2) in the MSP were ≥65 years of age, precluding meaningful interpretation of AE findings by age. In addition, small sample sizes for females, some race categories, and subjects who were hepatitis B and/or C positive should be considered in the analysis and interpretation of data in these subgroups.

5.2 Extrinsic Factors

The MSP was also used to evaluate safety by the extrinsic factor of geographical region (Africa, Asia/Pacific, Europe, Latin America, and North America). DOR and DOR/3TC/TDF had an overall safety profile that was similar among subjects from North America and subjects from other regions [Table 5.3.5.3.3-trtmtnve48wk: 79].

5.3 Drug Interactions

There were 16 Phase 1 trials conducted to investigate potential drug-drug interactions (DDI) 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. As described in [Sec. 2.7.2.1.3.1.3], moderate and strong inhibitors are expected to increase DOR AUC ~2 to 3 fold.

Based on the safety and tolerability data from the Phase 1 trials, the use of strong inhibitors was permitted in Phase 3 trials. Supporting data include Phase 1 trials where single doses as high as 1200 mg and multiple once-daily doses as high as 750 mg were administered to subjects without any safety issues. Other supporting data include the DDI trials with strong inhibitors (P002 and P010) and preclinical safety margins that provided at least a 3-fold exposure multiple over the increased DOR exposure when co-administered with strong inhibitors..

Concomitant use of strong and moderate CYP3A inducers is likely to reduce DOR PK to a clinically meaningful extent, which has the potential to affect efficacy of DOR but without impact on safety.

Clinical AE summary and counts tables were reviewed for subgroups based on concomitant use (for at least 7 days at any time during DOR treatment) of moderate or strong CYP3A inhibitors for subjects in the Main Combined DOR treatment group in the MSP. There were fewer subjects with concomitant use of moderate or strong CYP3A inhibitors (N=67) compared to the subjects without concomitant use of moderate or strong CYP3A inhibitors (N=788); this difference should be considered in the analysis and interpretation of data in these subgroups. Of the 67 subjects who were co-administered moderate or strong CYP3A inhibitors, 8 received co-administration after the initial 48-week period. The safety profile for these subjects while co-administered moderate or strong CYP3A inhibitors was similar to subjects without concomitant use of moderate or strong CYP3A inhibitor. 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 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 (25.4% 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) [Table 5.3.5.3.3-trtmtnve48wk: 82].

5.4 Safety Exposure-Response Analysis

As described in [Sec. 2.7.2.1.5.3], an exposure-response analysis was also conducted for the proportion of subjects with neuropsychiatric events by Week 48 following administration of 25 mg to 200 mg QD doses of DOR in the Phase 2b trial (P007) and 100 mg QD DOR/3TC/TDF in the Phase 3 trial (P021) in HIV-1 infected subjects. In this analysis, there was no association between the incidence of neuropsychiatric events and DOR steady state AUC 0-24 or Cmax ($p > 0.05$). This analysis supports the appropriateness of the 100 mg QD dose of DOR in the target population.

5.5 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 (1 [0.3%] in P007, 2 [0.3%] in P018, and 3 [0.4%] in P021) discontinued from these Phase 2b and Phase 3 trials due to pregnancy. Although not considered an adverse experience, all pregnancies occurring throughout the entire trial period were to be reported and followed for outcome whenever possible.

- In P007, 1 subject in the DOR 50 mg treatment group was discontinued from the trial due to pregnancy on Day 559 [Ref. 5.3.5.1: P007V01MK1439: 12.5]. Pregnancy outcome was a vaginal live birth with no congenital anomalies.
- In P018, 2 subjects in the DOR 100 mg treatment group discontinued from the trial due to pregnancy [Ref. 5.3.5.1: P018V01MK1439: 16.2.1]. One subject had a positive pregnancy test on Day 29, and was discontinued from the trial on the same day. The pregnancy outcome for this subject was a vaginal live birth with no congenital anomalies. The other subject was discontinued from trial medication on Day 451. The subject became pregnant with last menstrual period of Day 234; the pregnancy was confirmed by a pregnancy test on an unknown date. The pregnancy outcome was a spontaneous abortion. The causality assessment of the event was reported as not applicable.
- In P021, 3 subjects (1 in the DOR/3TC/TDF group and 2 in the EFV/FTC/TDF group) discontinued from the trial due to pregnancy [Ref. 5.3.5.1: P021V01MK1439A: 16.2.7.4]. The subject in the DOR/3TC/TDF group was discontinued from trial medication on Day 30. Pregnancy outcome was a spontaneous abortion on Day 47; the investigator considered this outcome to be not related to study drug or study procedure. One of the subjects in the EFV/FTC/TDF treatment group was discontinued from trial medication on Day 258, following a spontaneous abortion on Day 222. The investigator considered this outcome not related to study drug or study procedure. The other subject in the EFV/FTC/TDF treatment group was discontinued from trial medication on Day 428. The pregnancy outcome is pending.

The use of DOR and DOR/3TC/TDF in pregnancy and lactation is not recommended.

5.6 Overdose

If an AE was associated with ("resulted from") the overdose of DOR or DOR/3TC/TDF, the AE was reported as an SAE, even if no other seriousness criteria were met. If a dose of DOR or DOR/3TC/TDF meeting the protocol definition of overdose was taken without any associated clinical symptoms or abnormal laboratory results, the overdose was reported as a non-serious ECI, using the terminology "accidental or intentional overdose without adverse effect."

In the Phase 1 trials, overdose was defined as a subject taking (accidentally or intentionally) any drug administered as part of the protocol and exceeding the dose as prescribed by the protocol. There were no overdoses with DOR or DOR/3TC/TDF in any of the Phase 1 trials.

In the MSP, an overdose of DOR was reported by Week 48 for 3 subjects in the DOR 100 mg treatment group (0.4%), with all 3 enrolled in P007 [Table 2.7.4: 50] [Table 5.3.5.3.3-trtmtnve48wk: 85]. These 3 subjects were reported to have AE of accidental overdose while on blinded treatment that included DOR, placebo, and FTC/TDF. For 1 of these subjects, the overdose consisted of twice the protocol-specified dose of DOR (200 mg) for 2 days. For the other 2 subjects, there was no confirmed evidence of overdose for DOR (1 subject received no DOR and 1 subject received 100 mg DOR). No AEs were reported with any of the overdoses. The protocol definition of overdose is any dose higher than twice the recommended daily dose in a calendar day. Because these events do not fulfill the pre-defined protocol definition of "overdose" these events are not classified as true overdose. Each of the overdoses for DOR was accidental and none were considered to be drug-related events by the investigator.

In addition, 1 subject in Study P018 in the DOR treatment group was reported to have an overdose of DOR, which occurred beyond Week 48; the subject took three 100 mg tablets at once, no AEs were reported [Ref. 5.3.5.1: P018V01MK1439: 12.2.6.1].

Table 2.7.4: 50
Subjects With Adverse Events
(Incidence >0% in One or More Treatment Groups)
Report of ECI of Overdose without Adverse Effect
Main Safety Pool (P007 (DOR 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	3	(0.4)	0	(0.0)	8	(1.7)
with no adverse events	852	(99.6)	383	(100.0)	464	(98.3)
Injury, poisoning and procedural complications	3	(0.4)	0	(0.0)	8	(1.7)
Accidental overdose	3	(0.4)	0	(0.0)	7	(1.5)
Intentional overdose	0	(0.0)	0	(0.0)	1	(0.2)
Overdose	0	(0.0)	0	(0.0)	1	(0.2)

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: DOR 100 mg administered with FTC/TDF in P007 and P018 or ABC/3TC in P018, or fixed dose combination of DOR/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: EFV 600 mg administered with FTC/TDF in P007, or fixed dose combination of EFV/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]

5.7 Drug Abuse

No reports of abuse of DOR occurred in any subjects participating in the trials summarized in this Summary of Clinical Safety. Based upon the activity profile of this compound and lower proportion of subjects with CNS AEs versus active comparators, the abuse potential of DOR is considered low.

5.8 Withdrawal and Rebound

No specific trials have been conducted during the development program for DOR and DOR/3TC/TDF to assess the response to withdrawal and rebound. No withdrawal or rebound effects have been observed in the DOR and DOR/3TC/TDF clinical trials to date. DOR and DOR/3TC/TDF are not targeted to elicit a change in human physiology or biochemistry, but rather are anti-infective with activity against HIV-1. Therefore, the terms withdrawal and rebound are not applicable to these compounds.

5.9 Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability

Although no trials on the effects on the ability to drive and use machines have been performed, there is no information to suggest that DOR or DOR/3TC/TDF would affect the ability to drive and use machines. However, individual responses to DOR or DOR/3TC/TDF may vary.

6 POSTMARKETING DATA

DOR and DOR/3TC/TDF have not been approved for commercial use. Thus, postmarketing experience is not available.

7 CONCLUSIONS

- DOR and DOR/3TC/TDF are 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 adverse events by Week 48 in the three pre-specified categories: 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 trials (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<0.0001*])
  - Non-HDL-C: P018 (-5.30 vs 13.75 mg/dL [-19.34; *p<0.0001*]); P021 (-3.83 vs 13.26 mg/dL [-17.02; *p<0.0001*])
- 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

8 APPENDIX

Not Applicable

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The List of Abbreviations serves as the first use/definition of the terms used in this Summary of Clinical Safety. The following terms may be used interchangeably within the document:

- Participant / subject
- Study / trial
- Intervention / treatment / medication / study drug
- Adverse event / adverse experience
- MK-1439A / doravirine/lamivudine/tenofovir disoproxil fumarate (DOR/3TC/TDF)

Abbreviation/Term	Definition
3TC	Lamivudine
ABC	Abacavir
AE	Adverse event or adverse experience
AIDS	Acquired immune deficiency syndrome
ALT	Alanine transaminase
ARV	Antiretroviral
AST	aspartate transaminase
ATV	Atazanavir
CNS	central nervous system
DBL	data-base lock
DOR	Doravirine (MK-1439, PIFELTRO™)
DOR/3TC/TDF	Fixed-dose combination of doravirine, lamivudine and tenofovir disoproxil fumarate (MK-1439A, DELSTRIGO™)
DRV	Darunavir
DRV+r	Darunavir boosted with ritonavir
DSG	Delayed Switch Group
EFV	Efavirenz
EVG	Elvitegravir
FDC	Fixed-dose combination
FTC	Emtricitabine
HDL	High-density lipoprotein
HDL-C	High-density lipoprotein cholesterol

HIV-1	Human immunodeficiency virus type 1
InSTI	Integrase strand-transfer inhibitor
ISG	Immediate Switch Group
LDL	Low-density lipoprotein
LDL-C	low-density lipoprotein cholesterol
LPV	Lopinavir
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleos(t)ide reverse transcriptase inhibitors
NVP	Nevirapine
PDLC	Pre-Defined Limit of Change
PI	Protease inhibitor
QD	Once daily
RNA	Ribonucleic acid
RPV	Rilpivirine
SAE	Serious adverse event or serious adverse experience
SOC	System Organ Class
TDF	Tenofovir disoproxil fumarate

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1 EXPOSURE TO DOR/3TC/TDF

1.1 Overall Safety Evaluation Plan and Safety Study Summary

The objective of this supplemental application (Switch Application) is to update the prescribing information to include data from a single Phase 3 trial (P024) regarding 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. This Summary of Clinical Safety provides an overview of the clinical safety profile of DOR/3TC/TDF in this population. The trial supporting this supplemental application (Switch application) and contributing data to this Summary of Clinical Safety is a Phase 3 Switch trial (P024).

P024 is an ongoing, Phase 3, multicenter, multinational, randomized, open-label, active-controlled trial. P024 is being conducted to evaluate a switch to DOR/3TC/TDF in HIV-1 infected individuals who are virologically suppressed on a stable (minimum 6 months at baseline) antiretroviral regimen. The baseline antiretroviral regimen included a ritonavir- or cobicistat-boosted PI (specifically, ATV, DRV, or LPV), cobicistat-boosted EVG (an integrase strand-transfer inhibitor), or an NNRTI (specifically EFV, NVP, or RPV), each administered with 2 NRTIs.

Participants were randomized in a 2:1 ratio to either the Immediate Switch Group (ISG), who received DOR/3TC/TDF on Study Day 1, or the Delayed Switch Group (DSG), who started DOR/3TC/TDF at Study Week 24. A total of 852 participants were screened, 673 were randomized to study treatment, and 670 were treated. Of those treated, 447 were treated with DOR/3TC/TDF in the ISG and 223 continued baseline regimen in the DSG from Day 1 to Study Week 24. Of the 223 DSG participants who continued their baseline regimen, 209 (93.7%) switched to DOR/3TC/TDF at Study Week 24 [Ref. 5.3.5.1: P024MK1439A: 10.1].

The Week 48 efficacy and safety results of P024 are presented in the clinical study report [Ref. 5.3.5.1: P024MK1439A]. For this Summary of Clinical Safety, the Applicant has included tables for P024 and minimal introductory text.

Narratives of adverse events (AEs) leading to discontinuation, serious adverse events (SAEs), and deaths from other ongoing trials, including 2 Phase 3 (P018, P021) and 2 Phase 2 (P028, P030) trials, are provided in this Summary of Clinical Safety [Sec. 2.7.4.2.2-switch48wk] to provide supplemental safety information from ongoing trials. Descriptions of these trials are provided in [Table 2.7.4-switch48wk: 1]. Data from these trials are not included in the individual safety analyses of this application. Cut-off dates for these narratives for this application are in [Table 2.7.4-switch48wk: 2]. Of note, since the Week 96 (end of Base Study) data from P018 and P021 are the subject of separate supplemental applications being submitted in the same timeframe as the current switch supplemental application, the Applicant used the same data cut-off dates for the P018 and P021 data presented herein as were used for the data presented in the Week 96 applications, to ensure consistency across these supplemental applications.

Table 2.7.4-switch48wk: 1
Summary of Phase 3 Trials With Safety Included in this Application

Trial	Short Description	Trial Design	Treatments (N treated) [Duration]	Key Elements of Subject Population	Status (Data Included in Application)
Trial(s) with Safety Analyses Included in this Application					
P024	Phase 3 efficacy switch in virologically suppressed participants	Multicenter, open-label, randomized, active- controlled, immediate switch to DOR/3TC/TDF on Study Day 1 or delayed switch to DOR/3TC/TDF at Study Week 24	Immediate Switch Group: Immediate switch (at Study Day 1) from baseline regimen to DOR/3TC/TDF (n = 447) Delayed Switch Group: Participants continue their baseline regimen for 24 weeks and then switch to DOR/3TC/TDF (n = 223 randomized to this group, of which 209 subsequently received DOR/3TC/TDF). [48-week base study followed by 2 extensions].	International study in HIV-1 infected participants aged 18 or older and virologically suppressed while on a baseline regimen of a ritonavir- or cobicistat-boosted PI (specifically, ATV, DRV, or LPV), or cobicistat-boosted EVG (an InSTI), or an NNRTI (specifically EFV, NVP, or RPV), each administered with 2 NRTIs.	Ongoing (48-week data)

Trial	Short Description	Trial Design	Treatments (N treated) [Duration]	Key Elements of Subject Population	Status (Data Included in Application)
Ongoing Trial(s) with Narratives (Only) Included in this Application					
P018	Phase 3 in treatment-naïve adult participants	Multicenter, double-blind, randomized, active comparator controlled Participants randomized 1:1 to DOR or DRV+r	DOR 100 mg QD with FTC/TDF or ABC/3TC (n = 383) DRV+r (800 mg DRV+100mg r) with FTC/TDF or ABC/3TC (n = 383) [Base study for 96 weeks followed by an open label study extension]	International multicenter study in treatment naïve HIV-1 infected participants aged 18 or older.	Ongoing (Safety narratives for participants who experienced an SAE [including death] or discontinued due to AEs [drug related or not related] as of DBL for Week 96) .
DOR/3TC/TDF					
P021	Phase 3 in treatment-naïve adult participants	Multicenter, double-blind, randomized, active comparator controlled Participants randomized 1:1 to DOR/3TC/TDF or EFV/FTC/TDF	DOR/3TC/TDF (DOR 100 mg/ TDF 300 mg/ 3TC 300 mg) QD (n=364) EFV/FTC/TDF (EFV 600 mg/ FTC 200 mg/ TDF 300 mg) QD (n = 364) [96-week base study followed by an open label extension]	International study in treatment naïve HIV-1 infected participants aged 18 or older.	Ongoing (Safety narratives for participants who experienced an SAE [including death] or discontinued due to AEs [drug related or not related] as of DBL for Week 96).
P028	Phase 2b safety switch in virologically suppressed participants	Multicenter, double blind (with in-house blinding), randomized, active-controlled, Immediate switch to DOR/3TC/TDF on Study Day 1 (Immediate Switch Group) or continued treatment with EFV regimen for 12 weeks followed by switch to open label DOR/3TC/TDF (Deferred Switch Group).	Immediate Switch Group (ISG): Immediate switch (at Study Day 1) from a baseline EFV regimen to DOR/3TC/TDF for 12 weeks followed by treatment with open-label DOR/3TC/TDF for an additional 12 weeks (planned n=84) Deferred Switch Group (DSG): Participants receive EFV regimen for 12 weeks followed by treatment with open-label DOR/3TC/TDF 24 weeks. (planned n=84) [Base trial (24 weeks ISG and 36 weeks DSG) followed by 96–week extension.]	International (not in United States) multicenter study in HIV-1 infected participants aged 18 or older and virologically suppressed while on an EFV regimen and who have CNS intolerance.	Ongoing and enrolling (Safety narratives for participants who experienced an SAE [including death] or discontinued due to AEs [drug related or not related])

Trial	Short Description	Trial Design	Treatments (N treated) [Duration]	Key Elements of Subject Population	Status (Data Included in Application)
P030	Phase 2a in treatment-naïve participants with transmitted resistance to NNRTI	Multicenter, single-arm, open-label Long-term efficacy and safety data of DOR/3TC/TDF.	DOR/3TC/TDF QD (n =10) [96-week base trial and trial extension]	International multicenter study in treatment-naïve HIV-1 infected participants aged 18 or older and with transmitted resistance to NNRTI.	Ongoing (Safety narratives for participants who experienced an SAE [including death] or discontinued due to AEs [drug related or not related])

Abbreviations: 3TC = lamivudine AE = adverse event; ATV= atazanavir, CNS = central nervous system; DBL = database lock; DOR = doravirine; DRV = darunavir; DRV+r = darunavir boosted with ritonavir; EFV = efavirenz; EVG = elvitegravir; FTC = emtricitabine; HIV-1 = Human Immunodeficiency Virus type 1; InSTI = integrase strand-transfer inhibitor; LPV = lopinavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleos(t)ide reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; QD = once daily; RPV rilpivirine; SAE = serious adverse event; TDF = tenofovir disoproxil fumarate.

Table 2.7.4-switch48wk: 2
Last Patient Last Visit/ Data Cut-off Date
for Phase 2 and Phase 3 Trials Included in this Application

Trial	**Last Patient Last Visit Date/ Data Cutoff Date**
Trial(s) with Safety Analyses Included in this Application	
P024 Week 48 analysis	22-FEB-2018
Ongoing Trial(s) with Narratives (Only) Included in this Application	
P018	[redacted]-20[redacted]
P021	[redacted]-20[redacted]
P028	[redacted]-20[redacted]
P030	[redacted]-20[redacted]

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1.2 Overall Extent of Exposure

Table 2.7.4-switch48wk: 3

Extent of Exposure to DOR/3TC/TDF by Dose
ISG

DOR/3TC/TDF	≤ 4 wks	> 4 wks to 8 wks	> 8 wks to 16 wks	> 16 wks to 24 wks	> 24 wks to 36 wks	> 36 wks to 48 wks	> 48 wks	Total Subjects	Duration Range	Mean Duration
Any Dose	6	5	11	7	16	49	353	447	1 to 905 days	520.0 days
Doravirine 100 mg/lamivudine 300 mg/TDF 300 mg	6	5	11	7	16	49	353	447	1 to 905 days	519.8 days
Doravirine 200 mg/lamivudine 600 mg/TDF 600 mg	33	0	0	0	0	0	0	33	1 to 27 days	2.6 days

Each subject who received DOR/3TC/TDF is counted once on the "Any Dose" row in the column that reflects the total duration of exposure to DOR/3TC/TDF.
Each subject is counted again on one or more specific dose category rows that correspond to the actual dose(s) received. On each applicable specific dose row, the subject is counted once in the column that reflects the duration of exposure to that specific dose.

Source: [P024MK1439A: adam-adexsum]

Table 2.7.4-switch48wk: 4

Extent of Exposure to DOR/3TC/TDF by Dose
DSG

DOR/3TC/TDF	≤ 4 wks	> 4 wks to 8 wks	> 8 wks to 16 wks	> 16 wks to 24 wks	> 24 wks	Total Subjects	Duration Range	Mean Duration
Any Dose	3	4	5	22	175	209	1 to 734 days	379.2 days
Doravirine 100 mg/lamivudine 300 mg/TDF 300 mg	3	4	5	23	174	209	1 to 734 days	379.2 days
Doravirine 200 mg/lamivudine 600 mg/TDF 600 mg	9	0	0	0	0	9	1 to 3 days	1.4 days

Each subject who received DOR/3TC/TDF is counted once on the "Any Dose" row in the column that reflects the total duration of exposure to DOR/3TC/TDF.

Each subject is counted again on one or more specific dose category rows that correspond to the actual dose(s) received. On each applicable specific dose row, the subject is counted once in the column that reflects the duration of exposure to that specific dose.

Source: [P024MK1439A: adam-adexsum]

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Table 2.7.4-switch48wk: 5

Extent of Exposure to DOR/3TC/TDF by Dose
ISG and DSG combined

DOR/3TC/TDF	≤ 4 wks	> 4 wks to 8 wks	> 8 wks to 16 wks	> 16 wks to 24 wks	> 24 wks to 36 wks	> 36 wks to 48 wks	> 48 wks	Total Subjects	Duration Range	Mean Duration
Any Dose	9	9	16	29	33	101	459	656	1 to 905 days	475.2 days
Doravirine 100 mg/lamivudine 300 mg/TDF 300 mg	9	9	16	30	32	101	459	656	1 to 905 days	475.0 days
Doravirine 200 mg/lamivudine 600 mg/TDF 600 mg	42	0	0	0	0	0	0	42	1 to 27 days	2.4 days

Each subject who received DOR/3TC/TDF is counted once on the "Any Dose" row in the column that reflects the total duration of exposure to DOR/3TC/TDF.

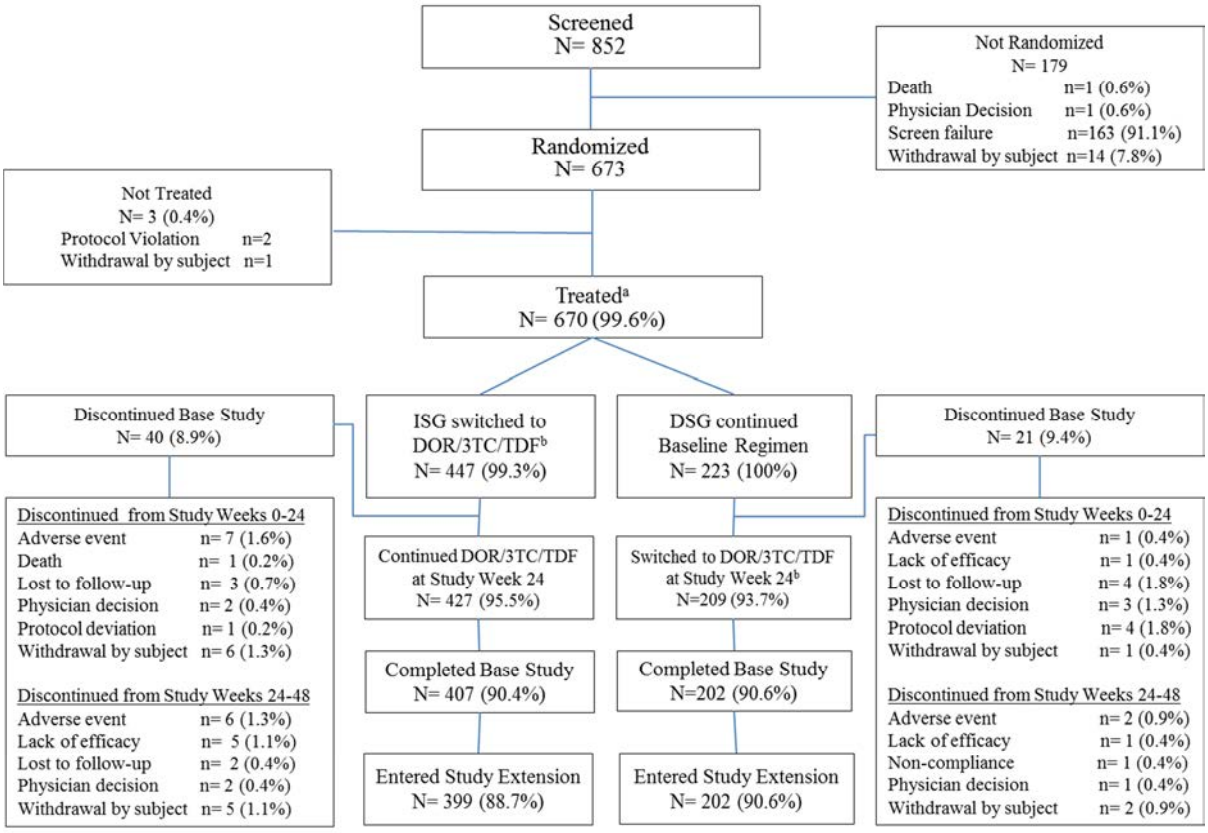
Each subject is counted again on one or more specific dose category rows that correspond to the actual dose(s) received. On each applicable specific dose row, the subject is counted once in the column that reflects the duration of exposure to that specific dose.

Source: [P024MK1439A: adam-adexsum]

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Subject Disposition

Figure 2.7.4-switch48wk: 1
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: Figure 10-1].

1.3 Demographic and Other Characteristics of Study Population

1.3.1 Baseline Demographics and Disease Characteristics

Table 2.7.4-switch48wk: 6

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)

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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]

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2 ADVERSE EVENTS

2.1 Analysis of Adverse Events

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Table 2.7.4-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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Table 2.7.4-switch48wk: 8

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 2.7.4-switch48wk: 9

Subjects With Adverse Events
(Incidence ≥ 5% in One or More Treatment Groups)
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 events	139	(31.1)	106	(47.5)	83	(39.7)	88	(19.7)	171	(26.1)
Gastrointestinal disorders	**98**	**(21.9)**	**18**	**(8.1)**	**37**	**(17.7)**	**130**	**(29.1)**	**167**	**(25.5)**
Diarrhoea	20	(4.5)	5	(2.2)	9	(4.3)	31	(6.9)	40	(6.1)
General disorders and administration site conditions	**34**	**(7.6)**	**12**	**(5.4)**	**9**	**(4.3)**	**51**	**(11.4)**	**60**	**(9.1)**
Infections and infestations	**113**	**(25.3)**	**56**	**(25.1)**	**53**	**(25.4)**	**185**	**(41.4)**	**238**	**(36.3)**
Nasopharyngitis	33	(7.4)	12	(5.4)	9	(4.3)	45	(10.1)	54	(8.2)
Injury, poisoning and procedural complications	**23**	**(5.1)**	**11**	**(4.9)**	**9**	**(4.3)**	**34**	**(7.6)**	**43**	**(6.6)**
Investigations	**29**	**(6.5)**	**11**	**(4.9)**	**15**	**(7.2)**	**52**	**(11.6)**	**67**	**(10.2)**
Metabolism and nutrition disorders	**12**	**(2.7)**	**4**	**(1.8)**	**4**	**(1.9)**	**24**	**(5.4)**	**28**	**(4.3)**
Musculoskeletal and connective tissue disorders	**43**	**(9.6)**	**20**	**(9.0)**	**12**	**(5.7)**	**78**	**(17.4)**	**90**	**(13.7)**
Back pain	9	(2.0)	4	(1.8)	1	(0.5)	23	(5.1)	24	(3.7)
Nervous system disorders	**69**	**(15.4)**	**8**	**(3.6)**	**21**	**(10.0)**	**92**	**(20.6)**	**113**	**(17.2)**

Subjects With Adverse Events
(Incidence ≥ 5% in One or More Treatment Groups)
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	(%)
Nervous system disorders	**69**	**(15.4)**	**8**	**(3.6)**	**21**	**(10.0)**	**92**	**(20.6)**	**113**	**(17.2)**
Headache	29	(6.5)	5	(2.2)	14	(6.7)	39	(8.7)	53	(8.1)
Psychiatric disorders	**45**	**(10.1)**	**10**	**(4.5)**	**15**	**(7.2)**	**59**	**(13.2)**	**74**	**(11.3)**
Respiratory, thoracic and mediastinal disorders	**19**	**(4.3)**	**8**	**(3.6)**	**7**	**(3.3)**	**39**	**(8.7)**	**46**	**(7.0)**
Skin and subcutaneous tissue disorders	**34**	**(7.6)**	**9**	**(4.0)**	**14**	**(6.7)**	**54**	**(12.1)**	**68**	**(10.4)**

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.

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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2.1.1 Drug-Related Adverse Events

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Table 2.7.4-switch48wk: 10

Subjects With Drug-Related Adverse Events
(Incidence ≥ 2% in One or More Treatment Groups)
Overall Drug Related
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 drug-related adverse events	87	(19.5)	5	(2.2)	29	(13.9)	100	(22.4)	129	(19.7)
with no drug-related adverse events	360	(80.5)	218	(97.8)	180	(86.1)	347	(77.6)	527	(80.3)
Gastrointestinal disorders	**36**	**(8.1)**	**1**	**(0.4)**	**9**	**(4.3)**	**39**	**(8.7)**	**48**	**(7.3)**
General disorders and administration site conditions	**9**	**(2.0)**	**0**	**(0.0)**	**2**	**(1.0)**	**10**	**(2.2)**	**12**	**(1.8)**
Investigations	**8**	**(1.8)**	**0**	**(0.0)**	**7**	**(3.3)**	**17**	**(3.8)**	**24**	**(3.7)**
Alanine aminotransferase increased	5	(1.1)	0	(0.0)	4	(1.9)	10	(2.2)	14	(2.1)
Nervous system disorders	**24**	**(5.4)**	**1**	**(0.4)**	**7**	**(3.3)**	**26**	**(5.8)**	**33**	**(5.0)**
Headache	7	(1.6)	1	(0.4)	5	(2.4)	7	(1.6)	12	(1.8)

Subjects With Drug-Related Adverse Events
(Incidence ≥ 2% in One or More Treatment Groups)
Overall Drug Related
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	(%)
Psychiatric disorders	**16**	**(3.6)**	**1**	**(0.4)**	**5**	**(2.4)**	**17**	**(3.8)**	**22**	**(3.4)**

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.

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]

2.1.2 Deaths

No randomized participants died during the study period in P024. 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 drug. [Ref. 5.3.5.1: P024MK1439A: 12.2.1.1]

Two additional participants, both in the ISG, died in a post-study period (>14 days after last recorded dose of study medication as reported by the participant at the time of the last visit). Given the amount of study medication dispensed at the last visit, these SAEs may have occurred while the subjects were continuing to take study medication.

Complete narratives for these 3 participants are provided in [Ref. 5.3.5.1: P024MK1439A: 16.2.7.2].

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2.1.3 Other Serious Adverse Events

Table 2.7.4-switch48wk: 11

Subjects With Serious Adverse Events
(Incidence > 0% in One or More Treatment Groups)
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 serious adverse events	13	(2.9)	8	(3.6)	4	(1.9)	22	(4.9)	26	(4.0)
with no serious adverse events	434	(97.1)	215	(96.4)	205	(98.1)	425	(95.1)	630	(96.0)
Cardiac disorders	**2**	**(0.4)**	**0**	**(0.0)**	**0**	**(0.0)**	**2**	**(0.4)**	**2**	**(0.3)**
Angina pectoris	1	(0.2)	0	(0.0)	0	(0.0)	1	(0.2)	1	(0.2)
Atrial fibrillation	1	(0.2)	0	(0.0)	0	(0.0)	1	(0.2)	1	(0.2)
Gastrointestinal disorders	**1**	**(0.2)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.2)**	**1**	**(0.2)**
Gastrooesophageal reflux disease	1	(0.2)	0	(0.0)	0	(0.0)	1	(0.2)	1	(0.2)
Infections and infestations	**1**	**(0.2)**	**4**	**(1.8)**	**1**	**(0.5)**	**4**	**(0.9)**	**5**	**(0.8)**
Appendicitis	0	(0.0)	0	(0.0)	1	(0.5)	1	(0.2)	2	(0.3)
Endocarditis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.2)	1	(0.2)
Pneumonia	1	(0.2)	3	(1.3)	0	(0.0)	1	(0.2)	1	(0.2)
Respiratory syncytial virus infection	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.2)	1	(0.2)
Shigella infection	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.2)	1	(0.2)
Tuberculous pleurisy	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Injury, poisoning and procedural complications	**1**	**(0.2)**	**0**	**(0.0)**	**1**	**(0.5)**	**1**	**(0.2)**	**2**	**(0.3)**
Foot fracture	1	(0.2)	0	(0.0)	0	(0.0)	1	(0.2)	1	(0.2)
Hand fracture	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	1	(0.2)

Subjects With Serious Adverse Events
(Incidence > 0% in One or More Treatment Groups)
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	(%)
Investigations	**3**	**(0.7)**	**0**	**(0.0)**	**0**	**(0.0)**	**7**	**(1.6)**	**7**	**(1.1)**
Alanine aminotransferase increased	1	(0.2)	0	(0.0)	0	(0.0)	2	(0.4)	2	(0.3)
Amylase increased	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.2)	1	(0.2)
Aspartate aminotransferase increased	1	(0.2)	0	(0.0)	0	(0.0)	2	(0.4)	2	(0.3)
Blood creatine phosphokinase increased	1	(0.2)	0	(0.0)	0	(0.0)	2	(0.4)	2	(0.3)
CD4 lymphocytes decreased	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.2)	1	(0.2)
Lipase increased	1	(0.2)	0	(0.0)	0	(0.0)	2	(0.4)	2	(0.3)
Musculoskeletal and connective tissue disorders	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.2)**	**1**	**(0.2)**
Intervertebral disc protrusion	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.2)	1	(0.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**0**	**(0.0)**	**1**	**(0.4)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**
Squamous cell carcinoma	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Nervous system disorders	**1**	**(0.2)**	**0**	**(0.0)**	**0**	**(0.0)**	**2**	**(0.4)**	**2**	**(0.3)**
Amyotrophic lateral sclerosis	1	(0.2)	0	(0.0)	0	(0.0)	1	(0.2)	1	(0.2)
Headache	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.2)	1	(0.2)
Lacunar infarction	1	(0.2)	0	(0.0)	0	(0.0)	1	(0.2)	1	(0.2)
Psychiatric disorders	**2**	**(0.4)**	**1**	**(0.4)**	**0**	**(0.0)**	**2**	**(0.4)**	**2**	**(0.3)**
Depression	1	(0.2)	1	(0.4)	0	(0.0)	1	(0.2)	1	(0.2)
Suicidal ideation	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)

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Subjects With Serious Adverse Events
(Incidence > 0% in One or More Treatment Groups)
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	(%)
Psychiatric disorders	**2**	**(0.4)**	**1**	**(0.4)**	**0**	**(0.0)**	**2**	**(0.4)**	**2**	**(0.3)**
Suicide attempt	1	(0.2)	0	(0.0)	0	(0.0)	1	(0.2)	1	(0.2)
Renal and urinary disorders	**0**	**(0.0)**	**2**	**(0.9)**	**1**	**(0.5)**	**1**	**(0.2)**	**2**	**(0.3)**
Nephrolithiasis	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Renal cyst	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Renal failure	0	(0.0)	0	(0.0)	1	(0.5)	1	(0.2)	2	(0.3)
Respiratory, thoracic and mediastinal disorders	**1**	**(0.2)**	**1**	**(0.4)**	**1**	**(0.5)**	**1**	**(0.2)**	**2**	**(0.3)**
Asthma	1	(0.2)	0	(0.0)	0	(0.0)	1	(0.2)	1	(0.2)
Chronic obstructive pulmonary disease	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Cough	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Sleep apnoea syndrome	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	1	(0.2)
Skin and subcutaneous tissue disorders	**1**	**(0.2)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.2)**	**1**	**(0.2)**

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Subjects With Serious Adverse Events
(Incidence > 0% in One or More Treatment Groups)
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	(%)
Skin and subcutaneous tissue disorders	**1**	**(0.2)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.2)**	**1**	**(0.2)**
Rash maculo-papular	1	(0.2)	0	(0.0)	0	(0.0)	1	(0.2)	1	(0.2)

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.

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 2.7.4-switch48wk: 12

Subjects With Serious Drug-Related Adverse Events
(Incidence > 0% in One or More Treatment Groups)
Overall Drug Related
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 serious drug-related adverse events	2	(0.4)	0	(0.0)	1	(0.5)	4	(0.9)	5	(0.8)
with no serious drug-related adverse events	445	(99.6)	223	(100.0)	208	(99.5)	443	(99.1)	651	(99.2)
Investigations	**1**	**(0.2)**	**0**	**(0.0)**	**0**	**(0.0)**	**3**	**(0.7)**	**3**	**(0.5)**
Alanine aminotransferase increased	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.2)	1	(0.2)
Amylase increased	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.2)	1	(0.2)
Aspartate aminotransferase increased	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.2)	1	(0.2)
Lipase increased	1	(0.2)	0	(0.0)	0	(0.0)	2	(0.4)	2	(0.3)
Psychiatric disorders	**1**	**(0.2)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.2)**	**1**	**(0.2)**
Depression	1	(0.2)	0	(0.0)	0	(0.0)	1	(0.2)	1	(0.2)
Renal and urinary disorders	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.5)**	**0**	**(0.0)**	**1**	**(0.2)**

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Subjects With Serious Drug-Related Adverse Events
(Incidence > 0% in One or More Treatment Groups)
Overall Drug Related
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	(%)
Renal and urinary disorders	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.5)**	**0**	**(0.0)**	**1**	**(0.2)**
Renal failure	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	1	(0.2)

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.

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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2.1.4 Other Significant Adverse Events

Table 2.7.4-switch48wk: 13

Subjects With Adverse Events Resulting in Discontinuation
(Incidence > 0% in One or More Treatment Groups)
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 resulting in discontinuation	11	(2.5)	1	(0.4)	4	(1.9)	15	(3.4)	19	(2.9)
with no adverse events resulting in discontinuation	436	(97.5)	222	(99.6)	205	(98.1)	432	(96.6)	637	(97.1)
Gastrointestinal disorders	**1**	**(0.2)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.2)**	**1**	**(0.2)**
Ascites	1	(0.2)	0	(0.0)	0	(0.0)	1	(0.2)	1	(0.2)
General disorders and administration site conditions	**2**	**(0.4)**	**0**	**(0.0)**	**0**	**(0.0)**	**2**	**(0.4)**	**2**	**(0.3)**
Fatigue	1	(0.2)	0	(0.0)	0	(0.0)	1	(0.2)	1	(0.2)
Generalised oedema	1	(0.2)	0	(0.0)	0	(0.0)	1	(0.2)	1	(0.2)
Hepatobiliary disorders	**1**	**(0.2)**	**0**	**(0.0)**	**1**	**(0.5)**	**1**	**(0.2)**	**2**	**(0.3)**
Hepatitis	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	1	(0.2)
Hepatitis alcoholic	1	(0.2)	0	(0.0)	0	(0.0)	1	(0.2)	1	(0.2)
Infections and infestations	**0**	**(0.0)**	**1**	**(0.4)**	**0**	**(0.0)**	**1**	**(0.2)**	**1**	**(0.2)**
Endocarditis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.2)	1	(0.2)
Tuberculous pleurisy	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Investigations	**3**	**(0.7)**	**0**	**(0.0)**	**1**	**(0.5)**	**6**	**(1.3)**	**7**	**(1.1)**
Alanine aminotransferase increased	2	(0.4)	0	(0.0)	1	(0.5)	2	(0.4)	3	(0.5)

Subjects With Adverse Events Resulting in Discontinuation
(Incidence > 0% in One or More Treatment Groups)
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	(%)
Investigations	**3**	**(0.7)**	**0**	**(0.0)**	**1**	**(0.5)**	**6**	**(1.3)**	**7**	**(1.1)**
Amylase increased	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.4)	2	(0.3)
Aspartate aminotransferase increased	1	(0.2)	0	(0.0)	1	(0.5)	2	(0.4)	3	(0.5)
Lipase increased	1	(0.2)	0	(0.0)	0	(0.0)	3	(0.7)	3	(0.5)
Metabolism and nutrition disorders	**1**	**(0.2)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.2)**	**1**	**(0.2)**
Decreased appetite	1	(0.2)	0	(0.0)	0	(0.0)	1	(0.2)	1	(0.2)
Musculoskeletal and connective tissue disorders	**1**	**(0.2)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.2)**	**1**	**(0.2)**
Myalgia	1	(0.2)	0	(0.0)	0	(0.0)	1	(0.2)	1	(0.2)
Nervous system disorders	**1**	**(0.2)**	**0**	**(0.0)**	**1**	**(0.5)**	**1**	**(0.2)**	**2**	**(0.3)**
Memory impairment	1	(0.2)	0	(0.0)	1	(0.5)	1	(0.2)	2	(0.3)
Psychiatric disorders	**2**	**(0.4)**	**0**	**(0.0)**	**0**	**(0.0)**	**2**	**(0.4)**	**2**	**(0.3)**
Depression	1	(0.2)	0	(0.0)	0	(0.0)	1	(0.2)	1	(0.2)
Sleep disorder	1	(0.2)	0	(0.0)	0	(0.0)	1	(0.2)	1	(0.2)
Renal and urinary disorders	**1**	**(0.2)**	**0**	**(0.0)**	**1**	**(0.5)**	**2**	**(0.4)**	**3**	**(0.5)**
Renal failure	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	1	(0.2)
Renal impairment	1	(0.2)	0	(0.0)	0	(0.0)	1	(0.2)	1	(0.2)
Renal pain	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.2)	1	(0.2)

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Subjects With Adverse Events Resulting in Discontinuation
(Incidence > 0% in One or More Treatment Groups)
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	(%)
Skin and subcutaneous tissue disorders	**2**	**(0.4)**	**0**	**(0.0)**	**0**	**(0.0)**	**2**	**(0.4)**	**2**	**(0.3)**
Rash macular	1	(0.2)	0	(0.0)	0	(0.0)	1	(0.2)	1	(0.2)
Rash maculo-papular	1	(0.2)	0	(0.0)	0	(0.0)	1	(0.2)	1	(0.2)

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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 2.7.4-switch48wk: 14

Adverse Event Summary by Region
Study Weeks 0-24; Base Study

	Asia/Pacific				Europe			
	DOR/3TC/TDF QD ISG		Baseline Regimen DSG		DOR/3TC/TDF QD ISG		Baseline Regimen DSG	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	19		12		268		137	
with one or more adverse events	14	(73.7)	6	(50.0)	189	(70.5)	76	(55.5)
with no adverse event	5	(26.3)	6	(50.0)	79	(29.5)	61	(44.5)
with drug-related[†] adverse events	4	(21.1)	0	(0.0)	60	(22.4)	3	(2.2)
with serious adverse events	1	(5.3)	1	(8.3)	7	(2.6)	4	(2.9)
with serious drug-related adverse events	0	(0.0)	0	(0.0)	2	(0.7)	0	(0.0)
who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to an adverse event	0	(0.0)	0	(0.0)	7	(2.6)	0	(0.0)
discontinued drug due to a drug-related adverse event	0	(0.0)	0	(0.0)	6	(2.2)	0	(0.0)
discontinued drug due to a serious adverse event	0	(0.0)	0	(0.0)	2	(0.7)	0	(0.0)
discontinued drug due to a serious drug-related adverse event	0	(0.0)	0	(0.0)	2	(0.7)	0	(0.0)

Adverse Event Summary by Region
Study Weeks 0-24; Base Study

	Latin America				North America			
	DOR/3TC/TDF QD ISG		Baseline Regimen DSG		DOR/3TC/TDF QD ISG		Baseline Regimen DSG	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	49		24		111		50	
with one or more adverse events	28	(57.1)	11	(45.8)	77	(69.4)	24	(48.0)
with no adverse event	21	(42.9)	13	(54.2)	34	(30.6)	26	(52.0)
with drug-related[†] adverse events	7	(14.3)	1	(4.2)	16	(14.4)	1	(2.0)
with serious adverse events	1	(2.0)	1	(4.2)	4	(3.6)	2	(4.0)
with serious drug-related adverse events	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to an adverse event	1	(2.0)	1	(4.2)	3	(2.7)	0	(0.0)
discontinued drug due to a drug-related adverse event	1	(2.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to a serious adverse event	0	(0.0)	1	(4.2)	2	(1.8)	0	(0.0)
discontinued drug due to a serious drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

[†] 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 2.7.4-switch48wk: 15

Adverse Event Summary by Age
Study Weeks 0-24; Base Study

	18 to 64				≥65			
	DOR/3TC/TDF QD ISG		Baseline Regimen DSG		DOR/3TC/TDF QD ISG		Baseline Regimen DSG	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	438		214		9		9	
with one or more adverse events	303	(69.2)	112	(52.3)	5	(55.6)	5	(55.6)
with no adverse event	135	(30.8)	102	(47.7)	4	(44.4)	4	(44.4)
with drug-related[†] adverse events	87	(19.9)	5	(2.3)	0	(0.0)	0	(0.0)
with serious adverse events	13	(3.0)	8	(3.7)	0	(0.0)	0	(0.0)
with serious drug-related adverse events	2	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)
who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to an adverse event	11	(2.5)	1	(0.5)	0	(0.0)	0	(0.0)
discontinued drug due to a drug-related adverse event	7	(1.6)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to a serious adverse event	4	(0.9)	1	(0.5)	0	(0.0)	0	(0.0)
discontinued drug due to a serious drug-related adverse event	2	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)

[†] 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 2.7.4-switch48wk: 16

Adverse Event Summary by Gender
Study Weeks 0-24; Base Study

	M				F			
	DOR/3TC/TDF QD ISG		Baseline Regimen DSG		DOR/3TC/TDF QD ISG		Baseline Regimen DSG	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	372		194		75		29	
with one or more adverse events	253	(68.0)	99	(51.0)	55	(73.3)	18	(62.1)
with no adverse event	119	(32.0)	95	(49.0)	20	(26.7)	11	(37.9)
with drug-related[†] adverse events	70	(18.8)	4	(2.1)	17	(22.7)	1	(3.4)
with serious adverse events	8	(2.2)	7	(3.6)	5	(6.7)	1	(3.4)
with serious drug-related adverse events	2	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)
who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to an adverse event	8	(2.2)	1	(0.5)	3	(4.0)	0	(0.0)
discontinued drug due to a drug-related adverse event	5	(1.3)	0	(0.0)	2	(2.7)	0	(0.0)
discontinued drug due to a serious adverse event	3	(0.8)	1	(0.5)	1	(1.3)	0	(0.0)
discontinued drug due to a serious drug-related adverse event	2	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)

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

M = Male; F = Female

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 2.7.4-switch48wk: 17

Adverse Event Summary by Race
Study Weeks 0-24; Base Study

	American Indian or Alaska Native				Asian				Black or African American			
	DOR/3TC/TDF QD ISG		Baseline Regimen DSG		DOR/3TC/TDF QD ISG		Baseline Regimen DSG		DOR/3TC/TDF QD ISG		Baseline Regimen DSG	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	5		2		17		8		56		34	
with one or more adverse events	3	(60.0)	2	(100.0)	11	(64.7)	2	(25.0)	38	(67.9)	18	(52.9)
with no adverse event	2	(40.0)	0	(0.0)	6	(35.3)	6	(75.0)	18	(32.1)	16	(47.1)
with drug-related[†] adverse events	1	(20.0)	0	(0.0)	6	(35.3)	0	(0.0)	7	(12.5)	1	(2.9)
with serious adverse events	0	(0.0)	0	(0.0)	1	(5.9)	1	(12.5)	1	(1.8)	2	(5.9)
with serious drug-related adverse events	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to an adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to a serious adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to a serious drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

Adverse Event Summary by Race
Study Weeks 0-24; Base Study

	Multiple				Native Hawaiian or Other Pacific Islander				White			
	DOR/3TC/TDF QD ISG		Baseline Regimen DSG		DOR/3TC/TDF QD ISG		Baseline Regimen DSG		DOR/3TC/TDF QD ISG		Baseline Regimen DSG	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	24		11		1		0		344		168	
with one or more adverse events	17	(70.8)	7	(63.6)	1	(100.0)	0	(0.0)	238	(69.2)	88	(52.4)
with no adverse event	7	(29.2)	4	(36.4)	0	(0.0)	0	(0.0)	106	(30.8)	80	(47.6)
with drug-related[†] adverse events	6	(25.0)	1	(9.1)	0	(0.0)	0	(0.0)	67	(19.5)	3	(1.8)
with serious adverse events	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	11	(3.2)	5	(3.0)
with serious drug-related adverse events	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.6)	0	(0.0)
who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to an adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	11	(3.2)	1	(0.6)
discontinued drug due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	7	(2.0)	0	(0.0)
discontinued drug due to a serious adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	4	(1.2)	1	(0.6)
discontinued drug due to a serious drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.6)	0	(0.0)

[†] 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 2.7.4-switch48wk: 18

Adverse Event Summary by Ethnicity
Study Weeks 0-24; Base Study

	Hispanic or Latino				Not Hispanic or Latino				Unknown			
	DOR/3TC/TDF QD ISG		Baseline Regimen DSG		DOR/3TC/TDF QD ISG		Baseline Regimen DSG		DOR/3TC/TDF QD ISG		Baseline Regimen DSG	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	99		45		341		175		7		3	
with one or more adverse events	66	(66.7)	20	(44.4)	239	(70.1)	96	(54.9)	3	(42.9)	1	(33.3)
with no adverse event	33	(33.3)	25	(55.6)	102	(29.9)	79	(45.1)	4	(57.1)	2	(66.7)
with drug-related[†] adverse events	19	(19.2)	1	(2.2)	67	(19.6)	4	(2.3)	1	(14.3)	0	(0.0)
with serious adverse events	3	(3.0)	2	(4.4)	10	(2.9)	5	(2.9)	0	(0.0)	1	(33.3)
with serious drug-related adverse events	0	(0.0)	0	(0.0)	2	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to an adverse event	4	(4.0)	1	(2.2)	7	(2.1)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to a drug-related adverse event	1	(1.0)	0	(0.0)	6	(1.8)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to a serious adverse event	2	(2.0)	1	(2.2)	2	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to a serious drug-related adverse event	0	(0.0)	0	(0.0)	2	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)

[†] 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]

Table 2.7.4-switch48wk: 19

Adverse Event Summary by Hepatitis B/C Status
Study Weeks 0-24; Base Study

	Hepatitis B and C Negative				Hepatitis B and/or C Positive			
	DOR/3TC/TDF QD ISG		Baseline Regimen DSG		DOR/3TC/TDF QD ISG		Baseline Regimen DSG	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	433		214		14		9	
with one or more adverse events	299	(69.1)	112	(52.3)	9	(64.3)	5	(55.6)
with no adverse event	134	(30.9)	102	(47.7)	5	(35.7)	4	(44.4)
with drug-related[†] adverse events	82	(18.9)	4	(1.9)	5	(35.7)	1	(11.1)
with serious adverse events	10	(2.3)	8	(3.7)	3	(21.4)	0	(0.0)
with serious drug-related adverse events	2	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)
who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to an adverse event	11	(2.5)	1	(0.5)	0	(0.0)	0	(0.0)
discontinued drug due to a drug-related adverse event	7	(1.6)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to a serious adverse event	4	(0.9)	1	(0.5)	0	(0.0)	0	(0.0)
discontinued drug due to a serious drug-related adverse event	2	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)

[†] 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]

Table 2.7.4-switch48wk: 20

Adverse Event Summary by Baseline CD4 Level
Study Weeks 0-24; Base Study

	<200 cells/mm3				≥200 cells/mm3			
	DOR/3TC/TDF QD ISG		Baseline Regimen DSG		DOR/3TC/TDF QD ISG		Baseline Regimen DSG	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	13		4		426		216	
with one or more adverse events	8	(61.5)	2	(50.0)	294	(69.0)	114	(52.8)
with no adverse event	5	(38.5)	2	(50.0)	132	(31.0)	102	(47.2)
with drug-related[†] adverse events	1	(7.7)	0	(0.0)	83	(19.5)	5	(2.3)
with serious adverse events	1	(7.7)	0	(0.0)	11	(2.6)	8	(3.7)
with serious drug-related adverse events	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)
who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to an adverse event	0	(0.0)	0	(0.0)	10	(2.3)	1	(0.5)
discontinued drug due to a drug-related adverse event	0	(0.0)	0	(0.0)	6	(1.4)	0	(0.0)
discontinued drug due to a serious adverse event	0	(0.0)	0	(0.0)	3	(0.7)	1	(0.5)
discontinued drug due to a serious drug-related adverse event	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)

[†] 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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2.2 Narratives

Narratives for participants with AEs resulting in death, SAEs, and AEs leading to discontinuation of study medication for all participants in P024 can be found in [Ref. 5.3.5.1: P024MK1439A].

Narratives for other ongoing trials (P018, P021, P028, and P030) are provided to provide supplemental safety information from ongoing trials. These narratives are for participants with AEs resulting in death, SAEs, and AEs leading to discontinuation of study medication as of the cut-off dates for the results reported in this Summary of Clinical Safety. A description of the study design of these clinical trials is provided in [Table 2.7.4-switch48wk: 1]. The reported data here are preliminary [Ref. 5.3.5.1: 050NDY], [Ref. 5.3.5.1: 050NF6], [Ref. 5.3.5.1: 050NFM], [Ref. 5.3.5.2: 05ONFP].

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3 CLINICAL LABORATORY EVALUATIONS

3.1 Change from Baseline in Fasting Lipids

Table 2.7.4-switch48wk: 21

Subject Baseline Antiretroviral Therapy and Baseline Lipid Lowering Therapy by Treatment Group

	ISG (N=447)	DSG (N=223)	Total (N=670)
Lipid Lowering Therapy[*] n (%)			
Yes	42 (9.4)	27 (12.1)	69 (10.3)
No	405 (90.6)	196 (87.9)	601 (89.7)
ART Class in Baseline Regimen[†] n (%)			
Ritonavir-boosted PI	311 (69.6)	155 (69.5)	466 (69.6)
Lipid-lowering Therapy at Study Day 1	26 (5.8)	13 (5.8)	39 (5.8)
Cobicistat-boosted PI	5 (1.1)	1 (0.4)	6 (0.9)
Lipid-lowering Therapy at Study Day 1	0 (0.0)	0 (0.0)	0 (0.0)
Cobicistat-boosted elvitegravir	25 (5.6)	12 (5.4)	37 (5.5)
Lipid-lowering Therapy at Study Day 1	4 (0.9)	1 (0.4)	5 (0.7)
NNRTI	106 (23.7)	55 (24.7)	161 (24.0)
Lipid-lowering Therapy at Study Day 1	12 (2.7)	13 (5.8)	25 (3.7)

[*]Based on the lipid lowering therapy received at screening.
[†]Based on the baseline regimen received, 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; adbase]

Table 2.7.4-switch48wk: 22

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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Table 2.7.4-switch48wk: 23

Change From Baseline in Fasting Lipids at Study Week 24
Subjects in Ritonavir-boosted PI Strata; Base Study
Excluding Subjects on Lipid-Lowering Therapy at Baseline

Treatment	N	Baseline Mean	Change from Baseline		Difference Estimates (ISG - DSG)	
			Mean Change (SD)	95% CI[†]	Difference[‡] 95% CI	2-sided p-Value
Fasting LDL Cholesterol (mg/dL)						
ISG	237	108.7	-16.3 (23.2)	(-19.3, -13.3)	-14.5 (-18.9, -10.1)	<0.0001
DSG	117	110.5	-2.6 (25.3)	(-7.2, 2.1)		
Fasting Non-HDL Cholesterol (mg/dL)						
ISG	244	138.6	-24.8 (29.6)	(-28.5, -21.0)	-22.8 (-27.9, -17.7)	<0.0001
DSG	124	138.8	-2.1 (28.3)	(-7.1, 2.9)		
Fasting Cholesterol (mg/dL)						
ISG	244	188.5	-26.1 (30.7)	(-29.9, -22.2)	-25.3 (-30.6, -20.1)	nps*
DSG	124	187.4	-0.2 (28.5)	(-5.3, 4.8)		
Fasting Triglyceride (mg/dL)						
ISG	244	153.1	-44.4 (94.2)	(-56.3, -32.6)	-43.1 (-59.0, -27.2)	nps*
DSG	124	151.4	-0.4 (117.3)	(-21.2, 20.5)		
Fasting HDL Cholesterol (mg/dL)						
ISG	244	50.0	-1.3 (10.1)	(-2.6, -0.0)	-2.8 (-4.7, -0.9)	nps*
DSG	124	48.5	1.9 (8.4)	(0.4, 3.4)		
Total Cholesterol to HDL Ratio						
ISG	244	4.0	-0.5 (1.1)	(-0.6, -0.3)	-0.4 (-0.6, -0.1)	nps*
DSG	124	4.6	-0.6 (5.7)	(-1.6, 0.4)		

Subjects on lipid-lowering agents at baseline were excluded from these analyses (ISG n = 26 and DSG n = 13). Subjects initiating a lipid-lowering therapy post-baseline had their last fasted on-treatment value carried forward for the Week 24 analysis (ISG n = 4 and DSG n = 2).

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 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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3.2 Pre-defined Limit of Change Evaluations

Table 2.7.4-switch48wk: 24

Analysis of Subjects With Laboratory Findings That Met Predetermined Criteria
(Incidence ≥1% in One or More Treatment Groups)
Worsening Grade; Study Weeks 0-24

Criterion†	DOR/3TC/TDF QD ISG n/m	DOR/3TC/TDF QD ISG (%)	Baseline Regimen DSG n/m	Baseline Regimen DSG (%)	Difference [DOR/3TC/TDF QD ISG - Baseline Regimen DSG] ‡ % (95% CI)
HEMATOLOGY					
Hemoglobin (g/dL)					
Grade 1: Male: 10.0 - 10.9 Female: 9.5 - 10.4	3/444	(0.7)	3/221	(1.4)	-0.7 (-3.3, 0.9)
CHEMISTRY					
Fasting LDL Cholesterol (mg/dL)					
Grade 1: 130 - <160	9/372	(2.4)	12/184	(6.5)	-4.1 (-8.8, -0.7)
Grade 2: 160 - <190	1/372	(0.3)	5/184	(2.7)	-2.4 (-6.0, -0.6)
Grade 3: >=190	0/372	(0.0)	3/184	(1.6)	-1.6 (-4.7, -0.6)
Fasting Cholesterol (mg/dL)					
Grade 1: 200 - <240	7/391	(1.8)	9/197	(4.6)	-2.8 (-6.8, 0.0)
Grade 2: 240 - <300	1/391	(0.3)	13/197	(6.6)	-6.3 (-10.7, -3.6)
Grade 3: >=300	0/391	(0.0)	2/197	(1.0)	-1.0 (-3.6, -0.0)
Fasting Triglyceride (mg/dL)					
Grade 1: 150 - 300	12/391	(3.1)	23/197	(11.7)	-8.6 (-14.0, -4.3)
Grade 2: >300 - 500	2/391	(0.5)	3/197	(1.5)	-1.0 (-3.9, 0.6)
Grade 3: >500 - 1000	1/391	(0.3)	2/197	(1.0)	-0.8 (-3.4, 0.6)
Fasting Glucose (mg/dL)					
Grade 1: 110 - 125	11/395	(2.8)	4/197	(2.0)	0.8 (-2.5, 3.3)
Grade 2: >125 - 250	4/395	(1.0)	2/197	(1.0)	-0.0 (-2.7, 1.7)
Grade 3: >250 - 500	1/395	(0.3)	2/197	(1.0)	-0.8 (-3.4, 0.5)
Total Bilirubin (mg/dL)					
Grade 1: 1.1 - <1.6 x ULN	14/444	(3.2)	9/221	(4.1)	-0.9 (-4.6, 1.9)
Grade 2: 1.6 - <2.6 x ULN	1/444	(0.2)	12/221	(5.4)	-5.2 (-9.0, -2.8)
Grade 3: 2.6 - <5.0 x ULN	0/444	(0.0)	5/221	(2.3)	-2.3 (-5.2, -1.0)
>2.5 - 5.0 x Baseline	4/444	(0.9)	4/221	(1.8)	-0.9 (-3.7, 0.8)

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Analysis of Subjects With Laboratory Findings That Met Predetermined Criteria (Incidence ≥1% in One or More Treatment Groups) Worsening Grade; Study Weeks 0-24

Criterion†	DOR/3TC/TDF QD ISG n/m	DOR/3TC/TDF QD ISG (%)	Baseline Regimen DSG n/m	Baseline Regimen DSG (%)	Difference [DOR/3TC/TDF QD ISG - Baseline Regimen DSG] ‡ % (95% CI)
Indirect Bilirubin (mg/dL)					
>2.5 - 5.0 x Baseline	2/444	(0.5)	4/221	(1.8)	-1.4 (-4.1, 0.2)
Creatinine (mg/dL)					
Grade 2: >1.3 - 1.8 x ULN or Increase of >0.3 mg/dL above baseline	6/444	(1.4)	1/221	(0.5)	0.9 (-1.2, 2.5)
Aspartate Aminotransferase (IU/L)					
Grade 1: 1.25 - <2.5 x ULN	37/444	(8.3)	7/221	(3.2)	5.2 (1.3, 8.6)
Grade 2: 2.5 - <5.0 x ULN	8/444	(1.8)	1/221	(0.5)	1.3 (-0.8, 3.1)
>2.5 - 5.0 x Baseline	17/444	(3.8)	2/221	(0.9)	2.9 (0.3, 5.3)
>5.0 x Baseline	7/444	(1.6)	1/221	(0.5)	1.1 (-1.0, 2.8)
Alanine Aminotransferase (IU/L)					
Grade 1: 1.25 - <2.5 x ULN	55/444	(12.4)	7/221	(3.2)	9.2 (5.1, 13.1)
Grade 2: 2.5 - <5.0 x ULN	11/444	(2.5)	2/221	(0.9)	1.6 (-0.9, 3.6)
>2.5 - 5.0 x Baseline	46/444	(10.4)	3/221	(1.4)	9.0 (5.6, 12.4)
>5.0 x Baseline	15/444	(3.4)	3/221	(1.4)	2.0 (-0.8, 4.4)
Alkaline Phosphatase (IU/L)					
Grade 1: 1.25 - <2.5 x ULN	3/444	(0.7)	5/221	(2.3)	-1.6 (-4.6, 0.2)
Lipase (IU/L)					
Grade 1: 1.1 - <1.5 x ULN	30/444	(6.8)	4/221	(1.8)	4.9 (1.7, 8.0)
Grade 2: 1.5 - <3.0 x ULN	15/444	(3.4)	2/221	(0.9)	2.5 (-0.1, 4.8)
Creatine Kinase (IU/L)					
Grade 1: 3.0 - <6.0 x ULN	6/444	(1.4)	11/221	(5.0)	-3.6 (-7.4, -1.0)
Grade 3: 10.0 - <20.0 x ULN	3/444	(0.7)	3/221	(1.4)	-0.7 (-3.3, 0.9)

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Analysis of Subjects With Laboratory Findings That Met Predetermined Criteria (Incidence ≥1% in One or More Treatment Groups) Worsening Grade; Study Weeks 0-24

Criterion[†]	DOR/3TC/TDF QD ISG n/m	(%)	Baseline Regimen DSG n/m	(%)	Difference [DOR/3TC/TDF QD ISG - Baseline Regimen DSG] [‡] % (95% CI)
Amylase (IU/L)					
Grade 1: 1.1 - <1.5 x ULN	10/444	(2.3)	3/221	(1.4)	0.9 (-1.8, 3.0)

[†] For graded criteria: subjects are counted once per test in the highest grade reported.

For inclusion in this analysis, both a baseline and at least one on-treatment laboratory value had to be present. Only subjects with a worsened grade from baseline were included. A subject was listed with a Grade X event if his/her highest grade during treatment was X.

[‡] The 95% CIs for the treatment differences in percent with PDLC were calculated using Miettinen and Nurminen method.

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 with post-baseline test results that met the predetermined criterion.

m = Number of subjects with at least one post-baseline test result.

LLN = Lower limit of normal range. ULN = Upper limit of normal range.

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-adlb]

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3.3 Evaluation of Each Laboratory Test

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Table 2.7.4-switch48wk: 25

Summary of Laboratory Tests
Study Weeks 0-48; Base Study

Study Week	DOR/3TC/TDF QD ISG			Baseline Regimen DSG			DOR/3TC/TDF QD DSG		
	N	Baseline Mean	Mean Change†(SD)	N	Baseline Mean	Mean Change†(SD)	N	Post-switch Baseline Mean	Mean Change†(SD)
Alanine Aminotransferase (IU/L)									
0	447	24.48		223	23.77				
4	443	24.52	9.63 (22.00)	219	23.76	0.38 (11.03)			
12	436	24.63	10.29 (24.79)	215	23.86	-0.35 (11.44)			
24‡	425	24.62	9.49 (31.70)	213	23.74	-0.27 (16.98)	209	22.90	
28‡	420	24.55	8.86 (24.47)				206	22.85	11.56 (24.17)
36‡	416	24.65	7.71 (23.16)				205	23.02	12.47 (30.84)
48‡	406	24.60	10.13 (34.17)				199	22.77	25.23 (177.00)
Alkaline Phosphatase (IU/L)									
0	447	81.21		223	82.34				
4	443	81.26	-1.56 (11.95)	219	82.50	-0.79 (10.90)			
12	436	81.37	-1.83 (15.14)	215	82.69	-1.06 (11.96)			
24‡	425	81.41	-3.13 (18.16)	213	81.35	-1.20 (16.95)	209	80.33	
28‡	420	81.31	-2.66 (15.56)				206	80.46	-2.12 (12.99)
36‡	416	81.30	-3.08 (16.95)				205	80.38	-2.58 (17.48)
48‡	406	81.04	-3.56 (16.82)				199	80.06	-2.01 (22.72)
Aspartate Aminotransferase (IU/L)									
0	447	24.50		223	24.46				
4	443	24.51	4.47 (17.74)	219	24.46	-1.77 (14.50)			
12	436	24.62	4.84 (19.02)	215	24.50	-0.92 (18.86)			
24‡	425	24.51	4.51 (22.86)	213	24.34	-2.57 (15.71)	209	21.72	
28‡	420	24.22	5.34 (26.21)				206	21.61	5.68 (13.81)
36‡	416	24.23	3.56 (15.02)				205	21.80	6.71 (18.26)
48‡	406	24.19	4.48 (23.79)				199	21.66	13.50 (98.25)
Total Bilirubin (mg/dL)									
0	447	0.87		223	0.89				
4	443	0.87	-0.31 (0.85)	218	0.89	0.01 (0.58)			

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Summary of Laboratory Tests
Study Weeks 0-48; Base Study

Study Week	DOR/3TC/TDF QD ISG			Baseline Regimen DSG			DOR/3TC/TDF QD DSG		
	N	Baseline Mean	Mean Change†(SD)	N	Baseline Mean	Mean Change†(SD)	N	Post-switch Baseline Mean	Mean Change†(SD)
12	436	0.86	-0.29 (0.84)	215	0.89	0.00 (0.50)			
24‡	425	0.87	-0.26 (0.86)	213	0.88	-0.03 (0.50)	209	0.84	
28‡	420	0.87	-0.29 (0.85)				206	0.85	-0.31 (0.87)
36‡	416	0.87	-0.30 (0.87)				205	0.85	-0.26 (0.89)
48‡	406	0.87	-0.24 (0.87)				199	0.87	-0.20 (1.08)
Fasting Cholesterol (mg/dL)									
0	424	192.92		215	189.38				
24‡	391	193.74	-29.17 (31.78)	197	189.17	-0.07 (28.86)	202	188.73	
48‡	376	193.82	-24.15 (32.14)				184	188.49	-21.46 (31.97)
Creatine Kinase (IU/L)									
0	447	179.01		223	260.62				
4	443	178.59	-10.73 (625.46)	219	262.31	-112.84 (1095.73)			
12	436	179.86	-9.38 (573.59)	215	263.70	-27.95 (1323.99)			
24‡	425	179.09	-17.02 (585.97)	213	266.30	-115.37 (1130.09)	209	152.60	
28‡	420	179.09	40.67 (1117.16)				206	152.60	98.90 (1538.47)
36‡	416	177.50	-24.22 (543.21)				205	150.47	-13.54 (191.43)
48‡	406	179.05	-14.72 (534.17)				199	150.61	2.66 (160.67)
Creatinine (mg/dL)									
0	447	0.89		223	0.90				
4	443	0.89	0.01 (0.08)	219	0.90	0.01 (0.07)			
12	436	0.89	0.02 (0.09)	215	0.90	0.01 (0.07)			
24‡	425	0.89	0.07 (0.65)	213	0.90	0.01 (0.09)	209	0.91	
28‡	420	0.89	0.03 (0.09)				206	0.91	0.01 (0.08)
36‡	416	0.89	0.03 (0.10)				205	0.91	0.03 (0.10)
48‡	406	0.89	0.03 (0.10)				199	0.90	0.02 (0.09)
Direct Bilirubin (mg/dL)									
0	447	0.17		223	0.16				

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Summary of Laboratory Tests
Study Weeks 0-48; Base Study

Study Week	DOR/3TC/TDF QD ISG			Baseline Regimen DSG			DOR/3TC/TDF QD DSG		
	N	Baseline Mean	Mean Change[†](SD)	N	Baseline Mean	Mean Change[†](SD)	N	Post-switch Baseline Mean	Mean Change[†](SD)
4	442	0.17	-0.04 (0.12)	219	0.16	-0.00 (0.08)			
12	436	0.17	-0.04 (0.12)	215	0.16	0.00 (0.08)			
24[‡]	425	0.17	-0.03 (0.13)	213	0.16	-0.00 (0.08)	209	0.16	
28[‡]	420	0.17	-0.04 (0.13)				206	0.16	-0.03 (0.12)
36[‡]	416	0.17	-0.04 (0.13)				205	0.16	-0.02 (0.13)
48[‡]	406	0.17	-0.03 (0.13)				199	0.16	0.01 (0.41)
Fasting Glucose (mg/dL)									
0	425	91.71		215	95.83				
24[‡]	395	91.62	0.93 (15.41)	197	96.22	1.13 (17.06)	202	96.98	
48[‡]	377	92.28	0.67 (12.63)				184	97.63	-2.43 (19.13)
Fasting HDL Cholesterol (mg/dL)									
0	424	50.13		215	49.38				
24[‡]	391	50.24	-2.46 (9.89)	197	49.74	1.09 (10.40)	202	50.98	
48[‡]	376	50.07	-2.88 (9.34)				184	51.24	-4.42 (11.74)
Hemoglobin (g/dL)									
0	447	14.48		223	14.59				
4	436	14.49	0.17 (0.68)	217	14.60	0.03 (0.61)			
12	432	14.48	0.29 (0.75)	214	14.56	0.07 (0.69)			
24[‡]	420	14.49	0.24 (0.85)	214	14.57	0.03 (0.74)	209	14.62	
28[‡]	413	14.50	0.17 (0.81)				206	14.62	0.11 (0.59)
36[‡]	413	14.48	0.31 (0.83)				205	14.64	0.29 (0.69)
48[‡]	396	14.51	0.38 (0.84)				201	14.62	0.37 (0.75)
Indirect Bilirubin (mg/dL)									
0	447	0.70		223	0.72				
4	442	0.70	-0.27 (0.74)	218	0.73	0.02 (0.52)			
12	436	0.69	-0.25 (0.73)	215	0.73	-0.00 (0.44)			
24[‡]	425	0.70	-0.23 (0.75)	213	0.71	-0.03 (0.45)	209	0.68	

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Summary of Laboratory Tests
Study Weeks 0-48; Base Study

Study Week	DOR/3TC/TDF QD ISG			Baseline Regimen DSG			DOR/3TC/TDF QD DSG		
	N	Baseline Mean	Mean Change†(SD)	N	Baseline Mean	Mean Change†(SD)	N	Post-switch Baseline Mean	Mean Change†(SD)
28‡	420	0.69	-0.25 (0.74)				206	0.69	-0.28 (0.76)
36‡	416	0.70	-0.26 (0.75)				205	0.69	-0.24 (0.77)
48‡	406	0.70	-0.22 (0.76)				199	0.70	-0.21 (0.81)
Fasting LDL Cholesterol (mg/dL)									
0	404	112.12		206	111.08				
24‡	372	112.72	-18.28 (24.36)	184	110.30	-2.46 (26.64)	195	106.73	
48‡	356	113.07	-13.15 (25.34)				176	105.58	-9.47 (25.91)
Neutrophils (10[3]/microL)									
0	447	3.59		223	3.56				
4	430	3.60	0.20 (1.52)	212	3.61	0.01 (1.46)			
12	429	3.58	0.15 (1.61)	211	3.61	0.00 (1.54)			
24‡	417	3.58	0.12 (1.95)	213	3.59	-0.08 (1.30)	209	3.51	
28‡	410	3.60	0.12 (1.55)				204	3.51	0.15 (1.13)
36‡	411	3.59	0.19 (1.44)				204	3.51	0.10 (1.22)
48‡	387	3.57	0.06 (1.55)				196	3.48	0.13 (1.42)
Platelets (10[3]/microL)									
0	445	227.60		222	232.17				
4	431	228.01	-0.06 (35.13)	213	231.46	0.70 (36.35)			
12	425	226.85	2.48 (36.27)	213	230.78	2.39 (40.24)			
24‡	414	227.36	-1.89 (46.79)	213	232.10	-2.62 (49.19)	209	228.73	
28‡	409	227.33	-1.73 (31.57)				206	228.20	-2.54 (38.59)
36‡	409	227.72	-1.89 (36.82)				204	228.61	-4.09 (36.32)
48‡	392	226.05	0.19 (36.00)				201	227.97	0.73 (40.67)
Triglyceride (mg/dL),Fasting									
0	424	160.19		215	158.20				
24‡	391	159.75	-45.84 (105.97)	197	157.87	0.87 (120.49)	202	159.49	
48‡	376	160.99	-45.45 (105.46)				184	160.27	-41.31 (105.70)

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Summary of Laboratory Tests
Study Weeks 0-48; Base Study

Study Week	DOR/3TC/TDF QD ISG			Baseline Regimen DSG			DOR/3TC/TDF QD DSG		
	N	Baseline Mean	Mean Change†(SD)	N	Baseline Mean	Mean Change†(SD)	N	Post-switch Baseline Mean	Mean Change†(SD)
Triacylglycerol Lipase (IU/L)									
0	447	32.08		223	28.61				
4	443	32.16	1.62 (35.02)	219	28.52	0.36 (14.01)			
12	437	32.11	3.37 (29.75)	215	28.78	0.40 (19.28)			
24‡	423	32.46	0.41 (24.84)	213	28.93	2.93 (37.27)	209	31.91	
28‡	420	32.50	3.09 (37.32)				206	31.81	1.47 (39.76)
36‡	417	32.46	3.50 (28.04)				205	32.15	1.83 (50.29)
48‡	406	31.70	7.14 (99.97)				199	32.31	-0.70 (49.42)
Amylase (IU/L)									
0	447	56.72		223	54.75				
4	442	56.85	0.52 (17.22)	219	54.64	-1.48 (17.22)			
12	437	56.75	0.32 (14.84)	215	54.73	-0.53 (18.91)			
24‡	423	57.39	-1.62 (15.46)	213	54.63	-0.43 (20.71)	209	54.16	
28‡	420	57.37	-1.75 (16.54)				206	54.36	-0.67 (13.10)
36‡	417	57.27	-1.35 (16.18)				205	54.60	-0.01 (19.64)
48‡	406	56.90	0.14 (29.56)				199	54.64	-0.38 (19.68)

†Change Scores are mean change from baseline and are based on the measurements of the subjects who were measured at baseline and the time point assessed.

‡Post-switch visits for DSG: Study Week 24 = post-switch baseline; Study Week 28 = post-switch Week 4; Study Week 36 = post-switch Week 12; Study Week 48 = post-switch Week 24.

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 the treatment group.

Source: [P024MK1439A: adam-adsl; adlb]

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4 VITAL SIGNS, PHYSICAL FINDINGS, AND OTHER OBSERVATIONS RELATED TO SAFETY

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Table 2.7.4-switch48wk: 26

Summary of Vital Signs
Study Weeks 0-48; Base Study

Study Week	DOR/3TC/TDF QD ISG			Baseline Regimen DSG			DOR/3TC/TDF QD DSG		
	N	Baseline Mean	Mean Change†(SD)	N	Baseline Mean	Mean Change†(SD)	N	Post-switch Baseline Mean	Mean Change†(SD)
Systolic Blood Pressure (mmHg)									
0	447	121.99		223	123.99				
4	441	121.98	0.41 (11.26)	219	124.23	0.50 (12.43)			
12	438	122.12	0.89 (12.07)	215	124.33	1.99 (10.91)			
24‡	427	122.08	-0.04 (13.34)	214	124.22	-0.64 (12.29)	209	123.64	
28‡	421	122.09	-0.22 (13.61)				205	123.71	0.65 (11.83)
36‡	416	122.11	0.07 (12.88)				206	123.61	1.14 (13.08)
48‡	406	122.10	0.83 (14.15)				202	123.70	-0.00 (11.59)
Diastolic Blood Pressure (mmHg)									
0	447	76.63		223	77.24				
4	441	76.62	0.54 (8.89)	219	77.41	0.30 (9.15)			
12	438	76.66	1.05 (9.07)	215	77.55	0.34 (8.95)			
24‡	427	76.58	0.45 (10.17)	214	77.48	0.28 (9.34)	209	77.77	
28‡	421	76.54	0.43 (9.45)				205	77.81	0.05 (8.48)
36‡	416	76.57	0.92 (9.36)				206	77.77	0.31 (9.44)
48‡	406	76.54	0.73 (9.64)				202	77.78	-0.32 (9.65)
Pulse Rate (beats/min)									
0	447	71.29		223	71.80				
4	440	71.21	0.68 (9.69)	219	71.83	1.90 (10.78)			
12	438	71.21	1.41 (9.79)	215	71.80	1.76 (10.38)			
24‡	426	71.06	0.47 (9.99)	214	72.07	0.50 (10.88)	209	72.53	
28‡	420	71.05	1.63 (10.22)				205	72.43	0.16 (9.70)
36‡	415	71.19	1.59 (9.52)				206	72.49	1.14 (10.27)
48‡	407	71.10	0.90 (10.25)				202	72.34	0.67 (9.88)
Respiratory Rate (breaths/min)									
0	447	15.41		223	15.48				
4	440	15.40	0.09 (2.01)	219	15.48	0.11 (2.16)			

Summary of Vital Signs
Study Weeks 0-48; Base Study

Study Week	DOR/3TC/TDF QD ISG			Baseline Regimen DSG			DOR/3TC/TDF QD DSG		
	N	Baseline Mean	Mean Change[†](SD)	N	Baseline Mean	Mean Change[†](SD)	N	Post-switch Baseline Mean	Mean Change[†](SD)
12	436	15.41	0.16 (2.12)	214	15.43	0.13 (2.38)			
24[‡]	426	15.43	0.01 (2.20)	214	15.43	-0.07 (2.34)	209	15.31	
28[‡]	418	15.39	-0.02 (2.25)				206	15.33	-0.02 (2.12)
36[‡]	411	15.41	-0.01 (2.32)				204	15.29	0.16 (2.15)
48[‡]	403	15.36	0.03 (2.26)				202	15.34	0.13 (2.28)
Temperature (C)									
0	447	36.42		223	36.39				
4	438	36.42	-0.00 (0.38)	219	36.39	-0.02 (0.43)			
12	436	36.42	-0.00 (0.41)	214	36.40	-0.01 (0.38)			
24[‡]	425	36.42	-0.00 (0.42)	214	36.40	0.00 (0.43)	209	36.40	
28[‡]	418	36.42	0.02 (0.43)				205	36.40	-0.01 (0.41)
36[‡]	413	36.42	0.00 (0.41)				205	36.40	-0.01 (0.36)
48[‡]	404	36.43	0.03 (0.40)				202	36.39	0.02 (0.38)
Weight (kg)									
0	447	79.39		223	79.17				
4	442	79.36	0.32 (1.66)	219	79.28	0.11 (1.90)			
12	438	79.42	0.59 (2.70)	215	79.23	-0.04 (2.53)			
24[‡]	427	79.35	0.68 (3.18)	214	79.29	-0.32 (3.57)	209	79.16	
28[‡]	421	79.50	0.74 (3.48)				206	79.12	0.10 (1.88)
36[‡]	417	79.51	0.74 (3.63)				206	78.84	0.21 (2.63)

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Summary of Vital Signs
Study Weeks 0-48; Base Study

Study Week	DOR/3TC/TDF QD ISG			Baseline Regimen DSG			DOR/3TC/TDF QD DSG		
	N	Baseline Mean	Mean Change[†](SD)	N	Baseline Mean	Mean Change[†](SD)	N	Post-switch Baseline Mean	Mean Change[†](SD)
48[‡]	408	79.48	0.74 (3.73)				202	78.85	0.55 (3.14)

[†]Change Scores are mean change from baseline and are based on the measurements of the subjects who were measured at baseline and the time point assessed.

[‡]Post-switch visits for DSG: Study Week 24 = post-switch baseline; Study Week 28 = post-switch Week 4; Study Week 36 = post-switch Week 12; Study Week 48 = post-switch Week 24.

Analysis of post-baseline data includes measurements 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 the treatment group.

Source: [P024MK1439A: adam-adsl; advs]

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5 SAFETY IN SPECIAL GROUPS AND SITUATIONS

5.1 Overdose

No participants reported overdose on P024.

5.2 Drug Abuse

No reports of abuse of DOR/3TC/TDF occurred in any individuals participating in P024. Based upon the activity profile of this compound, the abuse potential of DOR is considered low.

5.3 Withdrawal and Rebound

No specific trials have been conducted during the development program for DOR and DOR/3TC/TDF to assess the response to withdrawal and rebound. No withdrawal or rebound effects have been observed in the DOR and DOR/3TC/TDF clinical trials to date. DOR and DOR/3TC/TDF are not targeted to elicit a change in human physiology or biochemistry, but rather are anti-infective with activity against HIV-1. Therefore, the terms withdrawal and rebound are not applicable to these compounds.

5.4 Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability

No trials on the effects on the ability to drive and use machines have been performed. Fatigue, dizziness, and somnolence have been reported during treatment with DOR and DOR/3TC/TDF.

6 POSTMARKETING DATA

No postmarketing data were available at the time of the cut off for this application.

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7 CONCLUSIONS

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 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.

During the review of the original marketing authorization applications for DOR and DOR/3TC/TDF by the EU Committee for Medicinal Products for Human Use (CHMP), the Company was requested to provide a Company assessment of relatedness for uncommon adverse events that were assessed by the investigator as adverse reactions but seemed very unlikely to be related to DOR therapy.

To support the CHMP review of the current Switch Application, adverse events that were assessed by the investigator as drug related through Week 48 for P024 but assessed by the Company as unrelated to DOR are listed in Appendix 1.

1 APPENDIX

Appendix 1: Company Assessment of Adverse Events Assessed by the Investigator as Drug Reactions but Assessed by the Company as Unrelated to DOR – Protocol P024 through Week 48

Adverse Drug Reaction (as assessed by the investigator)	**Description of Event**	**Company Assessment**
Alcohol intolerance	Alcohol intolerance was reported in 1 subject. 1. TTO 1 day. Mild intensity. Dose not changed. Not recovered.	The subject experienced alcohol intolerance since day 1 of treatment. The available evidence does not suggest a relationship between the investigational therapy and the reported ADR.
Alopecia	Alopecia was reported on 1 subject. TTO 205 days. DOE: 1 week. Mild intensity. Dose not changed. Not yet recovered.	The subject had a history of hair loss prior to therapy start. In the opinion of the Applicant, the available evidence does not suggest a relationship between the investigational therapy and the reported AE.
Back pain	Back pain was reported in 1 subject. 1. TTO: 172 days. DOE: 10 days. Mild intensity. Recovered while still on treatment. Subject had previous history of back pain.	Resolution of the event while the continuing therapy suggests that the event was not related to study therapy.
Cognitive disorder	Cognitive disorder was reported in1 subject. 1. TTO: 158 days. DOE: 265 days.. Mild intensity. Dose not changed. Recovered. Subject had history of anxiety and depression and was taking alprazolam.	Resolution of the event while the subject was continuing therapy suggests that the event was not related to study therapy.
Decreased appetite	Decreased appetite was reported in 2 subjects. 1. TTO: 7 days day. DOE: 2 days. Mild intensity. Dose not changed. Recovered. 2. TTO 11 days. DOE 94 days. Mild intensity. Recovered. Subject experienced grade 4 CPK increase and Grade 1 AST increase around the time of reported event. Decreased appetite may be attributed to the reported laboratory abnormalities.	The available evidence does not suggest a relationship between the investigational therapy and the reported AE.

Adverse Drug Reaction **(as assessed by the investigator)**	**Description of Event**	**Company Assessment**
Dizziness postural	Dizziness postural was reported in 1subject. 1. TTO 17 days. DOE 154 days. Mild intensity. Dose not changed. Recovered. History of hypertension.	The recovery while on study therapy and history of hypertension and ramipril intake, for which dizziness is a labeled event, suggest that this event is not related to the investigational drug.
Dry mouth	Dry mouth was reported in 2 subjects. 1. TTO 86 days. DOE: 28 days. Mild intensity. Dose not changed. Recovered. 2. TTO 5 days. DOE 14 days. Mild intensity. Dose not changed. Recovered.	Resolution of the event while the subjects continued therapy suggests that the event was not related to study therapy.
Erectile dysfunction	Erectile dysfunction was reported in 2 subjects. 1. TTO 80 days. Mild intensity. Dose not changed. Not yet recovered. Subject was receiving CIALIS since screening. 2. TTO 172 days. Mild intensity. Dose not changed. Resolved.	CIALIS intake prior to study therapy suggests that erectile dysfunction was an underlying condition in the first subject. The other subject recovered while continuing on study therapy. The available evidence does not suggest a relationship between the investigational therapy and the reported AE.
Gastric PH decreased	Gastric PH decreased was reported in 1 subject. 1. TTO 173 days. Mild intensity. Dose not changed. Not yet recovered. Subject taking pantoprazole since screening.	In the opinion of the Applicant, the available evidence does not suggest a relationship between the investigational therapy and the reported AE.
Gastritis	Gastritis was reported in 1 subject. 2. TTO 31 days. DOE: 56 days. Mild intensity Dose not changed. Recovered. Subject received omeprazole since day 4 of therapy, and recovered while taking study medication.	The subject was receiving omeprazole since Day 4 of study therapy, 27 days prior to report of gastritis. This history and resolution of the event while the subject was continuing therapy suggest that the event was not related to study therapy.
Generalised oedema	Generalised oedema was reported in 1 subject. 1. TTO 167 days. Moderate intensity. Drug withdrawn. Not recovered.	The In the opinion of the Applicant, the available evidence and negative dechallenge do not suggest a relationship between the investigational therapy and the reported ADR.

Adverse Drug Reaction **(as assessed by the investigator)**	**Description of Event**	**Company Assessment**
Heart rate irregular	Heart rate irregular was reported in 1 subject. 1. TTO 199 days. Mild intensity. Not recovered.	Patient has history of "pancreatic failure". In the opinion of the Applicant, the available evidence and comorbidities do not suggest a relationship between the investigational therapy and the reported AE.
Hyperbilirubinaemia	Hyperbilirubinaemia was reported in 1 subject. 1. TTO 92 days. DOE: 106 days. Mild intensity. Dose not changed. Recovered.	Subject received tramadol at time of event, for which hyperbilirubinaemia is a labeled event. Resolution of the event while the subject was continuing therapy suggests that the event was not related to study therapy.
Hyperhidrosis	Hyperhidrosis was reported in 1 subject. TTO 121 days. Mild intensity. Dose not changed. Not yet resolved.	Subject on medications for zoster infection. Additionally varicella/zoster may be associated with hyperhidrosis. In the opinion of the Applicant, the available evidence does not suggest a relationship between the investigational therapy and the reported AE.
Hyperpyrexia	Hyperpyrexia was reported in 1 subject. 1. TTO 183 days. Moderate intensity. Dose not changed. Recovered. Subject took acetaminophen the day of event and recovered.	Resolution of the event while continuing therapy suggests that the event was not related to study therapy
Hypertriglyceridaemia	Hypertriglyceridaemia was reported in 2 subjects. 1. TTO 1 day. DOE 169 days. Severe intensity. Dose not changed. Recovered. 2. TTO 169 days (one day after switch to doravirine-containing regimen). DOE 62 days. Severe intensity. Dose not changed. Recovered. Subject had received other antiretroviral therapies which are known to increase triglycerides.	Documentation of the laboratory measure of elevated triglycerides on the day of initiation of study therapy suggests that the event was not related to study therapy.

Adverse Drug Reaction **(as assessed by the investigator)**	**Description of Event**	**Company Assessment**
Irritable bowel syndrome	Irritable bowel syndrome was reported in 1 subject. 1. TTO: 97 day. DOE: 27 days. Moderate intensity. Dose not changed. Recovered. Subject was receiving alendronate for osteoporosis, which is associated with GI disorders. In addition, subject had history of thyroid disorder which could explain the reported event.	Resolution of the event while the subject was continuing therapy suggests that the event was not related to study therapy.
Libido disorder	Libido disorder was reported in 1 subject. 1. TTO: 218days. Moderate intensity. Dose not changed. Not yet recovered. Subject had history of alcohol abuse which may explain the event.	In the opinion of the Applicant, the event is not related to study therapy.
Lymphogranuloma venereum	Lymphogranuloma venereum was reported in 1 subject. 1. TTO: 51 days. DOE: 22 days. Mild intensity. Dose not changed. Recovered.	There is no biologically plausible explanation for reported event (STD) in relation to study therapy.
Mental impairment	Mental impairment was reported in 1 subject. 1. TTO 173 days. DOE: 61 days. Mild intensity. Recovered.	Resolution of the event while the subject continued on therapy suggests that the event was not related to study therapy.
Migraine	Migraine was reported in 2 subjects. 1. TTO1 day. DOE 2 days. Mild intensity. Dose not changed. Resolved. Subject had history of polyneuropathy and migraines. 2. TTO 1 day. DOE 3 days. Mild intensity. Dose not changed. Resolved. Subject had history of elevated blood pressure and headaches.	Resolution of the event while the subjects were continuing therapy and prior history of headaches in both subjects suggest that the events were not related to study therapy.

Adverse Drug Reaction **(as assessed by the investigator)**	**Description of Event**	**Company Assessment**
Muscle spasms	Muscle spasms were reported in 1 subject. 1. TTO 173 days. DOE: 61 days. Mild intensity. Dose not changed. Resolved.	Resolution of the event while the subjects were continuing therapy suggests that the event was not related to study therapy.
Neutrophil count decreased	Neutrophil count decreased was reported in 1 subject. TTO 195 days. DOE 59 days. Moderate intensity. Dose not changed. Resolved. Subject had viral illness and was on multiple concomitant medications at time of the reported event.	Resolution of the event while the subject was continuing therapy suggests that the event was not related to study therapy.
Oral herpes	Oral herpes was reported in 1 subject. 1. TTO 255 days. DOE: 22 days. Mild intensity. Dose not changed. Resolved.	There is no biologically plausible explanation for reported event in relation to study therapy.
Palpitations	Palpitations were reported in 1 subject. 1. TTO 20 days. DOE 65 days. Mild intensity. Dose not changed. Resolved. Subject had prior history of hypertension.	Resolution of the event while the subject was continuing therapy suggests that the event was not related to study therapy.
Renal pain	Renal pain was reported in 1 subject. 1. TTO 196 days. Mild intensity. Drug withdrawn. Recovered. Patient also had myalgia, nausea and rash. In the absence of documentation for renal origin of pain, it is likely that the renal pain was musculoskeletal and related to the myalgia.	In the opinion of the Applicant, the available evidence does not suggest a relationship between the investigational therapy and the reported AE.
Tension headache	Tension headache was reported in 1 subject. 1. TTO 65 days. DOE: 121 days. Mild intensity. Dose not changed. Recovered.	Resolution of the event while the subject was continuing therapy suggests that the event was not related to study therapy.
Vertigo	Vertigo was reported in 1 subject. 1. TTO 48 days. DOE: 39 days. Mild intensity. Dose not changed. Recovered.	Resolution of the event while the subjects were continuing therapy suggests that the event was not related to study therapy.

Adverse Drug Reaction **(as assessed by the investigator)**	**Description of Event**	**Company Assessment**
Vision blurred	Vision blurred was reported in 1 subject. 1. TTO 148 days. DOE: 13 days. Mild severity. No dose adjustment. Recovered.	Resolution of the event while the subject was continuing therapy suggests that the event was not related to study therapy.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
3TC	lamivudine
ABC	abacavir
ABC/3TC	EPZICOM™ or KIVEXA™
AE	adverse event
AIDS	acquired immune deficiency syndrome
APAT	All Participants as Treated (population)
AUC	area under the curve
CI	confidence interval
CNS	central nervous system
CSR	clinical study report
CYP	cytochrome P450
DOR	doravirine (MK-1439; PIFELTRO™)
DOR/3TC/TDF	doravirine/ lamivudine / tenofovir disoproxil fumarate (MK-1439A; DELSTRIGO™)
DRV+r	darunavir boosted with ritonavir
ECI	event(s) of clinical interest
EFV	efavirenz
EFV/FTC/TDF	ATRIPLA™
FDC	fixed-dose combination
FTC	emtricitabine
FTC/TDF	TRUVADA™
HCV	hepatitis C virus
HDL-C	high-density lipoprotein cholesterol
HIV-1	human immunodeficiency virus type 1
IRIS	immune reconstitution syndrome
ISS	Integrated Summary of Safety
LDL-C	low-density lipoprotein cholesterol
MSP	Main Safety Pool
NNRTI	non-nucleoside reverse transcriptase inhibitor
OLE	open-label extension
PDLC	predefined limit of change
PT	preferred term
QD	once daily
SAE	serious adverse event

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Abbreviation	Definition
SOC	System Organ Class
SSP	Special Safety Pool
TDF	tenofovir disoproxil fumarate

1 EXPOSURE TO THE PRODUCT

1.1 Overall Safety Evaluation Plan and Safety Study Summaries

1.1.1 Overview of the Clinical Development Program

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). DOR has received marketing approval in the United States, Canada, and the European Union, as a once-daily (QD) oral treatment for HIV-1 infection in adults aged 18 years and older as both a single agent, DOR (100 mg), and as a fixed-dose combination (FDC) with lamivudine (3TC, 300 mg) and tenofovir disoproxil fumarate (TDF, 300 mg) (also known as DELSTRIGO™, MK-1439A, hereafter referred to as DOR/3TC/TDF).

The clinical development program for DOR and DOR/3TC/TDF includes 36 completed Phase 1 trials, 1 completed Phase 2b trial (P007), 2 ongoing Phase 2 trials (P028 and P030), and 3 ongoing Phase 3 trials (P018, P021, and P024). Data from the Phase 1 trials, P007, and data through Week 48 of P018 and P021 have been previously submitted.

The trials supporting this Supplemental Application and contributing data to this Summary of Clinical Safety are the Phase 2b dose-ranging trial (Protocol 007 [P007]), and 2 Phase 3 trials (P018 and P021; data through Week 96) in antiretroviral-naïve adults initiating therapy. Across these 3 trials, a total of 855 participants received at least 1 dose of DOR or DOR/3TC/TDF, as follows:

- A total of 232 participants in P007, a Phase 2 trial that was conducted as a 2-part dose-ranging trial in treatment-naïve HIV–1-infected participants.
  - Part I: 166 participants received DOR (in QD doses of 25 mg [n=40], 50 mg [n=43], 100 mg [n=42], and 200 mg [n=41]), and 42 participants received efavirenz (EFV); all doses were given in combination with open-label emtricitabine (FTC)/TDF (supplied as TRUVADA™).
  - Part II: After dose selection of 100 mg DOR, participants from Part I who were in the DOR 25-, 50-, and 200-mg dose groups who continued in the trial were switched to the 100-mg dose of DOR at their next planned study visit between Week 36 and Week 72, while maintaining the study blind. An additional 132 participants were randomized 1:1 to receive treatment with DOR 100 mg QD (n=66) or EFV (n=66) in combination with FTC/TDF. For participants randomized to DOR 100 mg (n=42 in Part I; n=108 Parts I and II combined), the mean (SD) total number of days that participants received blinded treatment was 582.1 (182.22) days (median: 664.5 days).

- A total of 747 participants in the 2 pivotal, international, multicenter Phase 3 trials, P018 and P021 (treatment-naïve HIV-1-infected participants). Safety data from both trials through Week 96 are provided to support this application.
  - **P018**: a Phase 3 trial to evaluate the antiretroviral activity of DOR 100 mg QD compared with darunavir+ritonavir (DRV+r: 800 mg/100 mg) QD—each given in combination with FTC/TDF (supplied as TRUVADA™) or abacavir (ABC)/3TC (supplied as either EPZICOM™ or KIVEXA™)—when administered to treatment-naïve HIV-1 infected participants. This trial comprises a 96-week double-blind base trial followed by an open-label extension (OLE), during which time all participants receive DOR. In the base study, participants were randomly allocated in a 1:1 ratio to receive either DOR or the fixed-dose combination of DRV+r. A total of 766 participants (383 in each treatment group) have received ≥1 dose of trial medication.
  - **P021**: a Phase 3 trial to evaluate the safety and efficacy of DOR/3TC/TDF QD compared with EFV/FTC/TDF QD when administered to treatment-naïve HIV-1-infected adults. The study consists of a 96-week blinded base study followed by a 96-week OLE, during which time all participants receive DOR/3TC/TDF. In the base trial, participants were randomly allocated in a 1:1 ratio to receive either DOR/3TC/TDF or EFV/FTC/TDF. A total of 728 participants (364 in each treatment group) have received ≥1 dose of trial medication.

Additional details of the trial designs for P007, P018, and P021 can be found in the individual clinical study reports (CSRs; [Ref. 5.3.5.1: P007V01MK1439] [Ref. 5.3.5.1: P018MK1439] [Ref. 5.3.5.1: P021MK1439A]).

Narratives of all deaths, serious adverse events (SAEs), and adverse events (AEs) leading to discontinuation are provided in this Summary of Clinical Safety, including those from 3 other ongoing trials (Phase 2: P028 and P030; Phase 3: P024). Cutoff dates for these narratives for this Application are in [Table 2.7.4-trtmtnve96wk: 1]. Of note, the data cutoff dates vary for each trial; participants have, therefore, been treated in OLEs for different lengths of time across the clinical program.

This Summary of Clinical Safety does not include safety data from the 3 ongoing trials (P028, P030, and P024) other than the previously mentioned narratives of all deaths, SAEs, and AEs leading to discontinuation. These ongoing trials are briefly described below.

- 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 enrolled and randomly assigned 1:1 to either an immediate or delayed switch to DOR/3TC/TDF.

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

- P024 is a Phase 3 trial in which 673 HIV-1-infected participants virologically suppressed on regimens that included a ritonavir- or cobicistat-boosted protease inhibitor (specifically, atazanavir, darunavir, or lopinavir), cobicistat-boosted elvitegravir, or an NNRTI (specifically, EFV, nevirapine, or rilpivirine) were enrolled and randomly assigned 2:1 to either an immediate or delayed switch to DOR/3TC/TDF.

Table 2.7.4-trtmtnve96wk: 1
Last Patient Last Visit/ Data Cutoff Date for Phase 2 and Phase 3 Trials Included in this Application

Trial	Last Patient Last Visit Date/ Data Cutoff Date
Trials with Safety Analyses Included in this Application	
P007	22-MAR-2016
P018	[redacted]-20[redacted]
P021	[redacted]-20[redacted]
Ongoing Trials with Narratives (Only) Included in this Application	
P024	22-FEB-2018
P028	[redacted]-20[redacted]
P030	[redacted]-20[redacted]

1.1.2 Overall Safety Assessment – Data Integration Plan

Safety data from trials P007, P018, and P021 are integrated in this Application. For each of these trials, 96-week safety data are presented.

Safety endpoints for the pooled Week 96 analysis and summaries follow the same approach as the Week 48 analysis provided in the original Application (Integrated Statistical Analysis Plan [Ref. 5.3.5.3: 04LVBJ]).

Safety analyses were based on the APAT population (all randomized participants who received at least 1 dose of any study medication). Integrated safety analyses were conducted for 2 pools of participants, the Main Safety Pool (MSP) and the Special Safety Pool (SSP) [Table 2.7.4-trtmtnve96wk: 2] [Figure 2.7.4-trtmtnve96wk: 1].

The MSP represents the primary dataset for the evaluation of all AEs and includes data from trials P007, P018, and P021. The DRV+r treatment group from P018 was not combined with the EFV/FTC/TDF-based treatment groups from P007 and P021, as these 2 treatments are associated with different safety profiles with regard to specific AEs and laboratory measurements. No formal statistical testing was performed. Descriptive summary data are presented for each treatment group.

Because EFV is associated with neuropsychiatric events, those participants from P007 and P021 who had an EFV-based regimen as a comparator arm formed the SSP group; all SSP analyses combine the DOR 100-mg group from P007 and the DOR/3TC/TDF group from P021. The SSP is used for the analyses of the proportion of participants who discontinued from trials P007 and P021 due to AEs, the time to discontinuation from the trials due to AEs, and the proportion of participants with neuropsychiatric events using a prespecified list of AEs (overall and in each category: Dizziness, Sleep disorders and disturbances, Altered Sensorium, Depression and suicide/self-injury, Psychosis and psychotic disorders).

Throughout this Summary of Clinical Safety, the referenced results of individual trials supporting this Supplemental Application can be found in the CSRs, located in [Ref. 5.3.5.1: P007V01MK1439] [Ref. 5.3.5.1: P018MK1439] [Ref. 5.3.5.1: P021MK1439A].

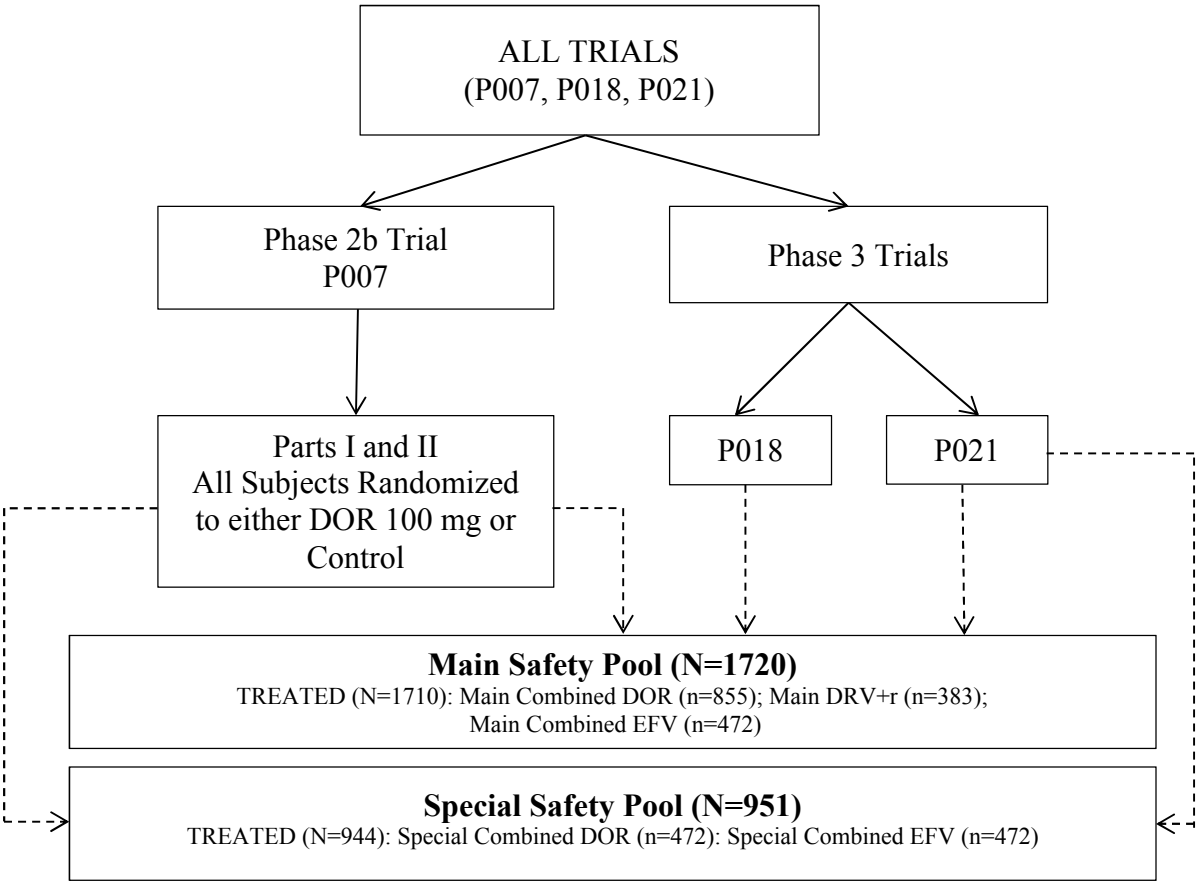
Table 2.7.4-trtmtnve96wk: 2
Integrated Safety Populations
Main Safety Pool and Special Safety Pool

Objective	Analysis	Trials Involved	Combined Treatment groups (N)
Main Safety Pool (N=1720 Participants Randomized)			
DOR or DOR/3TC/TDF vs. Controls	AEs, AEs by specific terms and SOC, PDLC, and change in laboratory measurement and vital signs (estimate by treatment group) [a]	P007 (100-mg arm) P018 P021	Main Combined DOR: DOR and DOR/3TC/TDF (N=855) **P007** 100-mg arm = 108 participants + **P018** = 383 participants + **P021** = 364 participants Main DRV+r: Darunavir (DRV+r) regimen (n=383) Main Combined EFV: EFV regimen (n=472) **P007** = 108 participants **P021** = 364 participants
Special Safety Pool (N=951 Participants Randomized)			
DOR or DOR/3TC/TDF vs. Controls	Proportion of participants discontinuing due to AE [b] and time to discontinuation due to AEs.[c] Proportion of participants with neuropsychiatric events.[d]	P007 (100-mg arm) P021	Special Combined DOR: DOR and DOR/3TC/TDF (N =472) **P007** 100-mg arm = 108 participants + **P021** = 364 participants Special Combined EFV: EFV regimen (n =472) **P007** = 108 participants **P021** = 364 participants

a. Descriptive statistics, no formal statistical testing.
b. Tier 1 endpoint, p-values and 95% Confidence Intervals (CI) provided
c. Kaplan-Meier product-limit estimates provided
d. 95% CI for between-treatment differences provided

Abbreviations: AE = adverse event; DOR = doravirine; DRV+r = Darunavir boosted with ritonavir; EFV = efavirenz; PDLC = predefined limit of change; SOC = System Organ Class; 3TC = lamivudine 300 mg; TDF = tenofovir disoproxil fumarate 300 mg

Figure 2.7.4-trtmtnve96wk: 1
Diagram of Integrated Safety Populations



Main Combined DOR Treatment Group (P018, and P021, and from 100 mg arm 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 from 100 mg arm 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 from 100 mg arm P007): EFV600 mg administered with FTC/TDF, or EFV/FTC/TDF

1.2 Overall Extent of Exposure to DOR

A total of 614 participants received any dose of DOR in trials P007 and P018 for a mean duration of 573.8 days [Table 2.7.4-trtmtnve96wk: 3].

A total of 364 participants received DOR as DOR/3TC/TDF for a mean duration of 587.4 days in P021 [Table 2.7.4-trtmtnve96wk: 4].

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Subject Disposition

Main Safety Pool

Overall, 99.3% of the randomized participants in the Combined DOR group, 99.7% of the participants in the DRV+r group, and 99.4% of the participants in the EFV group received ≥1 dose of study drug and are included in the MSP [Table 2.7.4-trtmtnve96wk: 5]. In all 3 treatment groups, similar proportions of participants discontinued from their respective study through Week 96 [Table 2.7.4-trtmtnve96wk: 5]; for those who discontinued due to an AE, the observed proportion of participants was higher in the Main Combined EFV group (7.8%) than in the Main DRV+r group (3.6%) or Main Combined DOR group (2.6%).

The proportion of participants who discontinued from the study due to lack of efficacy was similar among participants in the Main Combined DOR (6.0%), Main DRV+r (8.3%), and Main Combined EFV (5.1%) groups [Table 2.7.4-trtmtnve96wk: 5].

The disposition of participants in the MSP for all available data is shown in [Table 5.3.5.3.3-trtmtnve96wk: 43].

Special Safety Pool

In the SSP, 99.2% of the randomized participants in the Special Combined DOR group and 99.4% of participants in the Special Combined EFV group received ≥1 dose of study drug [Table 2.7.4-trtmtnve96wk: 6]. A greater observed proportion of participants in the Special Combined EFV group (23.6%) discontinued from their respective study through Week 96 compared with the proportion of participants in the Special Combined DOR group (18.7%) who discontinued. For those who discontinued due to an AE, the observed proportion of participants was higher in the Special Combined EFV group (7.8%) than in the Special Combined DOR group (3.4%).

The disposition of participants in the SSP for all available data is shown in [Table 5.3.5.3.3-trtmtnve96wk: 44].

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Table 2.7.4-trtmtnve96wk: 3
Extent of Exposure to Doravirine by Dose
P007 and P018 Combined
Weeks 0-96, Base Study (Double Blind)

Doravirine	≤ 4 wks	> 4 wks to 24 wks	> 24 wks to 48 wks	> 48 wks to 96 wks	> 96 wks	Total Subjects	Duration Range	Mean Duration
Any Dose	19	32	39	389	135	614	1 to 712 days	573.8 days
25 mg	3	3	24	12	0	42	1 to 421 days	296.2 days
50 mg	4	2	24	14	0	44	2 to 504 days	301.3 days
100 mg	13	31	94	337	113	588	1 to 712 days	533.1 days
200 mg	12	2	19	18	0	51	1 to 494 days	258.2 days
300 mg	1	0	0	0	0	1	1 to 1 days	1.0 days
Other	1	0	0	0	0	1	6 to 6 days	6.0 days

Each subject who received Doravirine is counted once on the "Any Dose" row in the column that reflects the total duration of exposure to Doravirine.

Each subject is counted again on one or more specific dose category rows that correspond to the actual dose(s) received. On each applicable specific dose row, the subject is counted once in the column that reflects the duration of exposure to that specific dose.

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

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Table 2.7.4-trtmtnve96wk: 4
Extent of Exposure to DOR/3TC/TDF by Dose
P021
Weeks 0-96, Base Study (Double Blind)

DOR/3TC/TDF	≤ 4 wks	> 4 wks to 24 wks	> 24 wks to 48 wks	> 48 wks to 96 wks	> 96 wks	Total Subjects	Duration Range	Mean Duration
Any Dose	6	18	23	217	100	364	1 to 756 days	587.4 days
Doravirine 100 mg/lamivudine 300 mg/TDF 300 mg	6	19	22	224	93	364	1 to 756 days	586.8 days
Doravirine 200 mg/lamivudine 600 mg/TDF 600 mg	56	2	0	0	0	58	1 to 60 days	3.8 days

Each subject who received DOR/3TC/TDF is counted once on the "Any Dose" row in the column that reflects the total duration of exposure to DOR/3TC/TDF.

Each subject is counted again on one or more specific dose category rows that correspond to the actual dose(s) received. On each applicable specific dose row, the subject is counted once in the column that reflects the duration of exposure to that specific dose.

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

Table 2.7.4-trtmtnve96wk: 5
Disposition of Subjects
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	(%)
Total Randomized	861		384		475	
Not Treated	6	(0.7)	1	(0.3)	3	(0.6)
Treated	855	(99.3)	383	(99.7)	472	(99.4)
Discontinued Study	180	(20.9)	110	(28.6)	112	(23.6)
Adverse Event	22	(2.6)	14	(3.6)	37	(7.8)
Death	4	(0.5)	1	(0.3)	4	(0.8)
Lack Of Efficacy	52	(6.0)	32	(8.3)	24	(5.1)
Lost To Follow-Up	38	(4.4)	24	(6.3)	13	(2.7)
Non-Compliance With Study Drug	15	(1.7)	6	(1.6)	4	(0.8)
Physician Decision	4	(0.5)	4	(1.0)	3	(0.6)
Pregnancy	4	(0.5)	1	(0.3)	2	(0.4)
Protocol Deviation	6	(0.7)	6	(1.6)	2	(0.4)
Withdrawal By Subject	35	(4.1)	22	(5.7)	23	(4.8)
Completed Base Study	675	(78.4)	273	(71.1)	360	(75.8)
Entered Study Extension	551	(64.0)	233	(60.7)	269	(56.6)
Did not Enter Study Extension	124	(14.4)	40	(10.4)	91	(19.2)

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

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.

Source: [ISS: analysis-adsl; dsplus]

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Table 2.7.4-trtmtnve96wk: 6
Disposition of Subjects
Special Safety Pool (P007 (Doravirine 100 mg q.d. Group) and Protocol 021 Combined)
Weeks 0-96, Base Study (Double Blind)

	Special Combined DOR		Special Combined EFV	
	n	(%)	n	(%)
Total Randomized	476		475	
Not Treated	4	(0.8)	3	(0.6)
Treated	472	(99.2)	472	(99.4)
Discontinued Study	89	(18.7)	112	(23.6)
Adverse Event	16	(3.4)	37	(7.8)
Death	1	(0.2)	4	(0.8)
Lack Of Efficacy	31	(6.5)	24	(5.1)
Lost To Follow-Up	10	(2.1)	13	(2.7)
Non-Compliance With Study Drug	6	(1.3)	4	(0.8)
Physician Decision	2	(0.4)	3	(0.6)
Pregnancy	2	(0.4)	2	(0.4)
Protocol Deviation	5	(1.1)	2	(0.4)
Withdrawal By Subject	16	(3.4)	23	(4.8)
Completed Base Study	383	(80.5)	360	(75.8)
Entered Study Extension	291	(61.1)	269	(56.6)
Did not Enter Study Extension	92	(19.3)	91	(19.2)

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

1.3 Demographic and Other Characteristics of Study Population

1.3.1 Baseline Demographic Characteristics

Main Safety Pool

Overall, the integrated treatment groups were generally well balanced with respect to demographic baseline characteristics [Table 2.7.4-trtmtnve96wk: 7].

Special Safety Pool

The baseline characteristics for participants in the SSP were similar to those noted in the MSP [Table 2.7.4-trtmtnve96wk: 8].

Table 2.7.4-trtmtnve96wk: 7
Subject Baseline Characteristics
Main Safety Pool (P007 (Doravirine 100 mg q.d. Group) and P018 and P021 Combined)

	Main Combined DOR (N = 855)	Main DRV+r (N = 383)	Main Combined EFV (N = 472)
Gender n (%)			
Male	723 (84.6)	326 (85.1)	412 (87.3)
Female	132 (15.4)	57 (14.9)	60 (12.7)
Race n (%)			
American Indian or Alaska Native	12 (1.4)	3 (0.8)	6 (1.3)
Asian	71 (8.3)	7 (1.8)	67 (14.2)
Black or African American	170 (19.9)	88 (23.0)	85 (18.0)
Multiple	58 (6.8)	2 (0.5)	57 (12.1)
Native Hawaiian or Other Pacific Islander	1 (0.1)	2 (0.5)	0 (0.0)
White	542 (63.4)	280 (73.1)	257 (54.4)
Missing	1 (0.1)	1 (0.3)	0 (0.0)
Ethnicity n (%)			
Hispanic or Latino	234 (27.4)	86 (22.5)	136 (28.8)
Not Hispanic or Latino	612 (71.6)	290 (75.7)	329 (69.7)
Unknown	9 (1.1)	7 (1.8)	7 (1.5)
Region n (%)			
Africa	60 (7.0)	22 (5.7)	27 (5.7)
Asia/Pacific	80 (9.4)	3 (0.8)	72 (15.3)
Europe	323 (37.8)	179 (46.7)	148 (31.4)
Latin America	127 (14.9)	33 (8.6)	87 (18.4)
North America	265 (31.0)	146 (38.1)	138 (29.2)
Age (years)			
18 to 64	850 (99.4)	379 (99.0)	470 (99.6)
>=65	5 (0.6)	4 (1.0)	2 (0.4)
Mean (SD)	34.5 (10.6)	35.7 (10.7)	33.2 (9.8)
Median (min, max)	32.0 (18, 70)	34.0 (18, 69)	31.0 (18, 69)
Baseline CD4 Cell Count (cells/mm^3)			
N[†]	855	383	472
Mean (SD)	433.5 (209.7)	411.9 (229.6)	422.9 (206.0)
Median (min, max)	410.0 (19, 1822)	393.0 (19, 1303)	393.5 (19, 1452)
Baseline CD4 Cell Counts n (%)			
<=50 cells/mm^3	15 (1.8)	19 (5.0)	10 (2.1)
>50 cells/mm^3 and <=200 cells/mm^3	78 (9.1)	48 (12.5)	46 (9.7)
>200 cells/mm^3	762 (89.1)	316 (82.5)	416 (88.1)
Baseline Plasma HIV-1 RNA (log_{10} copies/mL)			
N[†]	855	382	472
Mean (SD)	4.4 (0.7)	4.4 (0.7)	4.5 (0.7)
Median (min, max)	4.4 (2.0, 6.5)	4.4 (2.4, 6.5)	4.5 (2.6, 6.7)

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Subject Baseline Characteristics
Main Safety Pool (P007 (Doravirine 100 mg q.d. Group) and P018 and P021 Combined)

	Main Combined DOR (N = 855)	Main DRV+r (N = 383)	Main Combined EFV (N = 472)
Baseline Plasma HIV-1 RNA (copies/mL)			
N[†]	855	382	472
Geometric Mean	26864.2	26532.4	31279.8
Median (min, max)	26458.0 (105, 3106564)	27357.0 (235, 3272236)	31302.0 (403, 4631008)
Baseline Plasma HIV-1 RNA n (%)			
<=100,000 copies/mL	664 (77.7)	309 (80.7)	358 (75.8)
>100,000 copies/mL	191 (22.3)	73 (19.1)	114 (24.2)
Missing	0 (0.0)	1 (0.3)	0 (0.0)
Baseline Plasma HIV-1 RNA n (%)			
<=500,000 copies/mL	817 (95.6)	370 (96.6)	446 (94.5)
>500,000 copies/mL	38 (4.4)	12 (3.1)	26 (5.5)
Missing	0 (0.0)	1 (0.3)	0 (0.0)
History of AIDS n (%)			
Yes	86 (10.1)	37 (9.7)	60 (12.7)
No	769 (89.9)	346 (90.3)	412 (87.3)
Stratum n (%)			
Screening HIV-1 RNA<= 100,000	635 (74.3)	289 (75.5)	342 (72.5)
Screening HIV-1 RNA> 100,000	220 (25.7)	94 (24.5)	130 (27.5)
Baseline Hepatitis Status[††]			
Hep B and/or C Positive	22 (2.6)	18 (4.7)	9 (1.9)
Hep B Positive Only	13 (1.5)	12 (3.1)	8 (1.7)
Hep C Positive Only	9 (1.1)	6 (1.6)	1 (0.2)
Hep B and C Negative	833 (97.4)	365 (95.3)	463 (98.1)
Viral Subtype n (%)			
Clade B	573 (67.0)	272 (71.0)	339 (71.8)
Non-Clade B	280 (32.7)	111 (29.0)	133 (28.2)
Missing	2 (0.2)	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. P007 did not allow active hepatitis B and/or C positive subjects to be enrolled. Subjects with non-reactive hepatitis B surface antigen test and undetectable HCV RNA PCR test or without such tests were classified as hepatitis B and C negative.

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 randomized and treated in each treatment group.

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

Source: [ISS: analysis-adsl]

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Table 2.7.4-trtmtnve96wk: 8
Subject Baseline Characteristics
Special Safety Pool (P007 (Doravirine 100 mg q.d. Group) and P021 Combined)

	Special Combined DOR (N = 472)	Special Combined EFV (N = 472)
Gender n (%)		
Male	404 (85.6)	412 (87.3)
Female	68 (14.4)	60 (12.7)
Race n (%)		
American Indian or Alaska Native	9 (1.9)	6 (1.3)
Asian	64 (13.6)	67 (14.2)
Black or African American	84 (17.8)	85 (18.0)
Multiple	52 (11.0)	57 (12.1)
White	262 (55.5)	257 (54.4)
Missing	1 (0.2)	0 (0.0)
Ethnicity n (%)		
Hispanic or Latino	141 (29.9)	136 (28.8)
Not Hispanic or Latino	328 (69.5)	329 (69.7)
Unknown	3 (0.6)	7 (1.5)
Region n (%)		
Africa	37 (7.8)	27 (5.7)
Asia/Pacific	68 (14.4)	72 (15.3)
Europe	153 (32.4)	148 (31.4)
Latin America	89 (18.9)	87 (18.4)
North America	125 (26.5)	138 (29.2)
Age (years)		
18 to 64	469 (99.4)	470 (99.6)
>=65	3 (0.6)	2 (0.4)
Mean (SD)	34.3 (10.7)	33.2 (9.8)
Median (min, max)	32.0 (18, 70)	31.0 (18, 69)
Baseline CD4 Cell Count (cells/mm^3)		
N[†]	472	472
Mean (SD)	434.2 (211.0)	422.9 (206.0)
Median (min, max)	410.5 (19, 1399)	393.5 (19, 1452)
Baseline CD4 Cell Counts n (%)		
<=50 cells/mm^3	9 (1.9)	10 (2.1)
>50 cells/mm^3 and <=200 cells/mm^3	42 (8.9)	46 (9.7)
>200 cells/mm^3	421 (89.2)	416 (88.1)
Baseline Plasma HIV-1 RNA (log_{10} copies/mL)		
N[†]	472	472
Mean (SD)	4.4 (0.7)	4.5 (0.7)
Median (min, max)	4.4 (2.4, 6.5)	4.5 (2.6, 6.7)

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Subject Baseline Characteristics
Special Safety Pool (P007 (Doravirine 100 mg q.d. Group) and P021 Combined)

	Special Combined DOR (N = 472)	Special Combined EFV (N = 472)
Baseline Plasma HIV-1 RNA (copies/mL)		
N†	472	472
Geometric Mean	26871.4	31279.8
Median (min, max)	25955.5 (259, 3106564)	31302.0 (403, 4631008)
Baseline Plasma HIV-1 RNA n (%)		
<=100,000 copies/mL	364 (77.1)	358 (75.8)
>100,000 copies/mL	108 (22.9)	114 (24.2)
Baseline Plasma HIV-1 RNA n (%)		
<=500,000 copies/mL	451 (95.6)	446 (94.5)
>500,000 copies/mL	21 (4.4)	26 (5.5)
History of AIDS n (%)		
Yes	50 (10.6)	60 (12.7)
No	422 (89.4)	412 (87.3)
Stratum n (%)		
Screening HIV-1 RNA<= 100,000	345 (73.1)	342 (72.5)
Screening HIV-1 RNA> 100,000	127 (26.9)	130 (27.5)
Baseline Hepatitis Status††		
Hep B and/or C Positive	11 (2.3)	9 (1.9)
Hep B Positive Only	9 (1.9)	8 (1.7)
Hep C Positive Only	2 (0.4)	1 (0.2)
Hep B and C Negative	461 (97.7)	463 (98.1)
Viral Subtype n (%)		
Clade B	307 (65.0)	339 (71.8)
Non-Clade B	163 (34.5)	133 (28.2)
Missing	2 (0.4)	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. P007 did not allow active hepatitis B and/or C positive subjects to be enrolled. Subjects with non-reactive hepatitis B surface antigen test and undetectable HCV RNA PCR test or without such tests were classified as hepatitis B and C negative.

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 randomized and treated in each treatment group.

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

Source: [ISS: analysis-adsl]

1.3.2 Medical History

Main Safety Pool

Proportions of participants with secondary diagnoses were generally similar across treatment groups in the MSP. The most commonly reported medical history conditions in the

3 treatment groups were syphilis, acquired immunodeficiency syndrome (AIDS), lymphadenopathy, and hypertension. Numbers and percentages of participants with medical history present in ≥5% of participants in any treatment group and in >0% of participants in each treatment group in the MSP are presented in [Table 5.3.5.3.3-trtmtnve96wk: 49] [Table 5.3.5.3.3-trtmtnve96wk: 47].

Special Safety Pool

Proportions of participants with secondary diagnoses were generally similar across treatment groups in the SSP. The medical history of the participants in the SSP was similar to that of the participants in the MSP.

Numbers and percentages of participants with medical history present in ≥5% of participants in either treatment group and in >0% of participants in either treatment group in the SSP are presented in [Table 5.3.5.3.3-trtmtnve96wk: 50] [Table 5.3.5.3.3-trtmtnve96wk: 48].

1.3.3 Prior Medications

Main Safety Pool

More than half of all participants in each group of the MSP (Main Combined DOR, Main DRV+r, and Combined EFV) received ≥1 prior medication [Table 2.7.4-trtmtnve96wk: 9, Table 5.3.5.3.3-trtmtnve96wk: 51].

Although some differences were observed between treatment groups in proportions of participants who reported specific medications, these differences were not considered to be clinically important.

Special Safety Pool

More than half of all participants in each group of the SSP (Special Combined DOR and Special Combined EFV) received ≥1 prior medication [Table 2.7.4-trtmtnve96wk: 10, Table 5.3.5.3.3-trtmtnve96wk: 52]. Although some differences were observed between treatment groups in proportions of participants who reported specific medications, these differences were not considered to be clinically important.

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Table 2.7.4-trtmtnve96wk: 9
Subjects With Specific Prior Medications
(Incidence ≥5% in One or More Treatment Groups)
Main Safety Pool (P007 (Doravirine 100 mg q.d. Group) and P018 and P021 Combined)

	Main Combined DOR		Main DRV+r		Main Combined EFV	
	n	(%)	n	(%)	n	(%)
Subjects in population	855		383		472	
With one or more prior medications	491	(57.4)	214	(55.9)	272	(57.6)
With no prior medication	364	(42.6)	169	(44.1)	200	(42.4)
alimentary tract and metabolism						
drugs for acid related disorders	**34**	**(4.0)**	**23**	**(6.0)**	**19**	**(4.0)**
vitamins	**112**	**(13.1)**	**64**	**(16.7)**	**67**	**(14.2)**
vitamins (unspecified)	52	(6.1)	26	(6.8)	26	(5.5)
antiinfectives for systemic use						
antibacterials for systemic use	**157**	**(18.4)**	**83**	**(21.7)**	**94**	**(19.9)**
azithromycin	28	(3.3)	22	(5.7)	9	(1.9)
sulfamethoxazole (+) trimethoprim	56	(6.5)	37	(9.7)	31	(6.6)
vaccines	**51**	**(6.0)**	**18**	**(4.7)**	**33**	**(7.0)**
musculoskeletal system						
antiinflammatory and antirheumatic products	**72**	**(8.4)**	**27**	**(7.0)**	**40**	**(8.5)**
ibuprofen	46	(5.4)	18	(4.7)	23	(4.9)
nervous system						
analgesics	**84**	**(9.8)**	**39**	**(10.2)**	**64**	**(13.6)**
acetaminophen	38	(4.4)	11	(2.9)	33	(7.0)
psychoanaleptics	**47**	**(5.5)**	**21**	**(5.5)**	**23**	**(4.9)**
psycholeptics	**48**	**(5.6)**	**23**	**(6.0)**	**33**	**(7.0)**
respiratory system						
antihistamines for systemic use	**49**	**(5.7)**	**23**	**(6.0)**	**32**	**(6.8)**
drugs for obstructive airway diseases	**33**	**(3.9)**	**31**	**(8.1)**	**15**	**(3.2)**

Every subject is counted a single time for each applicable specific prior medication. A subject with multiple prior medications within a medication category is counted a single time for that category.

A medication class or specific medication 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.

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

Table 2.7.4-trtmtnve96wk: 10
Subjects With Specific Prior Medications
(Incidence ≥5% in One or More Treatment Groups)
Special Safety Pool (P007 (Doravirine 100 mg q.d. Group) and P021 Combined)

	Special Combined DOR		Special Combined EFV	
	n	(%)	n	(%)
Subjects in population	472		472	
With one or more prior medications	285	(60.4)	272	(57.6)
With no prior medication	187	(39.6)	200	(42.4)
alimentary tract and metabolism				
vitamins	**57**	**(12.1)**	**67**	**(14.2)**
vitamins (unspecified)	20	(4.2)	26	(5.5)
antiinfectives for systemic use				
antibacterials for systemic use	**87**	**(18.4)**	**94**	**(19.9)**
sulfamethoxazole (+) trimethoprim	31	(6.6)	31	(6.6)
vaccines	**37**	**(7.8)**	**33**	**(7.0)**
cardiovascular system				
lipid modifying agents	**24**	**(5.1)**	**17**	**(3.6)**
genitourinary system and sex hormones				
sex hormones and modulators of the genital system	**25**	**(5.3)**	**18**	**(3.8)**
musculoskeletal system				
antiinflammatory and antirheumatic products	**44**	**(9.3)**	**40**	**(8.5)**
ibuprofen	24	(5.1)	23	(4.9)
nervous system				
analgesics	**52**	**(11.0)**	**64**	**(13.6)**
acetaminophen	27	(5.7)	33	(7.0)
psychoanaleptics	**28**	**(5.9)**	**23**	**(4.9)**
psycholeptics	**29**	**(6.1)**	**33**	**(7.0)**
respiratory system				
antihistamines for systemic use	**29**	**(6.1)**	**32**	**(6.8)**

Every subject is counted a single time for each applicable specific prior medication. A subject with multiple prior medications within a medication category is counted a single time for that category.

A medication class or specific medication 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.

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] [ISS: tabulations-cmplus]

1.3.4 Concomitant Medications

Main Safety Pool

Through 96 weeks of treatment, most participants in the Main Combined DOR, Main DRV+r, and Main Combined EFV groups received concomitant medications

[Table 2.7.4-trtmtnve96wk: 11, Table 5.3.5.3.3-trtmtnve96wk: 55]. No clinically important differences across treatment groups in the proportions of participants with any concomitant therapy or with specific concomitant therapies were observed. While some differences were observed between treatment groups in the proportions of participants who reported concomitant medication use, these differences were not considered to be clinically important.

Special Safety Pool

In the SSP, the proportions of participants who used any concomitant therapy or any specific concomitant therapy through Week 96 [Table 2.7.4-trtmtnve96wk: 12, Table 5.3.5.3.3-trtmtnve96wk: 56] were generally similar to those in the MSP [Table 2.7.4-trtmtnve96wk: 11, Table 5.3.5.3.3-trtmtnve96wk: 55]. While some differences were observed between treatment groups in the proportions of participants who reported concomitant medication use, these differences were not considered to be clinically important.

Table 2.7.4-trtmtnve96wk: 11
Subjects With Specific Concomitant Medications
(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 concomitant medications	749	(87.6)	323	(84.3)	424	(89.8)
With no concomitant medication	106	(12.4)	60	(15.7)	48	(10.2)
alimentary tract and metabolism						
antidiarrheals, intestinal antiinflammatory/antiinfective agents	**75**	**(8.8)**	**32**	**(8.4)**	**40**	**(8.5)**
loperamide hydrochloride	24	(2.8)	21	(5.5)	9	(1.9)
drugs for acid related disorders	**109**	**(12.7)**	**50**	**(13.1)**	**65**	**(13.8)**
drugs for functional gastrointestinal disorders	**54**	**(6.3)**	**20**	**(5.2)**	**35**	**(7.4)**
vitamins	**174**	**(20.4)**	**90**	**(23.5)**	**89**	**(18.9)**
cholecalciferol	18	(2.1)	20	(5.2)	6	(1.3)
vitamins (unspecified)	64	(7.5)	34	(8.9)	34	(7.2)
antiinfectives for systemic use						
antibacterials for systemic use	**420**	**(49.1)**	**187**	**(48.8)**	**243**	**(51.5)**
amoxicillin	88	(10.3)	43	(11.2)	52	(11.0)
amoxicillin (+) clavulanate potassium	61	(7.1)	30	(7.8)	40	(8.5)
azithromycin	113	(13.2)	54	(14.1)	60	(12.7)
ceftriaxone	47	(5.5)	22	(5.7)	21	(4.4)
ciprofloxacin	52	(6.1)	17	(4.4)	29	(6.1)
doxycycline	61	(7.1)	18	(4.7)	28	(5.9)
metronidazole	44	(5.1)	19	(5.0)	28	(5.9)
penicillin G benzathine	48	(5.6)	19	(5.0)	29	(6.1)
sulfamethoxazole (+) trimethoprim	69	(8.1)	48	(12.5)	42	(8.9)
antimycotics for systemic use	**25**	**(2.9)**	**22**	**(5.7)**	**12**	**(2.5)**
fluconazole	23	(2.7)	22	(5.7)	11	(2.3)
antivirals for systemic use	**140**	**(16.4)**	**83**	**(21.7)**	**87**	**(18.4)**
acyclovir	43	(5.0)	16	(4.2)	24	(5.1)
valacyclovir hydrochloride	24	(2.8)	21	(5.5)	15	(3.2)
vaccines	**262**	**(30.6)**	**97**	**(25.3)**	**147**	**(31.1)**
hepatitis B virus vaccine (unspecified)	45	(5.3)	8	(2.1)	25	(5.3)
influenza virus sAg 3v vaccine inactivated	33	(3.9)	23	(6.0)	20	(4.2)
influenza virus split virion 3v vaccine inactivated	44	(5.1)	14	(3.7)	28	(5.9)
influenza virus vaccine (unspecified)	105	(12.3)	40	(10.4)	66	(14.0)
blood and blood forming organs						
antianemic preparations	**28**	**(3.3)**	**24**	**(6.3)**	**21**	**(4.4)**
blood substitutes and perfusion solutions	**25**	**(2.9)**	**19**	**(5.0)**	**22**	**(4.7)**

Subjects With Specific Concomitant Medications (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	(%)
cardiovascular system						
agents acting on the renin-angiotensin system	**61**	**(7.1)**	**20**	**(5.2)**	**23**	**(4.9)**
lipid modifying agents	**50**	**(5.8)**	**27**	**(7.0)**	**34**	**(7.2)**
dermatologicals						
antifungals for dermatological use	**84**	**(9.8)**	**44**	**(11.5)**	**39**	**(8.3)**
clotrimazole	26	(3.0)	21	(5.5)	12	(2.5)
corticosteroids, dermatological preparations	**61**	**(7.1)**	**28**	**(7.3)**	**25**	**(5.3)**
genitourinary system and sex hormones						
sex hormones and modulators of the genital system	**44**	**(5.1)**	**17**	**(4.4)**	**26**	**(5.5)**
urologicals	**36**	**(4.2)**	**19**	**(5.0)**	**22**	**(4.7)**
musculoskeletal system						
antiinflammatory and antirheumatic products	**245**	**(28.7)**	**105**	**(27.4)**	**132**	**(28.0)**
ibuprofen	162	(18.9)	69	(18.0)	86	(18.2)
nervous system						
analgesics	**347**	**(40.6)**	**136**	**(35.5)**	**182**	**(38.6)**
acetaminophen	234	(27.4)	70	(18.3)	116	(24.6)
antiepileptics	**38**	**(4.4)**	**19**	**(5.0)**	**19**	**(4.0)**
psychoanaleptics	**89**	**(10.4)**	**41**	**(10.7)**	**51**	**(10.8)**
psycholeptics	**107**	**(12.5)**	**53**	**(13.8)**	**89**	**(18.9)**
respiratory system						
antihistamines for systemic use	**165**	**(19.3)**	**72**	**(18.8)**	**126**	**(26.7)**
cetirizine hydrochloride	34	(4.0)	22	(5.7)	37	(7.8)
diphenhydramine hydrochloride	46	(5.4)	14	(3.7)	17	(3.6)
loratadine	46	(5.4)	8	(2.1)	34	(7.2)
cough and cold preparations	**109**	**(12.7)**	**37**	**(9.7)**	**53**	**(11.2)**
drugs for obstructive airway diseases	**73**	**(8.5)**	**46**	**(12.0)**	**42**	**(8.9)**
albuterol	32	(3.7)	20	(5.2)	17	(3.6)
nasal preparations	**47**	**(5.5)**	**15**	**(3.9)**	**20**	**(4.2)**
systemic hormonal preparations, excl. sex hormones and insulins						
corticosteroids for systemic use	**82**	**(9.6)**	**29**	**(7.6)**	**66**	**(14.0)**
various						

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Subjects With Specific Concomitant Medications
(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	(%)
various						
all other therapeutic products	**70**	**(8.2)**	**28**	**(7.3)**	**42**	**(8.9)**

Every subject is counted a single time for each applicable specific concomitant medication. A subject with multiple concomitant medications within a medication category is counted a single time for that category.

A medication class or specific medication 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.

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Table 2.7.4-trtmtnve96wk: 12
Subjects With Specific Concomitant Medications
(Incidence ≥5% in One or More Treatment Groups)
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	
	n	(%)	n	(%)
Subjects in population	472		472	
With one or more concomitant medications	423	(89.6)	424	(89.8)
With no concomitant medication	49	(10.4)	48	(10.2)
alimentary tract and metabolism				
antidiarrheals, intestinal antiinflammatory/antiinfective agents	**42**	**(8.9)**	**40**	**(8.5)**
drugs for acid related disorders	**54**	**(11.4)**	**65**	**(13.8)**
drugs for functional gastrointestinal disorders	**30**	**(6.4)**	**35**	**(7.4)**
vitamins	**94**	**(19.9)**	**89**	**(18.9)**
vitamins (unspecified)	26	(5.5)	34	(7.2)
antiinfectives for systemic use				
antibacterials for systemic use	**234**	**(49.6)**	**243**	**(51.5)**
amoxicillin	51	(10.8)	52	(11.0)
amoxicillin (+) clavulanate potassium	36	(7.6)	40	(8.5)
azithromycin	66	(14.0)	60	(12.7)
ceftriaxone	27	(5.7)	21	(4.4)
ciprofloxacin	28	(5.9)	29	(6.1)
doxycycline	31	(6.6)	28	(5.9)
metronidazole	23	(4.9)	28	(5.9)
penicillin G benzathine	27	(5.7)	29	(6.1)
sulfamethoxazole (+) trimethoprim	40	(8.5)	42	(8.9)
antivirals for systemic use	**77**	**(16.3)**	**87**	**(18.4)**
acyclovir	23	(4.9)	24	(5.1)
vaccines	**150**	**(31.8)**	**147**	**(31.1)**
hepatitis B virus vaccine (unspecified)	26	(5.5)	25	(5.3)
influenza virus split virion 3v vaccine inactivated	20	(4.2)	28	(5.9)
influenza virus vaccine (unspecified)	58	(12.3)	66	(14.0)
cardiovascular system				
agents acting on the renin-angiotensin system	**33**	**(7.0)**	**23**	**(4.9)**
lipid modifying agents	**29**	**(6.1)**	**34**	**(7.2)**
dermatologicals				
antifungals for dermatological use	**48**	**(10.2)**	**39**	**(8.3)**
corticosteroids, dermatological preparations	**42**	**(8.9)**	**25**	**(5.3)**
genitourinary system and sex hormones				
sex hormones and modulators of the genital system	**31**	**(6.6)**	**26**	**(5.5)**
urologicals	**24**	**(5.1)**	**22**	**(4.7)**
musculoskeletal system				
antiinflammatory and antirheumatic products	**143**	**(30.3)**	**132**	**(28.0)**

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Subjects With Specific Concomitant Medications
(Incidence ≥5% in One or More Treatment Groups)
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	
	n	(%)	n	(%)
musculoskeletal system				
antiinflammatory and antirheumatic products	**143**	**(30.3)**	**132**	**(28.0)**
ibuprofen	88	(18.6)	86	(18.2)
nervous system				
analgesics	**208**	**(44.1)**	**182**	**(38.6)**
acetaminophen	142	(30.1)	116	(24.6)
anesthetics	**27**	**(5.7)**	**22**	**(4.7)**
antiepileptics	**24**	**(5.1)**	**19**	**(4.0)**
psychoanaleptics	**55**	**(11.7)**	**51**	**(10.8)**
psycholeptics	**56**	**(11.9)**	**89**	**(18.9)**
respiratory system				
antihistamines for systemic use	**92**	**(19.5)**	**126**	**(26.7)**
cetirizine hydrochloride	18	(3.8)	37	(7.8)
loratadine	29	(6.1)	34	(7.2)
cough and cold preparations	**69**	**(14.6)**	**53**	**(11.2)**
drugs for obstructive airway diseases	**43**	**(9.1)**	**42**	**(8.9)**
nasal preparations	**36**	**(7.6)**	**20**	**(4.2)**
systemic hormonal preparations, excl. sex hormones and insulins				
corticosteroids for systemic use	**52**	**(11.0)**	**66**	**(14.0)**
various				
all other therapeutic products	**40**	**(8.5)**	**42**	**(8.9)**

Every subject is counted a single time for each applicable specific concomitant medication. A subject with multiple concomitant medications within a medication category is counted a single time for that category.

A medication class or specific medication 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.

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.

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2 ADVERSE EVENTS

This section provides the results of the integrated analysis of safety that was performed in 2 population pools, the MSP and SSP. 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: P007V01MK1439] [Ref. 5.3.5.1: P018MK1439] [Ref. 5.3.5.1: P021MK1439A].

The trials and treatment groups included in each pool are depicted in [Figure 2.7.4-trtmtnve96wk: 1].

2.1 Analysis of Adverse Events in the Main Safety Pool (P007, P018, and P021)

2.1.1 Common Adverse Events

Through Week 96, the incidence of AEs, drug-related AEs, and SAEs for participants in the MSP were similar for the Main Combined DOR group and the Main DRV+r group [Table 2.7.4-trtmtnve96wk: 13]. The incidence of participants discontinuing study medication due to AEs and drug-related AEs was also similar for these treatment groups.

Compared with the Main Combined EFV group, a lower proportion of participants in the Main Combined DOR group reported drug-related AEs, AEs that led to discontinuation, and drug-related AEs that led to discontinuation. Similar proportions of participants reported AEs in other categories in both treatment groups.

The most frequently reported (≥5%) AEs among participants in the Main Combined DOR group were (in descending order of frequency) diarrhea, headache, nasopharyngitis, upper respiratory tract infection, nausea, and dizziness [Table 2.7.4-trtmtnve96wk: 14]. The AE of diarrhea was more frequently observed among participants treated with DRV+r (23.8%) than among those treated with DOR (15.1%). The AE of dizziness was more frequently observed among participants treated with EFV (36.2%) through Week 96 than among those treated with DOR (8.5%). In addition, the AEs of abnormal dreams and of rash were more frequently observed among participants treated with EFV (13.3% and 11.4%) than those treated with DOR (3.5% and 3.5%).

Results for AEs through Week 96 are similar to those previously reported for Week 48 in the original Application.

A summary of AEs reported at an incidence >0% is provided in [Table 5.3.5.3.3-trtmtnve96wk: 61], and a summary with an incidence ≥10% is provided in [Table 5.3.5.3.3-trtmtnve96wk: 63].

Summaries of AEs for all data available through the data cutoff dates of P018 and P021 are provided in [Table 5.3.5.3.3-trtmtnve96wk: 60]. Preliminary results show that the incidence of AEs is consistent across base-study treatment groups, as are the incidences of SAEs (≤2.0% across groups), and discontinuations due to AEs (≤0.2% across groups) and drug-related AEs (0.0% in all groups).

Drug-Related Adverse Events (Overall)

In the MSP, the incidences of drug-related AEs were similar in the Main Combined DOR (32.4%) and Main DRV+r (32.1%), and higher in the Main Combined EFV (63.3%) [Table 2.7.4-trtmtnve96wk: 15]. The most frequently reported (≥5%) drug-related AEs for the Main Combined DOR group through Week 96 (in descending order of frequency) were nausea and dizziness.

Drug-related diarrhea was reported for a lower proportion of participants in the Main Combined DOR group (4.2%) and Main Combined EFV group (5.9%) than in the Main DRV+r (13.1%) group. Similarly, the incidence of drug-related dizziness was lower among participants in the Main Combined DOR (5.1%) and Main DRV+r (1.8%) groups than among participants in the Main Combined EFV group (30.9%), as was the incidence of drug-related rash (0.9%, 0.5%, and 7.2%, respectively) and drug-related abnormal dreams (3.3%, 0.3%, and 11.2%, respectively).

The incidence of all other drug-related AEs was comparable across each of the 3 groups.

These results for drug-related AEs reported for the MSP are consistent with those observed when drug-related AEs were analyzed based on a pooled analysis of P018 and P021 only (ie, with P007 results excluded) [Table 5.3.5.3.3-trtmtnve96wk: 72].

Drug-related AEs of moderate or severe intensity were reported for 9.5% of participants in the Main Combined DOR group, 8.4% in the Main DRV+r group, and 26.7% of participants in the Main Combined EFV group [Table 2.7.4-trtmtnve96wk: 16].

MSP results for drug-related AEs through Week 96 are similar to those previously reported through Week 48 in the original Application.

Drug-related AEs (>0% incidence) are provided for the MSP in [Table 5.3.5.3.3-trtmtnve96wk: 70]. Drug-related AE of moderate or severe intensity (>0% incidence) are provided for the MSP in [Table 5.3.5.3.3-trtmtnve96wk: 68].

Table 2.7.4-trtmtnve96wk: 13
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).

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Table 2.7.4-trtmtnve96wk: 14
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]

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Table 2.7.4-trtmtnve96wk: 15
Subjects With Drug-Related Adverse Events
(Incidence ≥2% in One or More Treatment Groups)
Overall Drug Related
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 drug-related adverse events	277	(32.4)	123	(32.1)	299	(63.3)
with no drug-related adverse events	578	(67.6)	260	(67.9)	173	(36.7)
Ear and labyrinth disorders	**1**	**(0.1)**	**0**	**(0.0)**	**11**	**(2.3)**
Gastrointestinal disorders	**114**	**(13.3)**	**88**	**(23.0)**	**81**	**(17.2)**
Diarrhoea	36	(4.2)	50	(13.1)	28	(5.9)
Nausea	53	(6.2)	31	(8.1)	32	(6.8)
Vomiting	15	(1.8)	5	(1.3)	13	(2.8)
General disorders and administration site conditions	**49**	**(5.7)**	**13**	**(3.4)**	**35**	**(7.4)**
Fatigue	35	(4.1)	8	(2.1)	16	(3.4)
Investigations	**15**	**(1.8)**	**6**	**(1.6)**	**21**	**(4.4)**
Metabolism and nutrition disorders	**12**	**(1.4)**	**9**	**(2.3)**	**17**	**(3.6)**
Nervous system disorders	**97**	**(11.3)**	**19**	**(5.0)**	**177**	**(37.5)**
Dizziness	44	(5.1)	7	(1.8)	146	(30.9)
Headache	40	(4.7)	10	(2.6)	23	(4.9)
Somnolence	12	(1.4)	1	(0.3)	26	(5.5)
Psychiatric disorders	**83**	**(9.7)**	**13**	**(3.4)**	**128**	**(27.1)**
Abnormal dreams	28	(3.3)	1	(0.3)	53	(11.2)
Insomnia	27	(3.2)	7	(1.8)	22	(4.7)
Nightmare	16	(1.9)	3	(0.8)	24	(5.1)
Sleep disorder	13	(1.5)	1	(0.3)	16	(3.4)
Skin and subcutaneous tissue disorders	**30**	**(3.5)**	**17**	**(4.4)**	**71**	**(15.0)**

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Subjects With Drug-Related Adverse Events
(Incidence ≥2% in One or More Treatment Groups)
Overall Drug Related
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	(%)
Skin and subcutaneous tissue disorders	**30**	**(3.5)**	**17**	**(4.4)**	**71**	**(15.0)**
Rash	8	(0.9)	2	(0.5)	34	(7.2)

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]

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Table 2.7.4-trtmtnve96wk: 16
Subjects With Drug-Related Adverse Events of Moderate or Severe Intensities
(Incidence ≥2% in One or More Treatment Groups)
Overall Drug Related
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 drug-related adverse events	81	(9.5)	32	(8.4)	126	(26.7)
with no drug-related adverse events	774	(90.5)	351	(91.6)	346	(73.3)
Gastrointestinal disorders	**22**	**(2.6)**	**12**	**(3.1)**	**13**	**(2.8)**
Diarrhoea	10	(1.2)	8	(2.1)	4	(0.8)
Investigations	**7**	**(0.8)**	**4**	**(1.0)**	**12**	**(2.5)**
Nervous system disorders	**15**	**(1.8)**	**6**	**(1.6)**	**46**	**(9.7)**
Dizziness	7	(0.8)	1	(0.3)	34	(7.2)
Psychiatric disorders	**27**	**(3.2)**	**5**	**(1.3)**	**40**	**(8.5)**
Abnormal dreams	3	(0.4)	0	(0.0)	14	(3.0)
Skin and subcutaneous tissue disorders	**9**	**(1.1)**	**5**	**(1.3)**	**38**	**(8.1)**
Rash	2	(0.2)	1	(0.3)	19	(4.0)

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.
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]

2.1.2 Deaths

A total of 11 deaths were reported in the MSP through Week 96 [Table 2.7.4-trtmtnve96wk: 5]. None of the deaths was considered by the investigators to be related to study drug.

All deaths occurred in P018 and P021. All deaths are further described below and in the individual CSRs ([Ref. 5.3.5.1: P007V01MK1439], [Ref. 5.3.5.1: P018MK1439], [Ref. 5.3.5.1: P021MK1439A]).

- **P018**:
  Two participants, 1 in each group, died during while on treatment during the base study. Each of these deaths was considered by the investigator to be unrelated to study medication:

  – DOR group: 1 participant died of natural causes

  – DRV+r group: 1 participant died of pulmonary embolism with associated right leg deep venous thrombosis

  In addition, 3 participants (2 in the DOR group, 1 in the DRV+r group) died >14 days after the last recorded dose of study medication. All 3 of these deaths were considered by the investigator to be unrelated to study medication.

  – DOR group: 1 participant died from myocardial infarction, and 1 participant died from cardiac failure. Both participants had not previously withdrawn or discontinued treatment, and, given the amount of study medication dispensed at the visit immediately prior to each death, their deaths are presumed to have occurred during treatment.

  – DRV+r group: 1 participant died from Hodgkin's disease. The death occurred approximately 14 weeks after the participant's last recorded dose (DRV+r) and withdrawal of consent from the trial.

- **P021**:
  Two participants, both in the EFV/FTC/TDF group, died while on treatment during the base study. Neither death was considered by the investigator to be related to study medication:

  – EFV/FTC/TDF group: 1 participant died of unknown causes; 1 participant committed suicide.

  In addition, 4 participants (2 in the DOR/3TC/TDF group, 2 in the EFV/FTC/TDF group) died >14 days after the last recorded dose of study medication. Given the amount of study medication dispensed at the last visit, these deaths are presumed to have occurred during treatment. All 4 of these deaths were considered by the investigator to be unrelated to study medication.

  – DOR/3TC/TDF group: 1 participant died from unknown causes, and 1 died from an accidental cocaine overdose.

  – EFV/FTC/TDF group: 1 participant died as a result of a motor vehicle accident, and 1 died from natural causes.

Listings of participants with AEs resulting in death through Week 96, through the data cutoff date, and through the data cutoff date including post-study (n=0) are in [Table 5.3.5.3.3-trtmtnve96wk: 74] [Table 5.3.5.3.3-trtmtnve96wk: 73] [Table 5.3.5.3.3-trtmtnve96wk: 75].

2.1.3 Other Serious Adverse Events

Through Week 96, similar proportions of participants in the 3 groups in the MSP reported SAEs [Table 2.7.4-trtmtnve96wk: 17]. The most frequently reported SAE was pneumonia, reported in 3 participants in the Main Combined DOR (0.4%), 1 participant in the Main DRV+r (0.3%), and in 1 participant in the Main Combined EFV (0.2%). No other individual SAE was reported in >2 participants in any group (Main Combined DOR, Main DRV+r, or Main Combined EFV). SAEs reported for 2 participants in any group included: appendicitis, anogenital warts, basal cell carcinoma, suicidal ideation, postprocedural hemorrhage, postprocedural infection, tuberculosis, and back pain. All other SAEs occurred in 1 participant each [Table 2.7.4-trtmtnve96wk: 17].

These Week 96 results are similar to those previously reported in the original Application for SAEs through Week 48.

A summary of SAEs through the data cutoff dates of P018 and P021 with incidence >0% is provided in [Table 5.3.5.3.3-trtmtnve96wk: 77]. Listings of SAEs for participants in the MSP through Week 96 and those being reported through the data cutoff dates of P018 and P021 are in [Table 5.3.5.3.3-trtmtnve96wk: 83] [Table 5.3.5.3.3-trtmtnve96wk: 84]. Narratives for participants with SAEs are provided in the individual CSRs [Ref. 5.3.5.1: P007V01MK1439: 16.2.7] [Ref. 5.3.5.1: P018MK1439: 16.2.7.2] [Ref. 5.3.5.1: P021MK1439A: 16.2.7.2].

Serious Drug-Related Adverse Events

Through Week 96, drug-related SAEs were reported for 2 participants in the Main Combined DOR, 1 participant in the Main DRV+r, and 7 participants in the Main Combined EFV group [Table 2.7.4-trtmtnve96wk: 18]. No specific drug-related SAE was reported for >1 participant, either within a group, or across groups.

In the Main Combined DOR group, the drug-related SAEs were concomitant SAEs of nausea and vomiting in 1 participant, and concomitant SAEs of asthenia, insomnia, and nightmares in 1 participant [Table 2.7.4-trtmtnve96wk: 18]. The SAEs of drug-related nausea and vomiting both resolved without dose interruption or modification. For the participant with drug-related SAEs of asthenia, insomnia, and nightmares, study drug was discontinued; the nightmares resolved, and the asthenia and insomnia were continuing.

In the Main DRV+r group, 1 participant experienced a drug-related SAE of peripheral edema.

In the Main Combined EFV group, the drug-related SAEs were dizziness, suicidal ideation, hepatitis toxic, hypertriglyceridemia, rash generalized, rash macular, and rash maculo-papular.

These results for drug-related SAEs through Week 96 are similar to those noted in the original Application through Week 48.

Narratives for these cases are found in the individual CSRs [Ref. 5.3.5.1: P007V01MK1439: 16.2.7] [Ref. 5.3.5.1: P018MK1439: 16.2.7.2] [Ref. 5.3.5.1: P021MK1439A: 16.2.7.2].

As noted above, listings of SAEs by participant (whether or not the SAEs were considered drug-related) through Week 96 and through the data cutoff dates are in [Table 5.3.5.3.3-trtmtnve96wk: 83] [Table 5.3.5.3.3-trtmtnve96wk: 84].

Table 2.7.4-trtmtnve96wk: 17
Subjects With Serious Adverse Events
(Incidence >0% 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 serious adverse events	59	(6.9)	33	(8.6)	43	(9.1)
with no serious adverse events	796	(93.1)	350	(91.4)	429	(90.9)
Blood and lymphatic system disorders	**1**	**(0.1)**	**0**	**(0.0)**	**0**	**(0.0)**
Normocytic anaemia	1	(0.1)	0	(0.0)	0	(0.0)
Cardiac disorders	**2**	**(0.2)**	**0**	**(0.0)**	**0**	**(0.0)**
Supraventricular tachycardia	1	(0.1)	0	(0.0)	0	(0.0)
Tachycardia	1	(0.1)	0	(0.0)	0	(0.0)
Ear and labyrinth disorders	**1**	**(0.1)**	**1**	**(0.3)**	**0**	**(0.0)**
Deafness	1	(0.1)	0	(0.0)	0	(0.0)
Vertigo	0	(0.0)	1	(0.3)	0	(0.0)
Endocrine disorders	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.2)**
Thyroid cyst	0	(0.0)	0	(0.0)	1	(0.2)
Gastrointestinal disorders	**5**	**(0.6)**	**3**	**(0.8)**	**1**	**(0.2)**
Abdominal distension	0	(0.0)	1	(0.3)	0	(0.0)
Abdominal pain	0	(0.0)	1	(0.3)	0	(0.0)
Anal fistula	1	(0.1)	1	(0.3)	0	(0.0)
Anal skin tags	1	(0.1)	0	(0.0)	0	(0.0)
Colitis	1	(0.1)	0	(0.0)	1	(0.2)
Inguinal hernia	0	(0.0)	1	(0.3)	0	(0.0)
Nausea	1	(0.1)	0	(0.0)	0	(0.0)
Oesophageal obstruction	1	(0.1)	0	(0.0)	0	(0.0)
Vomiting	1	(0.1)	0	(0.0)	0	(0.0)
General disorders and administration site conditions	**2**	**(0.2)**	**2**	**(0.5)**	**1**	**(0.2)**
Asthenia	1	(0.1)	0	(0.0)	0	(0.0)
Death	1	(0.1)	0	(0.0)	1	(0.2)
Non-cardiac chest pain	0	(0.0)	1	(0.3)	0	(0.0)
Oedema peripheral	0	(0.0)	1	(0.3)	0	(0.0)
Hepatobiliary disorders	**4**	**(0.5)**	**0**	**(0.0)**	**1**	**(0.2)**
Bile duct stone	1	(0.1)	0	(0.0)	0	(0.0)
Cholangitis	1	(0.1)	0	(0.0)	0	(0.0)
Cholecystitis	1	(0.1)	0	(0.0)	0	(0.0)
Cholecystitis acute	1	(0.1)	0	(0.0)	0	(0.0)
Hepatitis toxic	0	(0.0)	0	(0.0)	1	(0.2)

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Subjects With Serious Adverse Events
(Incidence >0% 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	(%)
Infections and infestations	**20**	**(2.3)**	**12**	**(3.1)**	**16**	**(3.4)**
Abdominal abscess	1	(0.1)	0	(0.0)	1	(0.2)
Acute hepatitis C	1	(0.1)	0	(0.0)	0	(0.0)
Acute sinusitis	0	(0.0)	1	(0.3)	0	(0.0)
Anal infection	1	(0.1)	0	(0.0)	0	(0.0)
Appendicitis	2	(0.2)	0	(0.0)	1	(0.2)
Atypical pneumonia	0	(0.0)	1	(0.3)	0	(0.0)
Bronchitis	0	(0.0)	1	(0.3)	0	(0.0)
Cellulitis	1	(0.1)	1	(0.3)	0	(0.0)
Cellulitis staphylococcal	1	(0.1)	0	(0.0)	0	(0.0)
Clostridium difficile infection	0	(0.0)	0	(0.0)	1	(0.2)
Diverticulitis	0	(0.0)	0	(0.0)	1	(0.2)
Endometritis	1	(0.1)	0	(0.0)	1	(0.2)
Epididymitis	0	(0.0)	0	(0.0)	1	(0.2)
Gastroenteritis	1	(0.1)	0	(0.0)	0	(0.0)
Gastroenteritis shigella	1	(0.1)	0	(0.0)	0	(0.0)
Gastrointestinal viral infection	0	(0.0)	0	(0.0)	1	(0.2)
Hepatitis A	1	(0.1)	0	(0.0)	1	(0.2)
Hepatitis C	0	(0.0)	0	(0.0)	1	(0.2)
Infectious colitis	0	(0.0)	0	(0.0)	1	(0.2)
Influenza	0	(0.0)	1	(0.3)	0	(0.0)
Lymphadenitis bacterial	0	(0.0)	0	(0.0)	1	(0.2)
Meningitis tuberculous	0	(0.0)	1	(0.3)	0	(0.0)
Nasopharyngitis	1	(0.1)	0	(0.0)	0	(0.0)
Necrotising fasciitis	1	(0.1)	0	(0.0)	0	(0.0)
Neurosyphilis	1	(0.1)	0	(0.0)	0	(0.0)
Oophoritis	0	(0.0)	0	(0.0)	1	(0.2)
Oral bacterial infection	0	(0.0)	0	(0.0)	1	(0.2)
Orchitis	0	(0.0)	1	(0.3)	0	(0.0)
Parotitis	1	(0.1)	0	(0.0)	0	(0.0)
Perirectal abscess	1	(0.1)	0	(0.0)	0	(0.0)
Pharyngitis	0	(0.0)	1	(0.3)	0	(0.0)
Pharyngotonsillitis	0	(0.0)	0	(0.0)	1	(0.2)
Pilonidal cyst	0	(0.0)	0	(0.0)	1	(0.2)
Pneumonia	3	(0.4)	1	(0.3)	1	(0.2)
Pneumonia bacterial	0	(0.0)	0	(0.0)	1	(0.2)
Post procedural infection	0	(0.0)	2	(0.5)	0	(0.0)
Respiratory syncytial virus infection	0	(0.0)	0	(0.0)	1	(0.2)
Scrotal abscess	0	(0.0)	1	(0.3)	0	(0.0)
Sepsis	0	(0.0)	0	(0.0)	1	(0.2)
Sinusitis	0	(0.0)	0	(0.0)	1	(0.2)
Subcutaneous abscess	1	(0.1)	0	(0.0)	0	(0.0)

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Subjects With Serious Adverse Events
(Incidence >0% 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	(%)
Infections and infestations	**20**	**(2.3)**	**12**	**(3.1)**	**16**	**(3.4)**
Tuberculosis	0	(0.0)	2	(0.5)	0	(0.0)
Tuberculosis of central nervous system	0	(0.0)	1	(0.3)	0	(0.0)
Viral infection	1	(0.1)	0	(0.0)	0	(0.0)
Injury, poisoning and procedural complications	**6**	**(0.7)**	**6**	**(1.6)**	**5**	**(1.1)**
Accidental overdose	0	(0.0)	1	(0.3)	0	(0.0)
Alcohol poisoning	0	(0.0)	0	(0.0)	1	(0.2)
Ankle fracture	0	(0.0)	0	(0.0)	1	(0.2)
Carbon monoxide poisoning	1	(0.1)	0	(0.0)	0	(0.0)
Femur fracture	1	(0.1)	0	(0.0)	0	(0.0)
Foreign body in gastrointestinal tract	0	(0.0)	0	(0.0)	1	(0.2)
Jaw fracture	1	(0.1)	0	(0.0)	0	(0.0)
Post procedural haemorrhage	1	(0.1)	2	(0.5)	0	(0.0)
Rectal injury	0	(0.0)	1	(0.3)	0	(0.0)
Subdural haematoma	0	(0.0)	1	(0.3)	1	(0.2)
Tendon rupture	0	(0.0)	0	(0.0)	1	(0.2)
Traumatic haemothorax	1	(0.1)	0	(0.0)	0	(0.0)
Traumatic intracranial haemorrhage	0	(0.0)	1	(0.3)	0	(0.0)
Wrist fracture	1	(0.1)	0	(0.0)	0	(0.0)
Investigations	**1**	**(0.1)**	**0**	**(0.0)**	**0**	**(0.0)**
Transaminases increased	1	(0.1)	0	(0.0)	0	(0.0)
Metabolism and nutrition disorders	**1**	**(0.1)**	**1**	**(0.3)**	**1**	**(0.2)**
Hypertriglyceridaemia	0	(0.0)	0	(0.0)	1	(0.2)
Hyponatraemia	0	(0.0)	1	(0.3)	0	(0.0)
Hypovolaemia	1	(0.1)	0	(0.0)	0	(0.0)
Musculoskeletal and connective tissue disorders	**2**	**(0.2)**	**3**	**(0.8)**	**3**	**(0.6)**
Back pain	0	(0.0)	2	(0.5)	0	(0.0)
Costochondritis	0	(0.0)	0	(0.0)	1	(0.2)
Intervertebral disc protrusion	1	(0.1)	0	(0.0)	0	(0.0)
Muscle spasms	0	(0.0)	0	(0.0)	1	(0.2)
Muscular weakness	1	(0.1)	0	(0.0)	0	(0.0)
Rhabdomyolysis	0	(0.0)	1	(0.3)	1	(0.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**9**	**(1.1)**	**3**	**(0.8)**	**4**	**(0.8)**
Anal squamous cell carcinoma	1	(0.1)	1	(0.3)	0	(0.0)

Subjects With Serious Adverse Events
(Incidence >0% 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	(%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**9**	**(1.1)**	**3**	**(0.8)**	**4**	**(0.8)**
Anogenital warts	2	(0.2)	0	(0.0)	0	(0.0)
B-cell unclassifiable lymphoma high grade	1	(0.1)	0	(0.0)	0	(0.0)
Basal cell carcinoma	1	(0.1)	0	(0.0)	2	(0.4)
Hodgkin's disease	1	(0.1)	0	(0.0)	0	(0.0)
Kaposi's sarcoma	1	(0.1)	0	(0.0)	1	(0.2)
Nervous system neoplasm benign	0	(0.0)	0	(0.0)	1	(0.2)
Pancreatic carcinoma	0	(0.0)	1	(0.3)	0	(0.0)
Prostate cancer	1	(0.1)	0	(0.0)	0	(0.0)
Squamous cell carcinoma	1	(0.1)	0	(0.0)	0	(0.0)
Squamous cell carcinoma of skin	0	(0.0)	1	(0.3)	0	(0.0)
Squamous cell carcinoma of the tongue	1	(0.1)	0	(0.0)	0	(0.0)
Nervous system disorders	**3**	**(0.4)**	**4**	**(1.0)**	**4**	**(0.8)**
Aphasia	0	(0.0)	1	(0.3)	0	(0.0)
Cerebrovascular accident	1	(0.1)	0	(0.0)	0	(0.0)
Dizziness	0	(0.0)	0	(0.0)	1	(0.2)
Facial paralysis	0	(0.0)	1	(0.3)	0	(0.0)
Headache	1	(0.1)	0	(0.0)	0	(0.0)
Hemiparesis	1	(0.1)	0	(0.0)	1	(0.2)
Hypoaesthesia	1	(0.1)	0	(0.0)	0	(0.0)
Osmotic demyelination syndrome	0	(0.0)	1	(0.3)	0	(0.0)
Peroneal nerve palsy	0	(0.0)	0	(0.0)	1	(0.2)
Seizure	1	(0.1)	0	(0.0)	0	(0.0)
Syncope	0	(0.0)	1	(0.3)	1	(0.2)
Pregnancy, puerperium and perinatal conditions	**2**	**(0.2)**	**0**	**(0.0)**	**1**	**(0.2)**
Abortion spontaneous	1	(0.1)	0	(0.0)	1	(0.2)
Post abortion haemorrhage	1	(0.1)	0	(0.0)	0	(0.0)
Psychiatric disorders	**6**	**(0.7)**	**2**	**(0.5)**	**5**	**(1.1)**
Bipolar I disorder	1	(0.1)	0	(0.0)	0	(0.0)
Completed suicide	0	(0.0)	0	(0.0)	1	(0.2)
Depression	0	(0.0)	1	(0.3)	1	(0.2)
Drug abuse	1	(0.1)	0	(0.0)	0	(0.0)
Insomnia	1	(0.1)	0	(0.0)	0	(0.0)
Nightmare	1	(0.1)	0	(0.0)	0	(0.0)
Psychotic disorder	1	(0.1)	0	(0.0)	0	(0.0)
Schizoaffective disorder depressive type	0	(0.0)	1	(0.3)	0	(0.0)

Subjects With Serious Adverse Events
(Incidence >0% 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	**6**	**(0.7)**	**2**	**(0.5)**	**5**	**(1.1)**
Substance-induced mood disorder	1	(0.1)	0	(0.0)	0	(0.0)
Suicidal ideation	1	(0.1)	0	(0.0)	2	(0.4)
Suicide attempt	0	(0.0)	0	(0.0)	1	(0.2)
Renal and urinary disorders	**1**	**(0.1)**	**1**	**(0.3)**	**2**	**(0.4)**
Acute kidney injury	1	(0.1)	0	(0.0)	1	(0.2)
Nephrolithiasis	0	(0.0)	1	(0.3)	0	(0.0)
Nephrotic syndrome	0	(0.0)	0	(0.0)	1	(0.2)
Respiratory, thoracic and mediastinal disorders	**1**	**(0.1)**	**3**	**(0.8)**	**1**	**(0.2)**
Asthma	1	(0.1)	0	(0.0)	1	(0.2)
Bronchospasm	0	(0.0)	1	(0.3)	0	(0.0)
Chronic obstructive pulmonary disease	0	(0.0)	1	(0.3)	0	(0.0)
Pulmonary embolism	0	(0.0)	1	(0.3)	0	(0.0)
Stridor	0	(0.0)	1	(0.3)	0	(0.0)
Skin and subcutaneous tissue disorders	**1**	**(0.1)**	**0**	**(0.0)**	**3**	**(0.6)**
Psoriasis	1	(0.1)	0	(0.0)	0	(0.0)
Rash generalised	0	(0.0)	0	(0.0)	1	(0.2)
Rash macular	0	(0.0)	0	(0.0)	1	(0.2)
Rash maculo-papular	0	(0.0)	0	(0.0)	1	(0.2)
Social circumstances	**1**	**(0.1)**	**0**	**(0.0)**	**0**	**(0.0)**
Drug abuser	1	(0.1)	0	(0.0)	0	(0.0)
Vascular disorders	**1**	**(0.1)**	**0**	**(0.0)**	**2**	**(0.4)**
Deep vein thrombosis	1	(0.1)	0	(0.0)	1	(0.2)
Malignant hypertension	0	(0.0)	0	(0.0)	1	(0.2)

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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).

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Table 2.7.4-trtmtnve96wk: 18
Subjects With Serious Drug-Related Adverse Events
(Incidence >0% in One or More Treatment Groups)
Overall Drug Related
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 serious drug-related adverse events	2	(0.2)	1	(0.3)	7	(1.5)
with no serious drug-related adverse events	853	(99.8)	382	(99.7)	465	(98.5)
Gastrointestinal disorders	**1**	**(0.1)**	**0**	**(0.0)**	**0**	**(0.0)**
Nausea	1	(0.1)	0	(0.0)	0	(0.0)
Vomiting	1	(0.1)	0	(0.0)	0	(0.0)
General disorders and administration site conditions	**1**	**(0.1)**	**1**	**(0.3)**	**0**	**(0.0)**
Asthenia	1	(0.1)	0	(0.0)	0	(0.0)
Oedema peripheral	0	(0.0)	1	(0.3)	0	(0.0)
Hepatobiliary disorders	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.2)**
Hepatitis toxic	0	(0.0)	0	(0.0)	1	(0.2)
Metabolism and nutrition disorders	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.2)**
Hypertriglyceridaemia	0	(0.0)	0	(0.0)	1	(0.2)
Nervous system disorders	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.2)**
Dizziness	0	(0.0)	0	(0.0)	1	(0.2)
Psychiatric disorders	**1**	**(0.1)**	**0**	**(0.0)**	**1**	**(0.2)**
Insomnia	1	(0.1)	0	(0.0)	0	(0.0)
Nightmare	1	(0.1)	0	(0.0)	0	(0.0)
Suicidal ideation	0	(0.0)	0	(0.0)	1	(0.2)
Skin and subcutaneous tissue disorders	**0**	**(0.0)**	**0**	**(0.0)**	**3**	**(0.6)**
Rash generalised	0	(0.0)	0	(0.0)	1	(0.2)
Rash macular	0	(0.0)	0	(0.0)	1	(0.2)

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Subjects With Serious Drug-Related Adverse Events
(Incidence >0% in One or More Treatment Groups)
Overall Drug Related
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	(%)
Skin and subcutaneous tissue disorders	**0**	**(0.0)**	**0**	**(0.0)**	**3**	**(0.6)**
Rash maculo-papular	0	(0.0)	0	(0.0)	1	(0.2)

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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).

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2.1.4 Other Significant Adverse Events

Through Week 96, a similar proportion of participants in the MSP discontinued study medication due to an AE in the Main Combined DOR group (2.6%) compared to the Main DRV+r group (3.4%) [Table 2.7.4-trtmtnve96wk: 13]. A higher proportion of participants in the Main Combined EFV group (8.1%) discontinued study medication due to an AE compared to participants in the Main Combined DOR group, most commonly due to AEs classified within the System Organ Classes (SOCs) of Skin and Subcutaneous Disorders (2.5% vs 0.4% DOR), Psychiatric Disorders (2.5% vs 0.6% DOR), and Nervous System Disorders (2.1% vs 0.1% DOR) [Table 5.3.5.3.3-trtmtnve96wk: 86].

These results for AEs leading to discontinuation through Week 96 are similar to those noted in the original Week 48 Application.

The number and percentage of participants with specific AEs that led to discontinuation of study medication, summarized by SOC and preferred term (PT) through the data cut-off dates are provided in [Table 5.3.5.3.3-trtmtnve96wk: 85]. A listing of all participants who discontinued due to AE through Week 96 is provided in [Table 5.3.5.3.3-trtmtnve96wk: 87]; a listing of participants who discontinued due to AE through the data cutoff dates is provided in [Table 5.3.5.3.3-trtmtnve96wk: 88].

2.1.5 Analysis of Adverse Events by Organ System or Syndrome

A review of AEs by organ system/syndrome in the MSP is presented for the important clinical event of rash, immune reconstitution syndrome (IRIS), and AIDS-defining

conditions. The event of clinical interest (ECI), overdose without an associated AE, is described in [Sec. 2.7.4-trtmtnve96wk: 5.4].

Listings of AEs by participant in P007, P018, and P021 can be found in [Ref. 5.3.5.1: P007V01MK1439: 16.2.7.1] [Ref. 5.3.5.1: P018MK1439: 16.2.7.1] [Ref. 5.3.5.1: P021MK1439A: 16.2.7.1]. The number and percentage of participants with specific AEs summarized by SOC and PT through Week 96 in the MSP are in [Table 5.3.5.3.3-trtmtnve96wk: 61].

Rash

Although rash was not defined as an ECI for any of the trials included in this application, it is considered to be an important clinical event given that rash is commonly associated with use of EFV and some members of the NNRTI class. To evaluate this event, an analysis of all PTs related to rash (exfoliative rash, follicular, generalized, macular, papular, maculo-papular, pruritic, vesicular, pustular, genital, viral, and rash not otherwise specified) was performed for the MSP.

A lower proportion of participants experienced ≥1 AE with a PT related to rash in the Main Combined DOR (8.2%) group and the Main DRV+r (9.7%) group compared with the Main Combined EFV group (16.3%) [Table 2.7.4-trtmtnve96wk: 19]. The proportions of participants with the PT of "rash" were lower for the Main Combined DOR (3.5%) group and the Main DRV+r (1.3%) group compared with the Main Combined EFV group (11.4%).

In the Main Combined DOR group, 2 participants (0.2%) had AEs with a PT of "rash" that were considered by the investigators to be moderate or severe (Main DRV+r: 1 participant [0.3%]; Main Combined EFV/FTC/TDF: 19 participants [4.0%]) [Table 5.3.5.3.3-trtmtnve96wk: 68].

Two participants in the Main Combined DOR group had AEs with PTs related to rash (1 participant with rash macular [severe intensity]; 1 participant with rash erythematous [moderate intensity]) that resulted in discontinuation of treatment; both events were considered by the investigator to be drug related, and neither met the criteria of an SAE [Table 5.3.5.3.3-trtmtnve96wk: 92]. In the Main DRV+r group, 1 participant had an AE of rash maculo-papular (moderate intensity) that led to treatment discontinuation; the AE was considered by the investigator to be drug related and did not meet the criteria of an SAE. In the Main Combined EFV group, 10 participants had AEs with PTs related to rash that resulted in discontinuation of treatment; all of these AEs were considered by the investigator to be drug related, and 3 of these events (rash macular, rash maculo-papular, and rash generalized) were reported as SAEs.

No participants in the Main Combined DOR or Main DRV+r groups had PTs related to rash that met the criteria of an SAE. A listing of participants with these AEs is found in [Table 5.3.5.3.3-trtmtnve96wk: 92].

Immune Reconstitution Syndrome

In the MSP, 14 participants (<1% of the MSP) experienced at least 1 AE identified by the investigator as probably related to IRIS through Week 96 [Table 2.7.4-trtmtnve96wk: 20]. A similar proportion of participants were observed in all 3 groups (Main Combined DOR 0.5%, Main DRV+r 1.8%, and Main Combined EFV 0.8%).

Across the treatment groups, most of these AEs were considered to be unrelated to study medication and most resolved with no action taken with regard to study medication [Table 5.3.5.3.3-trtmtnve96wk: 93].

Two participants had a total of 3 AEs associated with IRIS that met the criteria of an SAE (all in the Main DRV+r group): tuberculosis in 1 participant, and concurrent SAEs of tuberculosis of the central nervous system and meningitis tuberculosis in 1 participant. None of these events were considered by the investigator to be drug related, and none resulted in discontinuation of treatment.

A listing of participants with these events by Week 96 is found in [Table 5.3.5.3.3-trtmtnve96wk: 93].

AIDS-defining Conditions

Ten participants in the MSP (Main Combined DOR: n=2 [0.2%]; Main DRV+r: n=6 [1.6%]; Main Combined EFV: n=2 [0.4%]) had 1 or more AIDS-defining conditions recorded as a treatment-emergent AE [Table 2.7.4-trtmtnve96wk: 21]. None of the AEs was considered by the investigator to be drug-related [Table 5.3.5.3.3-trtmtnve96wk: 94].

A listing of participants with 1 or more AIDS-defining conditions is provided in [Table 5.3.5.3.3-trtmtnve96wk: 94].

Table 2.7.4-trtmtnve96wk: 19
Subjects With Adverse Events
(Incidence >0% in One or More Treatment Groups)
Rash
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	70	(8.2)	37	(9.7)	77	(16.3)
with no adverse events	785	(91.8)	346	(90.3)	395	(83.7)
Infections and infestations	**3**	**(0.4)**	**1**	**(0.3)**	**1**	**(0.2)**
Rash pustular	2	(0.2)	1	(0.3)	0	(0.0)
Viral rash	1	(0.1)	0	(0.0)	1	(0.2)
Reproductive system and breast disorders	**1**	**(0.1)**	**0**	**(0.0)**	**0**	**(0.0)**
Genital rash	1	(0.1)	0	(0.0)	0	(0.0)
Skin and subcutaneous tissue disorders	**66**	**(7.7)**	**37**	**(9.7)**	**76**	**(16.1)**
Exfoliative rash	0	(0.0)	0	(0.0)	1	(0.2)
Rash	30	(3.5)	5	(1.3)	54	(11.4)
Rash erythematous	8	(0.9)	6	(1.6)	4	(0.8)
Rash follicular	2	(0.2)	2	(0.5)	0	(0.0)
Rash generalised	4	(0.5)	0	(0.0)	7	(1.5)
Rash macular	5	(0.6)	9	(2.3)	4	(0.8)
Rash maculo-papular	8	(0.9)	6	(1.6)	4	(0.8)
Rash papular	7	(0.8)	10	(2.6)	2	(0.4)
Rash pruritic	3	(0.4)	0	(0.0)	2	(0.4)
Rash vesicular	1	(0.1)	0	(0.0)	0	(0.0)

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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).

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Table 2.7.4-trtmtnve96wk: 20
Subjects With Adverse Events
(Incidence >0% in One or More Treatment Groups)
Immune Reconstitution Syndrome
P018 and P021 Combined
Weeks 0-96, Base Study (Double Blind)

	DOR Regimen (P018, P021)		DRV+r (P018)		EFV/FTC/TDF (P021)	
	n	(%)	n	(%)	n	(%)
Subjects in population	747		383		364	
with one or more adverse events	4	(0.5)	7	(1.8)	3	(0.8)
with no adverse events	743	(99.5)	376	(98.2)	361	(99.2)
Blood and lymphatic system disorders	**0**	**(0.0)**	**1**	**(0.3)**	**0**	**(0.0)**
Lymphadenopathy	0	(0.0)	1	(0.3)	0	(0.0)
Gastrointestinal disorders	**0**	**(0.0)**	**1**	**(0.3)**	**0**	**(0.0)**
Gastrointestinal disorder	0	(0.0)	1	(0.3)	0	(0.0)
General disorders and administration site conditions	**0**	**(0.0)**	**1**	**(0.3)**	**0**	**(0.0)**
Pyrexia	0	(0.0)	1	(0.3)	0	(0.0)
Hepatobiliary disorders	**1**	**(0.1)**	**0**	**(0.0)**	**0**	**(0.0)**
Hepatitis	1	(0.1)	0	(0.0)	0	(0.0)
Infections and infestations	**1**	**(0.1)**	**5**	**(1.3)**	**3**	**(0.8)**
Acute sinusitis	0	(0.0)	0	(0.0)	1	(0.3)
Folliculitis	0	(0.0)	1	(0.3)	0	(0.0)
Gastroenteritis	0	(0.0)	0	(0.0)	1	(0.3)
Hepatitis B	0	(0.0)	1	(0.3)	0	(0.0)
Herpes simplex	1	(0.1)	0	(0.0)	0	(0.0)
Herpes zoster	0	(0.0)	0	(0.0)	1	(0.3)
Meningitis tuberculous	0	(0.0)	1	(0.3)	0	(0.0)
Molluscum contagiosum	0	(0.0)	1	(0.3)	0	(0.0)
Oral herpes	1	(0.1)	0	(0.0)	0	(0.0)
Tuberculosis	0	(0.0)	1	(0.3)	0	(0.0)
Tuberculosis of central nervous system	0	(0.0)	1	(0.3)	0	(0.0)
Investigations	**1**	**(0.1)**	**0**	**(0.0)**	**0**	**(0.0)**
Alanine aminotransferase increased	1	(0.1)	0	(0.0)	0	(0.0)
Aspartate aminotransferase increased	1	(0.1)	0	(0.0)	0	(0.0)
Skin and subcutaneous tissue disorders	**1**	**(0.1)**	**1**	**(0.3)**	**0**	**(0.0)**
Eczema	0	(0.0)	1	(0.3)	0	(0.0)

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Subjects With Adverse Events
(Incidence >0% in One or More Treatment Groups)
Immune Reconstitution Syndrome
P018 and P021 Combined
Weeks 0-96, Base Study (Double Blind)

	DOR Regimen (P018, P021)		DRV+r (P018)		EFV/FTC/TDF (P021)	
	n	(%)	n	(%)	n	(%)
Skin and subcutaneous tissue disorders	**1**	**(0.1)**	**1**	**(0.3)**	**0**	**(0.0)**
Eosinophilic pustular folliculitis	1	(0.1)	0	(0.0)	0	(0.0)

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Table 2.7.4-trtmtnve96wk: 21
Subjects With Adverse Events
(Incidence >0% in One or More Treatment Groups)
AIDS Defining Conditions
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	2	(0.2)	6	(1.6)	2	(0.4)
with no adverse events	853	(99.8)	377	(98.4)	470	(99.6)
Infections and infestations	**0**	**(0.0)**	**5**	**(1.3)**	**1**	**(0.2)**
Cryptosporidiosis infection	0	(0.0)	1	(0.3)	0	(0.0)
Cytomegalovirus infection	0	(0.0)	0	(0.0)	1	(0.2)
Meningitis tuberculous	0	(0.0)	1	(0.3)	0	(0.0)
Pulmonary tuberculosis	0	(0.0)	1	(0.3)	0	(0.0)
Tuberculosis	0	(0.0)	2	(0.5)	0	(0.0)
Tuberculosis of central nervous system	0	(0.0)	1	(0.3)	0	(0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**2**	**(0.2)**	**1**	**(0.3)**	**1**	**(0.2)**
B-cell unclassifiable lymphoma high grade	1	(0.1)	0	(0.0)	0	(0.0)
Kaposi's sarcoma	1	(0.1)	1	(0.3)	1	(0.2)

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]

2.1.6 Conclusions

In the MSP, DOR 100 mg and DOR/3TC/TDF were generally well tolerated by HIV-1-infected treatment-naïve participants through 96 weeks of treatment.

DOR 100 mg and DRV+r 800/100 mg, each in combination with FTC/TDF or ABC/3TC, demonstrated a similar safety profile. DOR had a similar proportion of participants who discontinued study medication due to an AE compared to DRV+r.

Relative to EFV, DOR had a lower proportion of participants who reported drug-related AEs, AEs that led to discontinuation, and drug-related AEs that led to discontinuation.

DOR was associated with a lower proportion of participants with neuropsychiatric AEs than EFV overall, particularly within the categories of dizziness and sleep disorders/disturbances.

DOR had a lower proportion of participants who experienced AEs of rash compared with EFV.

The results of these pooled analyses indicate that DOR has a favorable safety profile.

2.2 Adverse Events in the Special Safety Pool (P007 and P021)

As described in [Sec. 2.7.4-trtmtnve96wk: 1.1.2], the SSP is used for the analyses of:

- The proportion of participants who discontinued from trials P007 and P021 due to AEs through Week 96
- The time to discontinuation from the trials due to AEs through Week 96
- Neuropsychiatric events through Week 96 using a prespecified list of AEs

A description of the endpoints and time points assessed for the SSP is provided in [Sec. 2.7.4-trtmtnve96wk: 1.1.2]. The trials and treatment groups included in the SSP are depicted in [Figure 2.7.4-trtmtnve96wk: 1].

2.2.1 Discontinuation and Time to Discontinuation Due to Adverse Events

In the SSP, a lower proportion of participants in the Special Combined DOR group (3.4%) discontinued the study due to AEs compared with participants in the Special Combined EFV group (7.8%) (treatment difference of -4.4% [95% CI: -7.6, -1.6]) [Table 2.7.4-trtmtnve96wk: 22].

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

Table 2.7.4-trtmtnve96wk: 22
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.

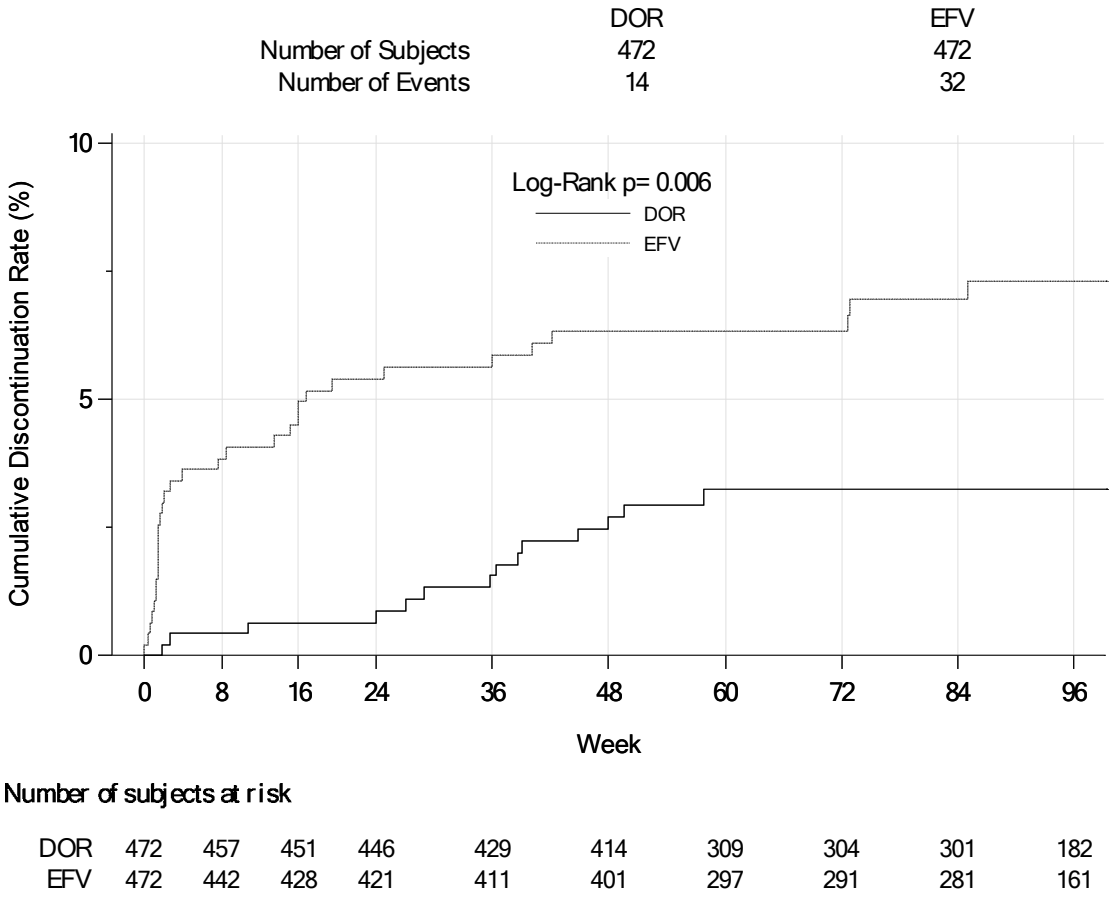
N = Number of subjects in each treatment group.

Source: [ISS: analysis-adsl; adtte]

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Figure 2.7.4-trtmtnve96wk: 2

Kaplan-Meier Plot for Time to Discontinuation Due to Adverse Event
Special Safety Pool (P007 (Doravirine 100 mg q.d. Group) and P021 Combined)
Weeks 0-96



DOR=Special Combined DOR; EFV=Special Combined EFV
Source: [ISS: analysis-adtte]

2.2.2 Neuropsychiatric Events

The frequencies of prespecified neuropsychiatric events through Week 96 were summarized in the SSP in the categories of dizziness, sleep disorders and disturbances, altered sensorium, depression and suicide/self-injury, and psychosis and psychotic disorders. A preselected list

of terms from the SOC Nervous System and Psychiatric Disorders were summarized in these categories.

The number and percentage of participants with neuropsychiatric events through Week 96 are presented in [Table 2.7.4-trtmtnve96wk: 23] [Table 5.3.5.3.3-trtmtnve96wk: 99]. Neuropsychiatric AEs through Week 96 were markedly less common among participants in the Special Combined DOR (28.4%) than in the Special Combined EFV group (57.6%) (treatment difference: -29.2% [95% CI: -35.2, -23.1]). The 95% CI for the treatment difference excluded 0 for 2 of the 5 predefined categories in favor of DOR: dizziness and sleep disorders/disturbances.

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Table 2.7.4-trtmtnve96wk: 23
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]

2.2.3 Conclusions

In the SSP, DOR 100 mg and DOR/3TC/TDF administered QD for 96 weeks in P007 and P021 were generally well tolerated by HIV-1-infected treatment-naïve participants. The results of this pooled analysis demonstrate the favorable safety profile of DOR compared with EFV.

The proportion of participants who discontinued from the study due to an AE was lower in the Special Combined DOR group compared with the Special Combined EFV group.

DOR demonstrated a more favorable safety profile compared with EFV through 96 weeks of treatment with respect to the neuropsychiatric event categories of dizziness and sleep disorders and disturbances.

2.3 Narratives

Narratives for participants with AEs resulting in death, SAEs, and AEs leading to discontinuation of study medication in the individual trials (P007, P018, and P021) can be found in [Ref. 5.3.5.1: P007V01MK1439: 16.2.7.2] [Ref. 5.3.5.1: P018MK1439: 16.2.7.2] [Ref. 5.3.5.1: P021MK1439A: 16.2.7.2], and for trials P024, P028, and P030 in [Ref. 5.3.5.1: 050NFD], [Ref. 5.3.5.1: 050NFN], [Ref. 5.3.5.2: 050NFQ].

3 CLINICAL LABORATORY EVALUATIONS

3.1 Main Safety Pool (P007, P018, and P021)

The following section provides results of the integrated analysis of safety that was performed for the MSP. A description of the endpoints and time points assessed for the MSP is provided in [Sec. 2.7.4-trtmtnve96wk: 1.1.2]. 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: P007V01MK1439] [Ref. 5.3.5.1: P018MK1439] [Ref. 5.3.5.1: P021MK1439A].

3.1.1 Predefined Limit of Change Evaluations

In the MSP, the proportions of participants with clinical laboratory results meeting the predefined limit of change (PDLC) criteria at Week 96 for selected laboratory parameters were generally similar. The between-group differences in the frequency of participants meeting PDLC criteria for any given parameter did not exceed 2% across the 3 groups [Table 2.7.4-trtmtnve96wk: 24], with few notable exceptions:

- Between-group differences in fasting lipid parameters were noted, as described in [Sec. 2.7.4-trtmtnve96wk: 3.1.2]. DOR was associated with decreases from baseline to Week 96 in mean values for fasting low-density lipoprotein cholesterol (LDL-C), fasting non-high-density lipoprotein cholesterol (HDL-C), and fasting triglycerides compared with increases in these values for both DRV+r and EFV.
- The PDLC criteria for Grade 1 and Grade 2 total bilirubin were met for a greater proportion of participants in the Main Combined DOR (5.9% and 1.9%, respectively) than for participants in the Main DRV+r (1.9%, 0.3%) or Main Combined EFV (0.6%, 0%) groups. This finding is similar to findings through Week 48, as reported in the original Application. Among participants in the DOR group, the incidence of Grade 1 bilirubin elevations increased by 12 participants from 4.5% at Week 48 to 5.9% at Week 96, and the incidence of Grade 2 bilirubin elevations increased by 1 participant from 1.8% to 1.9%. Grade 3 and 4 bilirubin elevations remained ≤0.2% (1 to 2 participants) among participants treated with DOR. None of the bilirubin elevations resulted in a participant being discontinuation from the trial, and no common etiology for the elevations has been identified.
- A higher observed proportion of participants in the Main Combined EFV group met the PDLC Grade 1 criteria for both alanine transaminase (ALT; 18.6%) and alkaline phosphatase (9.2%) compared with the Main Combined DOR (12.9% and 2.8%, respectively).

Numbers and percentages of participants with laboratory values that met the PDLC through the data cutoff dates are provided in [Table 5.3.5.3.3-trtmtnve96wk: 103]. Numbers and percentages of participants with laboratory values that met PDLCs that were Grade 2 or greater by Week 96 are provided in [Table 5.3.5.3.3-trtmtnve96wk: 104]. For participants who were hepatitis B and/or C positive and who were hepatitis B and C negative, numbers and percentages of participants with laboratory values that met PDLCs from baseline by

Week 96 are summarized in [Table 5.3.5.3.3-trtmtnve96wk: 106] [Table 5.3.5.3.3-trtmtnve96wk: 105].

Abnormal Laboratory Values of Potential Clinical Relevance (Grade 3 and Grade 4)

The incidence of Grade 3 laboratory abnormalities through Week 96 was generally similar for all 3 groups in the MSP; the greatest between-group differences (Main Combined DOR, Main DRV+r, and Main Combined EFV) were seen with Grade 3 fasting LDL-C (0.3%, 3.8%, and 1.7%, respectively) and fasting triglycerides (0.6%, 0.9%, and 2.9%) [Table 2.7.4-trtmtnve96wk: 24].

By Week 96, Grade 4 laboratory abnormalities occurring in ≥4 participants in any treatment group were similar for all 3 groups in the MSP. None of these laboratory abnormal values resulted in discontinuation of study drug and none was associated with a serious clinical condition (eg, pancreatitis relative to increased lipase). The most common (>1% in any treatment group) Grade 4 laboratory abnormalities meeting the PDLC among participants in the Main Combined DOR, Main DRV+r, and Main Combined EFV were increases in creatine kinase (1.7%, 2.1%, and 2.8%, respectively), lipase (1.1% each group), and ALT (0.2%, 1.1%, and 0.6%).

Table 2.7.4-trtmtnve96wk: 24
Subjects With Laboratory Findings That Met Predetermined Criteria
Main Safety Pool (P007 (Doravirine 100 mg q.d. Group) and P018 and P021 Combined)
Worsening Grade; Weeks 0-96, Base Study (Double Blind)

Criterion[†]	Main Combined DOR		Main DRV+r		Main Combined EFV	
	n/m	(%)	n/m	(%)	n/m	(%)
Subjects in population	855		383		472	
HEMATOLOGY						
Neutrophils (10^9/L)						
Grade 1: 0.800 - 1.000	12/848	(1.4)	5/378	(1.3)	4/467	(0.9)
Grade 2: 0.600 - 0.799	3/848	(0.4)	6/378	(1.6)	3/467	(0.6)
Grade 3: 0.400 - 0.599	3/848	(0.4)	2/378	(0.5)	3/467	(0.6)
Grade 4: <0.400	3/848	(0.4)	3/378	(0.8)	3/467	(0.6)
Hemoglobin (g/dL)						
Grade 1: Male: 10.0 - 10.9 Female: 9.5 - 10.4	19/849	(2.2)	6/378	(1.6)	7/467	(1.5)
Grade 2: Male: 9.0 - <10.0 Female: 8.5 - <9.5	6/849	(0.7)	6/378	(1.6)	3/467	(0.6)
Grade 3: Male: 7.0 - <9.0 Female: 6.5 - <8.5	4/849	(0.5)	2/378	(0.5)	1/467	(0.2)
Grade 4: Male: <7.0 Female: <6.5	0/849	(0.0)	0/378	(0.0)	0/467	(0.0)
Platelets (10^9/L)						
Grade 1: 100 - <124.999	9/845	(1.1)	5/376	(1.3)	2/465	(0.4)
Grade 2: 50 - <100	5/845	(0.6)	2/376	(0.5)	2/465	(0.4)
Grade 3: 25 - <50	0/845	(0.0)	0/376	(0.0)	0/465	(0.0)
Grade 4: <25	1/845	(0.1)	0/376	(0.0)	0/465	(0.0)
CHEMISTRY						
Fasting LDL Cholesterol (mg/dL)						
Grade 1: 130 - <160	58/764	(7.6)	43/319	(13.5)	45/409	(11.0)
Grade 2: 160 - <190	13/764	(1.7)	23/319	(7.2)	31/409	(7.6)
Grade 3: ≥190	2/764	(0.3)	12/319	(3.8)	7/409	(1.7)
Fasting Cholesterol (mg/dL)						
Grade 1: 200 - <240	82/772	(10.6)	59/326	(18.1)	83/419	(19.8)
Grade 2: 240 - <300	12/772	(1.6)	36/326	(11.0)	41/419	(9.8)
Grade 3: ≥300	2/772	(0.3)	2/326	(0.6)	3/419	(0.7)
Fasting Triglyceride (mg/dL)						
Grade 1: 150 - 300	113/772	(14.6)	82/326	(25.2)	79/419	(18.9)
Grade 2: >300 - 500	35/772	(4.5)	18/326	(5.5)	36/419	(8.6)
Grade 3: >500 - 1000	5/772	(0.6)	3/326	(0.9)	12/419	(2.9)

Subjects With Laboratory Findings That Met Predetermined Criteria
Main Safety Pool (P007 (Doravirine 100 mg q.d. Group) and P018 and P021 Combined)
Worsening Grade; Weeks 0-96, Base Study (Double Blind)

Criterion[†]	Main Combined DOR		Main DRV+r		Main Combined EFV	
	n/m	(%)	n/m	(%)	n/m	(%)
Fasting Triglyceride (mg/dL)						
Grade 4: >1000	0/772	(0.0)	2/326	(0.6)	0/419	(0.0)
Fasting Glucose (mg/dL)						
Grade 1: 110 - 125	65/774	(8.4)	33/326	(10.1)	38/420	(9.0)
Grade 2: >125 - 250	21/774	(2.7)	10/326	(3.1)	12/420	(2.9)
Grade 3: >250 - 500	4/774	(0.5)	1/326	(0.3)	3/420	(0.7)
Grade 4: >500	0/774	(0.0)	0/326	(0.0)	0/420	(0.0)
Total Bilirubin (mg/dL)						
Grade 1: 1.1 - <1.6 x ULN	50/850	(5.9)	7/378	(1.9)	3/467	(0.6)
Grade 2: 1.6 - <2.6 x ULN	16/850	(1.9)	1/378	(0.3)	0/467	(0.0)
Grade 3: 2.6 - <5.0 x ULN	1/850	(0.1)	0/378	(0.0)	0/467	(0.0)
Grade 4: ≥5.0 x ULN	2/850	(0.2)	0/378	(0.0)	1/467	(0.2)
>2.5 - 5.0 x Baseline	10/850	(1.2)	2/378	(0.5)	2/467	(0.4)
>5.0 -10.0 x Baseline	2/850	(0.2)	0/378	(0.0)	0/467	(0.0)
>10.0 x Baseline	2/850	(0.2)	0/378	(0.0)	1/467	(0.2)
Direct Bilirubin (mg/dL)						
>2.5 - 5.0 x Baseline	3/850	(0.4)	3/378	(0.8)	0/467	(0.0)
>5.0 - 10.0 x Baseline	0/850	(0.0)	0/378	(0.0)	1/467	(0.2)
>10.0 x Baseline	4/850	(0.5)	1/378	(0.3)	1/467	(0.2)
Indirect Bilirubin (mg/dL)						
>2.5 - 5.0 x Baseline	6/850	(0.7)	0/378	(0.0)	0/467	(0.0)
>5.0 - 10.0 x Baseline	2/850	(0.2)	0/378	(0.0)	0/467	(0.0)
>10.0 x Baseline	1/850	(0.1)	0/378	(0.0)	1/467	(0.2)
Creatinine (mg/dL)						
Grade 1: 1.1 - 1.3 x ULN	2/850	(0.2)	0/378	(0.0)	0/467	(0.0)
Grade 2: >1.3 - 1.8 x ULN or Increase of >0.3 mg/dL above baseline	30/850	(3.5)	22/378	(5.8)	7/467	(1.5)
Grade 3: >1.8 - <3.5 x ULN or Increase of 1.5 to <2.0 x above baseline	23/850	(2.7)	15/378	(4.0)	5/467	(1.1)
Grade 4: ≥3.5 x ULN or Increase of ≥2.0 x above baseline	4/850	(0.5)	0/378	(0.0)	1/467	(0.2)

Subjects With Laboratory Findings That Met Predetermined Criteria
Main Safety Pool (P007 (Doravirine 100 mg q.d. Group) and P018 and P021 Combined)
Worsening Grade; Weeks 0-96, Base Study (Double Blind)

Criterion[†]	Main Combined DOR		Main DRV+r		Main Combined EFV	
	n/m	(%)	n/m	(%)	n/m	(%)
Aspartate Aminotransferase (IU/L)						
Grade 1: 1.25 - <2.5 x ULN	90/850	(10.6)	36/378	(9.5)	65/467	(13.9)
Grade 2: 2.5 - <5.0 x ULN	32/850	(3.8)	14/378	(3.7)	13/467	(2.8)
Grade 3: 5.0 - <10.0 x ULN	9/850	(1.1)	8/378	(2.1)	12/467	(2.6)
Grade 4: ≥10.0 x ULN	2/850	(0.2)	0/378	(0.0)	3/467	(0.6)
>2.5 - 5.0 x Baseline	60/850	(7.1)	23/378	(6.1)	56/467	(12.0)
>5.0 x Baseline	30/850	(3.5)	14/378	(3.7)	20/467	(4.3)
Alanine Aminotransferase (IU/L)						
Grade 1: 1.25 - <2.5 x ULN	110/850	(12.9)	30/378	(7.9)	87/467	(18.6)
Grade 2: 2.5 - <5.0 x ULN	31/850	(3.6)	9/378	(2.4)	15/467	(3.2)
Grade 3: 5.0 - <10.0 x ULN	9/850	(1.1)	6/378	(1.6)	9/467	(1.9)
Grade 4: ≥10.0 x ULN	2/850	(0.2)	4/378	(1.1)	3/467	(0.6)
>2.5 - 5.0 x Baseline	72/850	(8.5)	20/378	(5.3)	71/467	(15.2)
>5.0 x Baseline	37/850	(4.4)	15/378	(4.0)	35/467	(7.5)
Alkaline Phosphatase (IU/L)						
Grade 1: 1.25 - <2.5 x ULN	24/850	(2.8)	13/378	(3.4)	43/467	(9.2)
Grade 2: 2.5 - <5.0 x ULN	2/850	(0.2)	2/378	(0.5)	2/467	(0.4)
Grade 3: 5.0 - <10.0 x ULN	0/850	(0.0)	1/378	(0.3)	1/467	(0.2)
Grade 4: ≥10.0 x ULN	0/850	(0.0)	0/378	(0.0)	0/467	(0.0)
>2.5 - 5.0 x Baseline	14/850	(1.6)	3/378	(0.8)	11/467	(2.4)
>5.0 x Baseline	0/850	(0.0)	3/378	(0.8)	1/467	(0.2)
Lipase (IU/L)						
Grade 1: 1.1 - <1.5 x ULN	63/850	(7.4)	32/378	(8.5)	36/467	(7.7)
Grade 2: 1.5 - <3.0 x ULN	57/850	(6.7)	23/378	(6.1)	25/467	(5.4)
Grade 3: 3.0 - <5.0 x ULN	16/850	(1.9)	10/378	(2.6)	13/467	(2.8)
Grade 4: ≥5.0 x ULN	9/850	(1.1)	4/378	(1.1)	5/467	(1.1)
Creatine Kinase (IU/L)						
Grade 1: 3.0 - <6.0 x ULN	59/743	(7.9)	29/378	(7.7)	23/359	(6.4)
Grade 2: 6.0 - <10.0 x ULN	21/743	(2.8)	13/378	(3.4)	10/359	(2.8)
Grade 3: 10.0 - <20.0 x ULN	22/743	(3.0)	15/378	(4.0)	12/359	(3.3)

Subjects With Laboratory Findings That Met Predetermined Criteria
Main Safety Pool (P007 (Doravirine 100 mg q.d. Group) and P018 and P021 Combined)
Worsening Grade; Weeks 0-96, Base Study (Double Blind)

Criterion[†]	Main Combined DOR		Main DRV+r		Main Combined EFV	
	n/m	(%)	n/m	(%)	n/m	(%)
Creatine Kinase (IU/L)						
Grade 4: ≥ 20.0 x ULN	13/743	(1.7)	8/378	(2.1)	10/359	(2.8)
Amylase (IU/L)						
Grade 1: 1.1 - <1.5 x ULN	30/743	(4.0)	21/378	(5.6)	16/359	(4.5)
Grade 2: 1.5 - <3.0 x ULN	12/743	(1.6)	10/378	(2.6)	5/359	(1.4)
Grade 3: 3.0 - <5.0 x ULN	0/743	(0.0)	2/378	(0.5)	1/359	(0.3)
Grade 4: ≥ 5.0 x ULN	0/743	(0.0)	0/378	(0.0)	0/359	(0.0)

[†]For graded criteria: subjects are counted once per test in the highest grade reported.

For baseline criteria: subjects are counted in the '>X-fold Baseline' if the highest test value during treatment fell in this category.

For inclusion in this analysis, both a baseline and at least one on-treatment laboratory value had to be present. Only subjects with a worsened grade from baseline were included. A subject was listed with a Grade X event if his/her highest grade during treatment was X.

n = Number of subjects with postbaseline test results that met the predetermined criterion.

m = Number of subjects with at least one postbaseline test result.

LLN = Lower limit of normal range. ULN = Upper limit of normal range.

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 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).

Source: [ISS: analysis-adsl; adlb]

3.1.2 Laboratory Changes from Baseline

Except for the changes in fasting lipid parameters discussed below, no clinically relevant differences between treatment groups were observed, and no apparent trends indicative of DOR-related effects on clinical laboratory parameters were noted in the MSP through 96 weeks of treatment [Table 5.3.5.3.3-trtmtnve96wk: 109].

Change from baseline in fasting LDL-C, fasting non–HDL-C, fasting cholesterol, fasting triglycerides, fasting HDL-C, and the fasting total-cholesterol-to-HDL ratio were evaluated in the MSP. DOR was associated with decreases from baseline to Week 96 in mean values for fasting LDL-C, fasting non-HDL-C, and fasting triglycerides compared with increases in these values for both DRV+r and EFV [Table 2.7.4-trtmtnve96wk: 25]. A small mean increase in fasting cholesterol was noted in the Main Combined DOR group, relative to larger mean increases in the DRV+r and EFV groups. Small increases in fasting HDL-C values were noted for each of the 3 treatment groups.

These lipid findings reported for the MSP are consistent with those observed in the sensitivity analyses of P018 [Table 5.3.5.3.3-trtmtnve96wk: 100] and P021 [Table 5.3.5.3.3-trtmtnve96wk: 101].

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Table 2.7.4-trtmtnve96wk: 25
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]

3.1.3 Overall Clinical Laboratory Conclusions

For both DOR and DOR/3TC/TDF, no participant had abnormal laboratory values of potential clinical relevance that resulted in study discontinuation.

In both Phase 3 trials (P018, P021), the lipid profile of DOR (specifically, fasting LDL-C and non-HDL-C) relative to the comparator groups (DRV+r and EFV/FTC/TDF, respectively) was evaluated as a safety endpoint. In both trials, the lipid profile of DOR was found to be favorable, with marked between-group differences favoring DOR over comparators for fasting LDL-C and non-HDL-C through Week 96 [Table 2.7.4-trtmtnve96wk: 26].

Table 2.7.4-trtmtnve96wk: 26
Change From Baseline in Fasting LDL-C and Non-HDL-C at Week 96
P018 and P021
Base Study (Double Blind)

Treatment	N	Baseline Mean	Change from Baseline at Week 96		Difference Estimates (Doravirine - Darunavir)
			Mean Change (SD)	95% CI[†]	Difference[‡] 95% CI
P018					
Fasting LDL Cholesterol (mg/dL)					
Doravirine 100 mg QD	325	91.31	-0.44 (21.45)	(-2.78, 1.90)	-14.57 (-18.18, -10.96)
Darunavir 800 mg + ritonavir 100 mg QD	317	91.86	14.00 (26.86)	(11.03, 16.97)	
Fasting Non-HDL Cholesterol (mg/dL)					
Doravirine 100 mg QD	327	113.41	-0.48 (25.59)	(-3.27, 2.30)	-18.40 (-22.54, -14.26)
Darunavir 800 mg + ritonavir 100 mg QD	324	114.56	17.65 (30.26)	(14.34, 20.96)	
P021					
Fasting LDL Cholesterol (mg/dL)					
DOR/3TC/TDF QD	330	92.03	-0.62 (25.56)	(-3.39, 2.15)	-11.10 (-14.83, -7.37)
EFV/FTC/TDF QD	306	90.79	10.78 (24.60)	(8.01, 13.55)	
Fasting Non-HDL Cholesterol (mg/dL)					
DOR/3TC/TDF QD	333	115.23	-2.14 (25.33)	(-4.87, 0.59)	-17.03 (-21.06, -13.01)
EFV/FTC/TDF QD	315	114.92	14.95 (28.11)	(11.83, 18.07)	

Modified from [Ref. 5.3.5.1: P018MK1439: Table 12-7], [Ref. 5.3.5.1: P021MK1439A: Table 12-7]

4 VITAL SIGNS, PHYSICAL FINDINGS, AND OTHER OBSERVATIONS RELATED TO SAFETY

In the MSP, there were no clinically meaningful changes from baseline in vital signs or physical findings in any of the treatment groups through Week 96 [Table 5.3.5.3.3-trtmtnve96wk: 111]. Analyses of vital signs and other safety observations 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: P007V01MK1439] [Ref. 5.3.5.1: P018MK1439] [Ref. 5.3.5.1: P021MK1439A].

5 SAFETY IN SPECIAL GROUPS AND SITUATIONS

The safety of DOR and DOR/3TC/TDF was assessed in the MSP for special groups and situations considered to be the most likely to be encountered in the clinical practice of treating HIV-1 infected patients. The MSP represents 1710 treated participants [Sec. 2.7.4-trtmtnve96wk: 1.1.2]. This section discusses the influence of intrinsic factors, such as demographic characteristics and comorbid conditions encountered in the HIV-1 population (such as gender, race, age, hepatitis B and/or C infection status, and baseline $CD4^+$ T-cell count), on the safety profile of DOR and DOR/3TC/TDF. These factors/settings may affect the safety profile of DOR and DOR/3TC/TDF directly or indirectly through changes in drug exposure. The impact of these factors on the safety profile of DOR and DOR/3TC/TDF was assessed by comparing AEs and laboratory parameters in the presence or absence of a particular factor.

5.1 Intrinsic Factors

Clinical and laboratory AEs were reviewed for participant subgroups in the MSP based on age, gender, race, and ethnicity, as well as hepatitis B and/or C infection status, and baseline $CD4^+$ T-cell count.

In all cases, differences between treatment groups were generally small across subgroups defined by baseline factors. In the MSP, although some differences were evident, the prevalence of AEs by SOC was similar for men and women for all 3 treatment groups (Main Combined DOR, Main DRV+r and Main Combined EFV) [Table 5.3.5.3.3-trtmtnve96wk: 114, 122]; the gender data should be interpreted with caution due to the relatively small numbers of women enrolled compared with men.

For all other intrinsic factors evaluated for the MSP, the incidence of treatment-emergent AEs were generally similar among the 3 treatment groups by ethnicity [Table 5.3.5.3.3-trtmtnve96wk: 113, 120], baseline hepatitis status [Table 5.3.5.3.3-trtmtnve96wk: 116, 126], and baseline $CD4^+$ T-cell count [Table 5.3.5.3.3-trtmtnve96wk: 117, 119].

With respect to age, participants were categorized as being within the age ranges of 18 to 64 years or ≥65 years; only 11 participants in the MSP were ≥65 years of age (none >70 years), precluding meaningful interpretation of AE findings by age [Table 5.3.5.3.3-trtmtnve96wk: 112, 118]. In addition, small sample sizes for females, some race categories, and participants who were hepatitis B and/or C positive should be considered in the analysis and interpretation of data in these subgroups.

5.2 Drug Interactions

Based on the metabolic pathway of DOR, only cytochrome P450 (CYP)3A modulators have the potential to affect the exposure of DOR. DOR exposure is increased when it is co-administered with CYP3A inhibitors; however, the increase is not considered to be clinically meaningful.

Clinical AE summary and counts tables were reviewed for subgroups based on concomitant use (for ≥7 days at any time during DOR treatment) of moderate or strong CYP3A inhibitors

for participants in the Main Combined DOR group in the MSP. Through Week 96, there were 86 (of 855 [10.1%]) participants who reported the concomitant use of moderate or strong CYP3A inhibitors, and 769 (of 855 [89.9%]) participants who did not report the use of these inhibitors; this difference should be considered in the analysis and interpretation of data in these subgroups.

The 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-trtmtnve96wk: 127] [Table 5.3.5.3.3-trtmtnve96wk: 128] [Table 5.3.5.3.3-trtmtnve96wk: 64] [Table 5.3.5.3.3-trtmtnve96wk: 79].

Although the proportions of participants with 1 or more AEs were similar for participants with or without the concomitant use of moderate or strong CYP3A inhibitors, the incidences of a few specific AEs were higher in participants with concomitant use of moderate or strong CYP3A inhibitors compared to participants without concomitant use of these therapies (eg, diarrhea, nausea, headache, bronchitis, and pharyngitis) [Table 5.3.5.3.3-trtmtnve96wk: 128]. 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.

Overall, the safety profiles for participants with and without concomitant use of moderate or strong CYP3A inhibitors were similar, consistent with that observed at Week 48.

5.3 Use in Pregnancy and Lactation

The use of DOR and DOR/3TC/TDF in pregnancy and lactation is not recommended. Females who were pregnant and/or lactating were excluded from enrollment into any of the clinical trials.

In total, 8 treated participants (1 [0.3%] in P007, 3 [0.4%] in P018, and 4 [0.5%] in P021) became pregnant during these Phase 2b and Phase 3 trials and were discontinued from the trials.

In P007, 1 treated participant in the DOR 50-mg treatment group was discontinued from the trial due to pregnancy on Day 559 [Ref. 5.3.5.1: P007V01MK1439: 12.5]. Pregnancy outcome was a vaginal live birth with no congenital anomalies.

In P018, 2 treated participants in the DOR treatment group and 1 treated participant in the DRV+r group discontinued from the trial due to pregnancy [Ref. 5.3.5.1: P018MK1439: 16.2.1]. In the DOR group, 1 participant discontinued on Day 29 due to pregnancy, and reported a vaginal live birth with no congenital anomalies. The second participant in the DOR group was discontinued from the trial on Day 451; the pregnancy outcome for this participant was a live birth via Caesarean section with no congenital anomalies. (Note: This pregnancy outcome was incorrectly reported as a spontaneous abortion in the original Application.) In the DRV+r group, 1 participant discontinued from the trial on Day 645 due to pregnancy, and reported delivery of a full-term baby who had no congenital abnormalities.

In P021, 4 treated participants (2 in the DOR/3TC/TDF group and 2 in the EFV/FTC/TDF group) discontinued from the trial due to pregnancy [Ref. 5.3.5.1: P021MK1439A: 16.2.1]. One participant in the DOR/3TC/TDF group was discontinued on Day 30. The pregnancy outcome was a spontaneous abortion on Day 47; the investigator considered this outcome to be not related to study drug or study procedure. The other participant in the DOR/3TC/TDF group was discontinued on Day 497 due to pregnancy (last reported dose on Day 493), and reported a spontaneous abortion (fetal age <20 weeks) on Day 507. One of the participants in the EFV/FTC/TDF treatment group had a spontaneous abortion on Day 222 (fetal age 4 weeks) during hospitalization for aggravation of chronic endometritis and chronic oophoritis; the participant was discontinued from the trial on Day 258. The investigator considered this outcome not related to study drug or study procedure. The other participant in the EFV/FTC/TDF treatment group was discontinued from the trial on Day 428; the outcome was a premature vaginal live birth (delivered at 38 weeks), and at last contact, the baby was developing normally.

5.4 Overdose

Adverse events associated with (ie, "resulting from") an overdose of DOR or DOR/3TC/TDF, were reported as SAEs, even if no other seriousness criteria were met. If a dose of DOR or DOR/3TC/TDF meeting the protocol definition of overdose was taken (DOR doses >200 mg in P007; doses >2× daily dose in a calendar day in P018 and P021) or without any associated clinical symptoms or abnormal laboratory results, the overdose was reported as a nonserious ECI, using the terminology "accidental or intentional overdose without adverse effect."

In the MSP, an overdose of DOR was reported by Week 96 for 4 participants in the DOR 100-mg treatment group (0.5%) [Table 2.7.4-trtmtnve96wk: 27]; no AEs were reported with any of the overdoses. Of the 4 participants with overdoses, 3 were enrolled in P007. In P018, 1 participant had an accidental overdose of 300-mg DOR on Day 399. Each of the overdoses for DOR was accidental and none were considered to be drug-related events by the investigator.

Because none of these events fulfill the predefined protocol definition of "overdose," these events are not classified as true overdoses.

Table 2.7.4-trtmtnve96wk: 27
Subjects With Adverse Events
(Incidence >0% in One or More Treatment Groups)
Report of ECI of Accidental Overdose without Adverse Effect
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	4	(0.5)	1	(0.3)	9	(1.9)
with no adverse events	851	(99.5)	382	(99.7)	463	(98.1)
Injury, poisoning and procedural complications	**4**	**(0.5)**	**1**	**(0.3)**	**9**	**(1.9)**
Accidental overdose	4	(0.5)	0	(0.0)	8	(1.7)
Intentional overdose	0	(0.0)	1	(0.3)	1	(0.2)
Overdose	0	(0.0)	0	(0.0)	1	(0.2)

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]

5.5 Drug Abuse

No reports of abuse of DOR occurred in any participants participating in the trials summarized in this Summary of Clinical Safety. Based upon the activity profile of this compound and the lower proportion of participants with CNS AEs in the Main Combined DOR group than in the comparator groups, the abuse potential of DOR is considered low.

5.6 Withdrawal and Rebound

No specific trials have been conducted during the development program for DOR and DOR/3TC/TDF to assess the response to withdrawal and rebound. No withdrawal or rebound effects have been observed in the DOR and DOR/3TC/TDF clinical trials to date. DOR and DOR/3TC/TDF are not targeted to elicit a change in human physiology or biochemistry, but rather are anti-infective with activity against HIV-1. Therefore, the terms withdrawal and rebound are not applicable to these compounds.

5.7 Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability

Although no trials on the effects on the ability to drive and use machines have been performed, there is no information to suggest that DOR or DOR/3TC/TDF would affect the ability to drive and use machines. However, individual responses to DOR or DOR/3TC/TDF may vary.

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6 POSTMARKETING DATA

DOR/3TC/TDF and DOR were not approved for commercial use prior to the cut off for this Application. Thus, postmarketing data are not available.

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7 CONCLUSIONS

- The safety profile of DOR and DOR/3TC/TDF through Week 96 was similar to the Week 48 safety profile noted in the original Application; no new safety concerns have been identified.

- DOR and DOR/3TC/TDF are generally well tolerated in HIV-1 infected treatment-naïve participants treated with the 100-mg dose of DOR for at least 96 weeks.

- The lipid profile of DOR was found to be favorable, with marked between-group differences, favoring DOR over controls, for fasting LDL-C and non-HDL-C through Week 96.

- In a pooled analysis combining data from P007 and P021, a lower proportion of participants who discontinued due to an adverse event by Week 96 was seen for the combined DOR and DOR/3TC/TDF group (3.0%) compared with the combined EFV/FTC/TDF group (6.8%) (treatment difference of -3.8% [95% CI: 6.7, 1.1]).

- The results of the individual trials and pooled analyses demonstrated that 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.

8 APPENDIX

Not applicable.

CTD 第 2 部

2.7　臨床概要

2.7.5　参考文献

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[Ref. 5.4: 04QB8R] U.S. Prescribing Information: FARXIGA® (dapagliflozin) tablets, for oral use: 2017.

[Ref. 5.4: 04QBY6] U.S. Product Circular: Diabeta (glyburide) Tablets USP: 2017.

[Ref. 5.4: 04QBYP] U.S. Prescribing Information: VICTOZA (liraglutide) Injection, for subcutaneous use: 2016.

[Ref. 5.4: 04QBYQ] U.S. Prescribing Information: ONGLYZA (saxagliptin) tablets, for oral use: 2017.

[Ref. 5.4: 04QBYX] U.S. Prescribing Information: JARDIANCE (empagliflozin) tablets, for oral use: 2016.

[Ref. 5.4: 04QBYY] U.S. Prescribing Information: ACTOS (pioglitazone) Tablets: 2016.

[Ref. 5.4: 04QBYZ] U.S. Prescribing Information: AMARYL (glimepiride) tablets: 2013.

[Ref. 5.4: 04QBZ0] U.S. Product Circular: GLUCOTROL (glipizide) tablets for oral use: 2016.

[Ref. 5.4: 04QBZ3] U.S. Prescribing Information: SUBOXONE (buprenorphine and naloxone) sublingual film, for sublingual or buccal use CIII: 2017.

[Ref. 5.4: 04QBZM] U.S. Prescribing Information: AVANDIA (rosiglitazone maleate) Tablets: 2016.

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[Ref. 5.4: 04QC8B] U.S. Prescribing Information: PRILOSEC (omeprazole) delayed-release capsules and PRILOSEC (omeprazole magnesium) for delayed-release oral suspension: 2016.

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[Ref. 5.4: 04R37J] U.S. Prescribing Information: VICTRELIS (boceprevir) Capsules: 2011.

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