CTD 第 2 部

2.2　緒言

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2.2 INTRODUCTION

Doravirine (DOR) is a novel non-nucleoside reverse transcriptase inhibitor (NNRTI) being developed by the Applicant as a once-daily (QD) oral treatment for Human immunodeficiency virus type 1 (HIV-1) infection. DOR is being developed as both the single agent (for use in combination with other antiretroviral medicinal products) and as a fixed-dose combination (FDC) with the nucleoside analog reverse transcriptase inhibitors lamivudine (3TC) and tenofovir disoproxil fumarate (TDF). The FDC, hereafter referred to as DOR/3TC/TDF, is intended for use as a single tablet, complete antiretroviral regimen. The 3TC and TDF components of DOR/3TC/TDF are nucleoside analog reverse transcriptase inhibitors (NRTIs) and are the active pharmaceutical ingredients in EPIVIR and VIREAD, respectively, both approved by the Food and Drug Administration (FDA), the European Medicines Agency (EMA), and other health authorities. DOR and DOR/3TC/TDF have been developed in a hybrid clinical program that includes mutually supportive Phase 2 and Phase 3 trials of the single entity and the FDC.

HIV/acquired immunodeficiency syndrome (AIDS) is associated with significant morbidity and mortality. The World Health Organization (WHO) reported an estimated 36.7 million people around the world were living with HIV-1 infection in 2016 [1]. Of these, approximately 1.8 million adults and children were newly infected and an estimated1.0 million people died from AIDS-related illnesses. Approximately 2.1 million adults and children were living with HIV infection in western and central Europe and North America, with approximately 73,000 being newly infected.

DOR is a highly potent NNRTI and suppresses the replication of HIV-1 WT virus with EC_{50} of 12 nM in the presence of 100% normal human serum. In addition, DOR is active against commonly transmitted NNRTI-associated mutants containing K103N, Y181C, and G190A substitutions with EC_{50}s of 21, 31, and 55 nM under the same conditions, respectively. DOR displays a superior in vitro resistance profile overall to that of efavirenz (EFV), when its antiviral activity is tested in a broad array of clinical NNRTI resistant viruses, and is also active against rilpivirine (RPV) resistant viruses containing E138K/M184I and E138K/M184V substitutions. In vitro resistance selection studies also demonstrate that DOR exhibits unique mutation profiles, with V106 variants leading the majority of mutation pathways. A two-drug in vitro combination study indicated that DOR does not act antagonistically with any of 18 U.S. Food and Drug Administration (FDA)-licensed drugs for treatment of HIV-1 infection. In addition, selectivity and cytotoxicity studies confirmed that DOR is a highly specific HIV-1 NNRTI with minimum off-target activities.

A comprehensive program of nonclinical studies has been conducted with DOR and supports the favorable benefit/risk profile, including primary and secondary pharmacodynamics; safety pharmacology; absorption, distribution, metabolism, and elimination (ADME); and nonclinical safety studies.

The clinical pharmacology program included 36 Phase 1 trials characterizing the safety, tolerability, and pharmacokinetics (PK) of DOR and DOR/3TC/TDF in 678 subjects. There are no clinically meaningful drug interactions between the components of DOR/3TC/TDF. Furthermore, in a relative bioavailability trial (P026), the PK of DOR, 3TC, and tenofovir

following administration of the DOR/3TC/TDF final market image (FMI) was shown to be similar to the PK following co-administration of the individual components. Thus, the clinical pharmacology profile for each individual component is applicable to DOR/3TC/TDF.

The efficacy and safety of DOR administered either in combination with 2 NRTIs or as DOR/3TC/TDF have been evaluated in one Phase 2 trial (P007) and two pivotal Phase 3 trials (P018 and P021) in 855 HIV-1 infected treatment-naïve subjects treated with the 100 mg dose of DOR for at least 48 weeks. Results of these clinical trials demonstrate that:

- DOR and DOR/3TC/TDF are non-inferior to ritonavir-boosted darunavir (DRV+r) and EFV with respect to the proportion of subjects with HIV-1 RNA <50 copies/mL at Week 48.
- DOR and DOR/3TC/TDF have comparable efficacy to DRV+r and EFV with respect to proportions of subjects with HIV-1 RNA < 40 c/mL and < 200 c/mL, and change 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.
- 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 protocol-defined virologic failure (PDVF) that are consistent with those observed for the comparators; development of treatment-emergent drug resistance was rare.
- DOR and DOR/3TC/TDF have a favorable safety profile when compared with DRV+r and EFV/FTC/TDF, and were generally well tolerated.
- In P021, a statistically significantly lower proportion of DOR/3TC/TDF-treated subjects compared to EFV/FTC/TDF-treated subjects reported neuropsychiatric AEs by Week 48 in the three pre-specified categories of: 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]), and altered sensorium (4.4% vs. 8.2% [-3.8; p= 0.033]).
- With regard to pre-specified comparisons of LDL- and non-HDL-cholesterol in P018 and P021, the differences in the mean change from baseline at Week 48 were statistically significant showing superiority for DOR for both parameters:
  - LDL-C: P018 (-4.51 vs. 9.92 mg/dL [-14.61; *p<0.0001*]); P021 (-1.58 vs. 8.74 mg/dL [-10.01; *p<0.001*])
  - Non-HDL-C: P018 (-5.30 vs. 13.75 mg/dL [-19.34; *p<0.001*]); P021 (-3.83 vs. 13.26 mg/dL [-17.02; *p<0.001*])
- In a pooled analysis combining data from P007 and P021, a statistically significantly lower proportion of subjects who discontinued due to an adverse event by Week 48 was

seen for the combined DOR and DOR/3TC/TDF group (2.8%) compared with the combined EFV/FTC/TDF group (6.1%) [treatment difference -3.4%, p-value 0.012].

Efavirenz (EFV) and rilpivirine (RPV) are among the most commonly prescribed NNRTIs in the U.S. and in the EU. Both drugs, however, have liabilities; treatment-limiting neuropsychiatric adverse events are associated with EFV [2] and efficacy in patients with HIV-1 RNA levels >100,000 copies/mL is suboptimal with RPV [3]. In addition, various antiretroviral therapy (ART) agents (including boosted protease inhibitors [PIs]) are known to negatively impact serum lipids. Therefore, there is an unmet need for an NNRTI that provides efficacy comparable to EFV while avoiding the neuropsychiatric toxicities common with EFV (which can lead to discontinuation of treatment with EFV), and an agent that lacks the dyslipidemia associated with other commonly used ART agents. As evidenced by the clinical data summarized above, DOR and DOR/3TC/TDF will address this unmet need.

This new marketing authorization application is being submitted for DOR, which has been developed, in combination with other antiretroviral medicinal products, for the treatment of HIV-1 infection in adults. The recommended dosage of DOR in adults is one 100-mg tablet taken orally QD with or without food. The proposed indication text varies by country according to regulatory guidelines. For specific proposed indication, please refer to the proposed product labeling included with the application.

A separate new marketing authorization application is being submitted in parallel for DOR/3TC/TDF.

References:

1. Joint United Nations Programme on HIV/AIDS. Fact sheet July 2017 Global HIV statistics [Internet]. Geneva: UNAIDS; 2016. Available from: http://www.unaids.org/sites/default/files/ media_asset/UNAIDS_FactSheet_en.pdf
2. Treisman GJ, Soudry O. Neuropsychiatric effects of HIV antiviral medications. Drug Saf. 2016 Oct; 39 (10):945-57.
3. Cohen CJ, Molina JM, Cassetti I, Chetchotisakd P, Lazzarin A, Orkin C, et al. Week 96 efficacy and safety of rilpivirine in treatment-naive, HIV-1 patients in two Phase III randomized trials. AIDS. 2013 Mar 27; 27(6):939-50.

2.2 INTRODUCTION

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, as a single agent (for use in combination with other antiretroviral medicinal products) or as a fixed-dose combination (FDC) with the nucleoside analog reverse transcriptase inhibitors (NRTIs) lamivudine (3TC) and tenofovir disoproxil fumarate (TDF), has been approved in the United States (U.S.), European Union (EU), and Canada for the treatment of HIV-1 infection in adults. The recommended dosage of DOR in adults is one 100 mg tablet taken orally once daily (QD), with or without food. The recommended dose of the FDC (hereafter referred to as DOR/3TC/TDF) is one tablet (containing 100 mg of DOR, 300 mg of 3TC, and 300 mg TDF) taken orally QD, with or without food. The original marketing applications for DOR and DOR/3TC/TDF provided 1) chemistry, manufacturing and control data; 2) non-clinical pharmacology, pharmacokinetic (PK) data, and toxicology data; 3) clinical pharmacology data (including PK and Phase 1 safety data) and modeling and simulation data; and 4) safety and efficacy data from 2 pivotal Phase 3 trials (P018 and P021) and a single Phase 2b trial (P007) to support the use of DOR in HIV-1-infected adults. The objective of this supplemental application (Switch Application) is to update the prescribing information for DOR to include data from a single Phase 3 trial (P024) in HIV-1-infected virologically suppressed participants switching from a stable antiretroviral regimen to DOR/3TC/TDF. This supplemental application does not contain any updates to the Chemistry, Manufacturing and Controls sections or Non-Clinical sections of the original marketing application.

HIV/acquired immunodeficiency syndrome (AIDS) is associated with significant morbidity and mortality. The Joint United Nations Programme on HIV and AIDS (UNAIDS) reported that in 2017, an estimated 36.9 million people around the world were living with HIV-1 infection, with approximately 2.2 million adults and children living with HIV infection in western and central Europe and North America [1].

Currently more than 30 antiretroviral drugs are commercially available worldwide for use in combination antiretroviral therapy (cART) for the treatment of HIV-1 infection. The expanding number of antiretroviral drugs and drug combinations has made it possible for patients to consider switching from one effective regimen to another. Several factors that may warrant a change in therapy include: simplification of regimens by reducing pill burden or dosing frequency, tolerability, safety, prevention or mitigation of drug-drug interactions, and elimination of food requirements. The fundamental principle of regimen switching is to maintain viral suppression without risking future treatment options. The use of three-drug regimens, either within-class or between-class, is generally recommended and patients with no resistance mutations can likely switch to a regimen that has been shown to be effective in treatment-naïve patients. Advances in antiretroviral drugs and improved understanding of HIV drug resistance make it possible for patients to switch to another regimen that addresses one or more of the situations listed above.

As presented in the original marketing applications, DOR and DOR/3TC/TDF provide robust efficacy, a favorable safety and resistance profile, and convenient treatment options for HIV-1 infected adults. Additionally, DOR addresses many of the limitations of other currently

available NNRTIs, with fewer neuropsychiatric AEs as compared to efavirenz (EFV)-based regimens, and a superior lipid profile when compared with EFV and ritonavir-boosted darunavir (DRV+r).

In P024, HIV-1 infected, virologically suppressed participants on a stable baseline antiretroviral regimen were randomized in a 2:1 ratio to either the Immediate Switch Group (ISG) to receive DOR/3TC/TDF on Study Day 1 or to the Delayed Switch Group (DSG) to start DOR/3TC/TDF at Study Week 24. Baseline regimens were comprised of a ritonavir- or cobicistat-boosted PI (specifically, atazanavir [ATV], DRV, or lopinavir [LPV]), an integrase strand transfer inhibitor (InSTI, specifically cobicistat-boosted elvitegravir [EVG]), or an NNRTI (specifically EFV, nevirapine [NVP], or rilpivirine [RPV]), each administered with 2 NRTIs. The results of this clinical trial demonstrate that:

- 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.
- 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 with 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.
- 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.
- 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.

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

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A separate Switch Application is being submitted in parallel for DOR/3TC/TDF.

References:

1. Joint United Nations Programme on HIV/AIDS. Fact sheet July 2017 Global HIV statistics [Internet]. Geneva: UNAIDS; 2016. Available from: http://www.unaids.org/sites/default/files/ media_asset/UNAIDS_FactSheet_en.pdf

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The objective of this Week 96 supplemental application is to update the Prescribing Information to include Week 96 safety and efficacy data from the two pivotal Phase 3 trials (P018 and P021). In the pivotal Phase 3 clinical trials, DOR and DOR/3TC/TDF at Week 96 showed:

- Non-inferior efficacy compared with DRV+r and EFV based regimens, as measured by the proportions of participants achieving HIV-1 RNA <50 copies/mL.
- Robust immunological response with increases in $CD4^+$ T-cell counts from baseline similar to DRV+r and EFV.
- A favorable resistance profile with low rates of development of viral genotypic and phenotypic drug resistance to DOR.
- An overall safety profile similar to that seen at Week 48.

The data provided in this supplemental application demonstrate the durable efficacy of DOR and DOR/3TC/TDF through 96 weeks, the low rate of development of viral drug resistance, and maintenance of a favorable safety profile. These data support an update of the current Prescribing Information to reflect the efficacy and safety results for DOR and DOR/3TC/TDF through 96 weeks.