545. Rational Design of Doravirine (DOR): A Review of Development From Bench to Patients

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Background. First-generation NNRTIs with nucleoside reverse transcriptase inhibitors are effective in sustaining HIV-1 suppression but development of resistant mutants is often seen in patients whose regimens fail. These NNRTIs are also associated with safety/tolerability issues, such as CNS and rash. Despite intensive efforts in developing NNRTIs with improved resistance and safety profiles, only two next-generation NNRTIs were successfully developed over the last decade, etravirine (ETR) and rilpivirine (RPV). RPV is less efficacious in patients with high viral load and ETR is only approved for treating experienced patients. Lessons from the limitations of approved NNRTIs and past development failures informed a rational approach to the development of DOR.

Methods. This review describes the development of DOR, which applied resistance selection and crystallography studies to improve resistance profiles, qEEG studies to evaluate CNS effects, and animal studies to optimize pharmacokinetic profiles, with confirmation in clinical trials.

Results. DOR demonstrated potent in vitro activity against wild-type virus and mutant viruses containing common NNRTI resistance mutations (K103N, Y181C, G190A, E138K, and K103N/Y181C), and selection studies suggested a unique resistance profile characterized by the emergence of a mutation at position 106 (V106A/M) with additional substitutions, such as F227C, required for high-level resistance. Related analogs were devoid of qEEG effects in rats and nonhuman primates. The metabolic profile was devoid of induction potential, suggesting a benign drug interaction profile. In the ongoing clinical studies, resistance rates were lower than first-generation NNRTIs, with no clinically meaningful drug interactions, and DOR has been generally well tolerated with favorable safety, neuropsychiatric, and lipid profiles.

Conclusion. Current clinical experience confirmed the preclinical profile of DOR. DOR is a unique NNRTI, distinguished by its low risk of resistance and excellent tolerability. DOR demonstrated a superior neuropsychiatric profile compared with EFV, a superior lipid profile vs. DRV+r and EFV, and a favorable drug–drug interaction profile comparable to integrase strand transfer inhibitors.

Disclosures. **C. Hwang**, Merck & Co., Inc.: Employee and Shareholder, Salary. **M. T. Lai**, Merck & Co., Inc.: Employee and Shareholder, Salary. **D. Hazuda**, Merck & Co., Inc.: Employee and Shareholder, Salary.

546. No Difference in MK-8591 and Doravirine Pharmacokinetics After Co-Administration

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Background. MK-8591 is a novel, highly potent, nucleoside reverse transcriptase translocation inhibitor (NRTTI) that is in development for the treatment of HIV-1 infection. MK-8591 is not expected to be a perpetrator or victim of drug–drug interactions (DDI), as it does not interact with renal or hepatic transporters, or with cytochrome P450 (CYP) enzymes in vitro. Doravirine (DOR), a novel non-nucleoside reverse transcriptase inhibitor (NNRTI), does not interact significantly with hepatic transporters or CYP enzymes but is metabolized by CYP3A4 in vitro. As MK-8591 is neither an inducer nor an inhibitor of CYP3A4, an interaction between MK-8591 and DOR was not expected. Currently, MK-8591 is being evaluated in a Phase 2 trial in combination with DOR.

Methods. The two-way interaction between MK-8591 and DOR was investigated in a double-blind, placebo-controlled, randomized, fixed-sequence, two-way drug–drug interaction study in 14 healthy adult subjects. Subjects received 5 days of 100 mg DOR or placebo QD, followed by 19 days of 2.25 mg MK-8591 or placebo QD, with 100 mg DOR or placebo co-administered QD for the last 5 days. Ten subjects received active drug and four received placebo throughout the trial.

Results. Multiple daily doses of MK-8591 and DOR alone and in combination were generally well tolerated. As noted in the table, the DOR area under the curve from time zero to 24 hours (AUC0-24), concentration at 24 hours (C24), and maximum concentration (Cmax) were similar with and without MK-8591, and the MK-8591 AUC0-24 and Cmax were similar with and without DOR.

Table: Geometric Mean Ratio (GMR) with 90% Confidence Interval, Relative to Single Agent Administration ($N = 10$)

	DOR	MK-8591
AUC0-24	1.13 [1.01, 1.28]	1.06 [1.01, 1.12]
C24[†]	1.12 [0.95, 1.32]	
Cmax	1.11 [0.99, 1.25]	1.08 [0.91, 1.27]

[†]C24 for parent MK-8591 is not related to efficacy and therefore not included.

Conclusion. No clinically significant differences in PK were observed when MK-8591 and DOR were co-administered, which supports the Phase 2 co-dosing of MK-8591 and DOR. Consistent across trials, MK-8591 does not appear to interact with CYP3A4-mediated metabolism.

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547. Results of Patient-Reported Outcome Data From the Phase III BRIGHTE Study of Fostemsavir

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Background. The Phase 3 BRIGHTE study evaluated fostemsavir in heavily treatment experienced HIV-1 patients failing their current antiretroviral (ARV) regimen and unable to construct a viable regimen from remaining available agents. Week 24 efficacy and safety have been previously reported—fostemsavir resulted in virological and immunological improvements and was generally well tolerated. The objective of this abstract is to report analyses of patient-reported outcomes (PROs) from BRIGHTE.

Methods. BRIGHTE included two cohorts: the randomized cohort (RC) had one to two classes of ARV therapy available; the nonrandomized cohort (NRC) had no ARV classes available. RC patients received fostemsavir or placebo + existing failing regimen for 8 days, and thereafter fostemsavir + optimized background therapy (OBT); NRC received fostemsavir + OBT throughout. PROs included the Functional Assessment of HIV Infection (FAHI), the EuroQol-5D-3L (EQ-5D) and associated visual analogue scale (VAS).

Results. Both cohorts had advanced disease, low CD4 counts (median of 99.5 in RC and 41 in NRC) and high proportions of patients with AIDS (84% in RC and 90% in NRC). This was reflected in fairly low baseline FAHI scores. Improvements from baseline to Week 24 were observed in FAHI total score, physical well-being and emotional well-being subscales, with limited/no change in function/ global well-being, social well-being and cognitive function. Improvements in the RC were close to published values for minimum clinically important differences, with smaller improvements in the NRC. EQ-5D utilities were similar at Week 24 to baseline in both cohorts, with improvements in the EQ-5D VAS (11% in the RC, 8% in the NRC).

		FAHI						EQ-5D	
Cohort		Total Score	Physical Well-Being	Emotional Well-Being	Function and Global Well-Being	Social Functioning	Cognitive Functioning	Utility Score (US Norms)	VAS
RC	Baseline	122.5	30.7	26.2	35.3	22.1	8.4	0.831	74.6
	Change from Baseline (CFB) Week 24	+6.7	+2.8	+3.1	+1.0	−0.1	0.0	+0.02	+8.1
NRC	Baseline	114.3	29.1	24.9	31.8	20.6	7.9	0.818	70.8
	CFB Week 24	+2.1	+1.2	+1.6	+0.7	−1.6	+0.2	+0.03	+5.6

Conclusion. The BRIGHTE study demonstrated improvements in PROs in heavily treatment experienced HIV patients, complementing previously published efficacy and safety results.

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548. Antiretroviral Therapy Regimen Characteristics Within an Urban, Safety-Net Clinic in the United States

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Background. Contemporary antiretroviral-therapy (ART) regimens have simple dosing, low toxicity, minimal side-effects, and few drug interactions. We evaluated ART regimens in an urban, safety-net, adult HIV clinic in the United States to determine proportions of patients on contemporary ART and identify opportunities to optimize ART for patients on older regimens.

Methods. Data including current ART regimen, HIV-1 RNA level, and age were extracted from the electronic medical record (EMR) for all patients seen in the prior 13 months. Viral suppression was defined as HIV-1 RNA < 200 copies/mL. A patient was "off-ART" if there were no fills within 270 days or ART had a stop date >90 days prior to end of the study. Unclear regimens from the EMR (n = 179) were chart