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551. MK-8591 Does Not Alter the Pharmacokinetics of the Oral Contraceptives Ethinyl Estradiol and Levonorgestrel

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Background. Over 2 million girls and young women are living with HIV, being newly infected at disproportionately high rates. HIV infection adds risks to pregnancy, including vertical transmission and maternal death. Hormonal contraceptives are among the most effective reversible contraceptives, but they have clinically meaningful drug–drug interactions (DDI) with many antiretrovirals (ARV). MK-8591 is a novel nucleoside reverse transcriptase translocation inhibitor (NRTTI) currently in Phase 2 clinical development for treatment of HIV. Unlike many ARVs, MK-8591 is not an inhibitor or inducer of major CYP enzymes and is not expected to alter the pharmacokinetics (PK) of hormonal contraceptives. This clinical study evaluated the DDI of MK-8591 with levonorgestrel (LNG) and ethinyl estradiol (EE) to support use of hormonal contraceptives with MK-8591.

Methods. This was an open-label, two-period, fixed-sequence DDI study in 14 healthy, postmenopausal or oopherectomized females aged 50–64. A single dose of LNG 0.15 mg/EE 0.03 mg was given followed by a 7-day washout. MK-8591 20 mg was then dosed once weekly for 3 weeks; a single dose of LNG 0.15 mg/EE 0.03 mg was given concomitantly with the third dose of MK-8591. PK samples were collected for evaluation of LNG and EE levels. Individual values of AUC0-inf and Cmax were natural log-transformed prior to analysis and evaluated separately using a linear mixed effects model with a fixed effects term for treatment. An unstructured covariance matrix was used to allow for unequal treatment variances and to model the correlation between the treatment measurements within each subject.

Results. The PK of EE and LNG were not meaningfully altered by co-administration with MK-8591. For the comparison of (MK-8591 + LNG/EE) / (LNG/EE alone), the geometric mean ratios (GMRs) (90% confidence intervals (CIs)) for LNG AUC0-inf and Cmax were 1.13 (1.06, 1.20) and 0.965 (0.881, 1.06), respectively. For EE the GMRs (90% CI) for AUC0-inf and Cmax were 1.05 (0.981, 1.11) and 1.02 (0.971, 1.08), respectively. Co-administration of all three drugs was generally well tolerated.

Conclusion. The results of this study support use of hormonal contraceptives in HIV-infected patients receiving MK-8591.

Disclosures. **W. Ankrom**, Merck & Co, Inc.: Employee and Shareholder, Salary. **D. Jonathan**, Merck: Employee, Salary. **D. Rudd**, Merck & Co., INC.: Employee, Salary. **S. Zhang**, Merck & Co, Inc.: Employee, Salary. **K. Fillgrove**, Merck & Co., Inc.: Employee, Salary. **K. Gravesande**, Kezia Gravesande: Research Contractor, Salary. **R. Matthews**, Merck: Employee, Salary. **A. Stoch**, Merck & Co, Inc.: Employee and Shareholder, Salary. **M. Iwamoto**, Merck & Co, Inc.: Employee and Shareholder, Salary.

552. Evaluation of Relationships Between *UGT1A1* Genotypes and Cabotegravir Long-Acting Injection Pharmacokinetics Among HIV-Infected Subjects in the LATTE-2 Study

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Background. Cabotegravir (CAB), an HIV integrase inhibitor primarily metabolized by UGT1A1, is in development as an oral tablet and long-acting (LA) intramuscular (IM) injection for the treatment and prevention of HIV infection. CAB LA has a prolonged absorption phase, typical of flip-flop PK, which yields prolonged drug exposure compared with oral administration. Genetic variation in *UGT1A1* affects enzymatic activity, impacting drug exposure. A previous analysis in healthy and HIV-infected subjects demonstrated that *UGT1A1* genotypes conferring poor metabolizer status were significantly associated with steady-state oral CAB PK parameters, with ~1.5-, 1.4-, and 1.3-fold increases in mean Cτ, AUC, and Cmax, respectively, in subjects with low vs. normal genetically predicted UGT1A1 activity. These increases are not considered clinically relevant. This analysis evaluated the impact of *UGT1A1* genotypes on CAB PK in subjects who received both oral CAB and CAB LA in the LATTE-2 study.

Methods. DNA was genotyped for *UGT1A1* in 215 HIV-infected subjects with PGx consent who received CAB LA every 4 or 8 weeks in LATTE-2. *UGT1A1* variants (*6, *28, *36 and *37) were used to classify subjects with genetically predicted UGT1A1 low (n = 33), reduced (n = 100), or normal (n = 82) enzyme activity. Genetically predicted enzyme activity was assessed for association with CAB LA PK parameters at study Weeks 32 and 48. Covariates of age, weight, treatment regimen, BMI, and gender were considered, and linear regression models were applied with adjustment for significant covariates. The impact of *UGT1A1* genotypes on oral and LA plasma CAB concentrations was descriptively analyzed.

Results. Genetically predicted UGT1A1 activity was statistically associated with CAB LA Cτ, AUC(0-τ), and Cmax ($P < 0.05$) at study Weeks 32 and 48. Mean LA PK parameters increased ~1.2-fold in subjects with low vs. normal genetically predicted UGT1A1 activity. The impact of *UGT1A1* genotypes was smaller than observed for oral CAB.

Conclusion. *UGT1A1* reduced function polymorphisms as anticipated had less impact on CAB PK following LA IM administration vs. oral CAB in HIV-infected patients with no requirement for CAB dose adjustment for either formulation due to *UGT1A1* polymorphisms.

Disclosures. **All authors:** No reported disclosures.

553. A Retrospective Study to Evaluate the Safety and Efficacy of a Nucleoside-Sparing Regimen of Darunavir, Ritonavir, and Dolutegravir

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Background. Nucleoside reverse transcriptase inhibitors (NRTIs) may contribute to or exacerbate cardiovascular risk, bone loss, and renal dysfunction. Darunavir (DRV) and dolutegravir (DTG) have a high barrier to resistance and proven tolerability profile, but have not been well studied as part of an NRTI sparing regimen. The purpose of this study was to determine the real-world efficacy and safety of an NRTI-sparing regimen of boosted DRV and DTG.

Methods. We conducted a retrospective chart review (NCT03198884) of ~400 HIV+ patients at an urban Federally Qualified Health Center to identify those who started an NRTI-sparing regimen of ritonavir(r) boosted DRV and DTG once-daily (QD). Included subjects were ^{3} 18 years of age, receiving DRV/r QD + DTG QD for ^{3} 24 weeks, and had 48 weeks of laboratory data available. Subjects were excluded if they, missed >5 doses over 2 weeks prior study visit, or had missing laboratory data for ^{3} two study time points. The primary endpoints were the percent of patients with HIV-1 RNA <50 copies/mL at 48 weeks and the change in mean serum creatinine (SCr) from baseline to 48 weeks. Analysis used was the Snapshot algorithm and Wilcoxon signed rank testing, respectively. Additional secondary endpoints included changes in CD4+ cell counts, and incidence and severity of adverse events.

Results. Twenty subjects were identified for inclusion. The mean age of the cohort was 51 years with an average of 12.5 years of HIV seropositivity. The mean baseline CD4+ was 485 cells/mm^3 with an HIV-1 RNA of 20,000 copies/mL. The percentage of subjects with HIV-1 RNA <50 copies increased from 45% at baseline to 95% at Week 48 (P = 0.002), 95% CI [2.24; NA], with one subject not having data in the 48-week window. There were no significant differences in SCr from baseline to 48 weeks (P = 0.5753) and no significant changes in CD4+ cell count from baseline at time points 24, 36 or 48 weeks. No subjects experienced virologic failure during the study period, or required genotypic resistance testing. No patients reported adverse events that led to discontinuation of the study regimen.