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

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Methods. This was an open-label, two-period, fixed-sequence DDI study in 14 healthy, postmenopausal or oophorectomized 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 LNG (MK-8591 + LNG/EE) vs. (LNG/EE alone), the geometric mean ratio (GMR) (90% confidence intervals (CIs)) for LNG AUC0-inf and Cmax were 1.05 (0.981, 1.11) and 1.02 (0.971, 1.08), respectively. For EE the geometric mean ratios (GMRs) (90% CI) for 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 (1.01, 1.11) and 1.02 (0.971, 1.08), respectively. Co-administration of all three drugs was generally well tolerated.

Conclusion. This study supports use of hormonal contraceptives in HIV-infected patients receiving MK-8591.

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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 C, 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 PGs 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 Cr, AUC(0-<->), 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 administration vs. oral CAB in HIV-infected patients with no requirement for CAB dose adjustment for either formulation due to UGT1A1 polymorphisms.

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