Pharmacokinetics, Safety, and Tolerability of the HIV Integrase Inhibitor Dolutegravir Co-Administered with Rifabutin in Healthy Subjects

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Study Design and Methods

- Phase 1, open label, pharmacokinetic (PK) drug interaction study
- Healthy male and female HIV- and HCV-seronegative volunteers

- Blood samples for steady state PK analysis were collected pre-dose and 1, 2, 3, 4, 5, 6, 8, 12, and 24 hours post-dose
- Plasma DTG concentrations were determined using LC-MS/MS
- Non-compartmental PK analysis and GMR for comparison
Mean (SE) Dolutegravir Concentration by Period

**Dolutegravir Concentration (μg/mL)**

- **Period 1**
  - Dolutegravir 50 mg QD

- **Period 2**
  - Dolutegravir 50 mg QD + Rifabutin 300 mg QD

**Time After Dose (Hours)**

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Limitations and Conclusions

Conclusions

- **Safety**: 4 Grade 2 lipase elevations. 1 grade 3 lymphopenia and 1 grade 4 fever, nausea, arthralgias, and lymphopenia, consistent with rifamycin hypersensitivity syndrome, but with atypical features.
- DTG 50 mg + RBT 300 mg daily resulted in overall plasma DTG AUC similar to DTG 50 mg once daily alone.
- Trough concentrations of DTG were reduced by about 30%, which is unlikely to be clinically significant based on DTG’s PK/PD relationship and data from a Phase 2b dose ranging study (SPRING-1).
- Once-daily DTG plus rifabutin may offer an additional treatment option for patients co-infected with TB and HIV.

Limitations

- Small sample size limits safety evaluation of dolutegravir (DTG) and rifabutin (RBT) co-administration
- Single site at Johns Hopkins Hospital in Baltimore, MD