Background

Dolutegravir (DTG), grazoprevir (GZR), and elbasvir (EBR) are oral, once-daily, fixed-sequence antiretroviral protease inhibitors. DTG is a dolutegravir/protease dual inhibitor and is under development as a pan HIV-1 protease inhibitor and as an HCV NS3/4A inhibitor. GZR and EBR are oral, once-daily, fixed-sequence HCV protease inhibitors. The purpose of this fixed-sequence study was to evaluate the pharmacokinetics of DTG, GZR, and EBR when coadministered with DTG, when coadministered with GZR, and when coadministered with EBR in healthy volunteers.

Methods

The study was a double-blind, placebo-controlled, randomized, fixed-sequence, parallel-group study in healthy subjects (n=12). DTG was administered at a dose of 50 mg in healthy subjects. GZR and EBR were administered at doses of 200 mg and 50 mg, respectively, in healthy subjects. DTG, GZR, and EBR were administered under fasted conditions on Day 1, followed by the administration of the coadministered drug(s) on Days 8 and 9 of Period 2. During Period 1, the coadministered drug(s) were administered with DTG, GZR, and EBR. During Period 2, the order of administration was GZR with EBR and DTG.

Results

The PK of DTG when coadministered with DTG was generally well tolerated in the healthy subjects. The most common treatment-emergent adverse events (AEs) were headache, flatulence, and nausea. No major changes in vital signs or ECG assessments were observed. The PK of GZR and EBR when coadministered with DTG were not affected by coadministration of DTG, with AUC (0-24 h) GZR and EBR increased by 25.17% (20.04-31.21) compared to the AUC of DTG alone. On all other days, subjects fasted for 1 hour prior to dosing of DTG, GZR, and EBR. A single dose of DTG alone, multiple doses of GZR and EBR coadministered with a single oral dose of DTG were generally well tolerated in the healthy adult male and female subjects in the study. No deaths, serious AEs, or AEs leading to study discontinuation occurred during the study.

Conclusions

Overall, these results suggest that GZR and EBR can be coadministered in HIV/HCV-coinfected patients without the coadministration of a single oral dose of 50 mg dolutegravir in healthy adult subjects.