Rifampin, a potent CYP3A4 inducer, markedly decreased VCV exposure when dosed.

This was a 5-part, open-label, single-center, drug interaction study in healthy adults. Each part of the study was a fixed-sequence one-way crossover design with VCV at a dose of 30 mg, with or without ritonavir (RTV).

In a randomized, placebo-controlled Phase 2b study (VICTOR-E1), vicriviroc 30 or 20 mg demonstrated sustained superior virologic and immunologic efficacy to block HIV entry into uninfected CD4+ cells via antagonism of the CCR5 coreceptor. VCV plasma half-life of >24 hours allows for once-daily dosing. 

The objective of this study was to investigate vicriviroc (VCV) as a CYP3A4 substrate or inhibitor in healthy adults. The study was conducted in 2 parts, Part 1 and Part 5.

### Results

#### Part 1 Pharmacokinetic Results

VCV exposure was substantially increased (503% based on AUC) when administered concurrently with MDZ. MDZ exposure (AUC and Cmax) was not affected when coadministered with VCV alone. The effect of VCV alone on MDZ exposure was 103-125% with 90% CI of 80-125% for AUC and 25.3% for Cmax.

VCV plasma half-life is 1-1.5 h, allowing for once-daily dosing. Co-administration of rifampin, rifabutin, and carbamazepine increased VCV exposure. Coadministration of rifampin with VCV in a PI/r-containing regimen is not recommended; however, if rifabutin is coadministered with VCV in a PI/r-containing regimen, it is recommended to coadminister rifabutin at a reduced dose.

#### Part 4 Pharmacokinetic Results

VCV exposure was substantially increased (503% based on AUC) when administered concurrently with MDZ. MDZ exposure (AUC and Cmax) was not affected when coadministered with VCV alone. The effect of VCV alone on MDZ exposure was 103-125% with 90% CI of 80-125% for AUC and 25.3% for Cmax.

#### Part 5 Pharmacokinetic Results

VCV exposure was substantially increased (503% based on AUC) when administered concurrently with MDZ. MDZ exposure (AUC and Cmax) was not affected when coadministered with VCV alone. The effect of VCV alone on MDZ exposure was 103-125% with 90% CI of 80-125% for AUC and 25.3% for Cmax.

#### Conclusions

VCV administered alone did not affect midazolam exposure in a clinical setting. VCV coadministration with 80 mg BID rifampin increased midazolam exposure 8-fold. Coadministration of rifampin with VCV in a PI/r-containing regimen is not recommended. If rifabutin is coadministered with VCV in a PI/r-containing regimen, it is recommended to coadminister rifabutin at a reduced dose.

**Methods**

- Part 1: A 5-part, open, single-center, drug interaction study in healthy adults; 74 healthy adults. Each part of the study was a fixed-sequence one-way crossover design with VCV at a dose of 30 mg, with or without ritonavir (RTV).
- Each part of the study was a fixed-sequence one-way crossover design with VCV at a dose of 30 mg, with or without ritonavir (RTV). Two tablet formulations of VCV were used in the trial.
- Coadministration of rifampin with VCV in a PI/r-containing regimen is not recommended; however, if rifabutin is coadministered with VCV in a PI/r-containing regimen, it is recommended to coadminister rifabutin at a reduced dose.
- Data from laboratory safety tests, FVGH assessments, and VCV were not haloed and therefore safety findings were not masked.
- **Conclusion:** Vicriviroc with or without RTV coadministration was generally safe and well tolerated, and there were no remarkable or treatment-related changes.

**Results**

#### Characteristics and Baseline Characteristics

- Table 1: Subject Demographic Characteristics, All Study Parts
  - Table 2: Subject Demographic Characteristics, Part 1a
  - Table 3: Subject Demographic Characteristics, Part 1b
  - Table 4: Subject Demographic Characteristics, Part 2
  - Table 5: Subject Demographic Characteristics, Part 3
  - Table 6: Subject Demographic Characteristics, Part 4

#### Pharmacokinetic Results

- **VCV/RTV vs. VCV alone:**
  - AUC0-24h: 368 vs. 1354 ng/mL·h (p<0.0001)
  - Cmax: 669 vs. 15.4% (90% CI: 8.8-15.4)

- **VCV/RTV vs. VCV with Rifabutin:**
  - AUC0-24h: 368 vs. 1354 ng/mL·h (p<0.0001)
  - Cmax: 669 vs. 15.4% (90% CI: 8.8-15.4)

- **VCV/RTV vs. VCV with Carbamazepine:**
  - AUC0-24h: 368 vs. 1354 ng/mL·h (p<0.0001)
  - Cmax: 669 vs. 15.4% (90% CI: 8.8-15.4)

**Statistical Methods**

The trial used analysis of variance (ANOVA) to compare treatment groups. The data were analyzed using a mixed-effects model, with treatment as the fixed effect and subject as the random effect. The 90% confidence intervals were calculated using the least squares means with a significance level of 0.05.

**Conclusions**

- Vicriviroc with or without RTV coadministration was generally safe and well tolerated, and there were no remarkable or treatment-related changes.
- MDZ exposure (AUC and Cmax) was not affected when coadministered with VCV alone.
- Coadministration of rifampin with VCV in a PI/r-containing regimen is not recommended; however, if rifabutin is coadministered with VCV in a PI/r-containing regimen, it is recommended to coadminister rifabutin at a reduced dose.
- Data from laboratory safety tests, FVGH assessments, and VCV were not haloed and therefore safety findings were not masked.

**References**

1. Zingman B, Suleiman J, DeJesus E, et al. 15th CROI; February 3-6, 2008; Boston, MA. Abstract 39LB.
4. Zingman B, Suleiman J, DeJesus E, et al. 15th CROI; February 3-6, 2008; Boston, MA. Abstract 39LB.