Bioequivalence of the Co-Formulation of Emtricitabine/Rilpivirine/Tenofovir DF

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Introduction

- Clinical studies have demonstrated that single tablet HAART regimens lead to high levels of adherence and patient preference, resulting in durable suppression of HIV-1 RNA and improved clinical outcomes[1,2]
- The availability of Efavirenz/Emtricitabine/Tenofovir DF (Atripla®) single tablet regimen as well as other combination tablets has enabled simplification of HIV treatment
- There still remains a need for new single tablet regimens composed of potent agents exhibiting favorable tolerability, minimal short and long-term toxicity, and convenient dosing to maximize patient adherence
- Rilpivirine (RPV, TMC278) 25mg QD has demonstrated, in a Phase 2b study, efficacy similar to efavirenz with an improved safety profile with respect to CNS adverse events, lipid abnormalities, incidence of rash and is not teratogenic[3]
- RPV is under evaluation in Phase 3 clinical trials in treatment-naïve HIV-1 patients in combination with NRTI backbone agents including, DHHS- and EACS-preferred emtricitabine (FTC 200mg) and tenofovir disoproxil fumarate (TDF 300mg)
  - Refer to Abstract THLBB206 for summary of 48-week efficacy and safety data from RPV Phase 3 studies
- Gilead has co-formulated RPV and the standard-of-care NRTI backbone FTC/TDF into a single tablet regimen

Bioequivalence Study Objectives

- To evaluate the pharmacokinetics and bioequivalence of a fixed-dose combination tablet (FDC)
  - 200mg FTC/25mg RPV/300mg TDF
  - Compared to individual components FTC + RPV + TDF
- To assess the safety of FTC, RPV and TDF administered as single tablet regimen and co-administered as individual dosage forms in healthy subjects

Methods

- A randomized, single-dose, open-label, Phase 1 study in healthy subjects
  - Test Treatment: 200mg FTC/25mg RPV/300mg TDF FDC
  - Reference Treatment: 200mg FTC capsule + 25mg RPV tablet + 300mg TDF tablet
- All study drugs administered under fed conditions (~ 400 kcal)
- Pharmacokinetics sampling
  - 192 hours (8 days)
  - Additional 7 day wash out due to long plasma RPV half-life
- FTC, RPV and tenofovir (TFV) in plasma measured by LC/MS/MS
- Descriptive statistics and 90% confidence interval (CI) for geometric mean ratios (GMR of Test vs. Reference) for FTC, RPV and TFV C_{max}, AUC_{last}, and AUC_{inf} calculated using ANOVA
- Formulation bioequivalence concluded if 90% CI for the GMR for FTC, RPV and TFV C_{max}, AUC_{last}, and AUC_{inf} was contained within bounds of 80% –125%
- Safety was evaluated by physical examination, adverse events (AE) and laboratory assessments

Results

Demographics

- 36 healthy subjects enrolled and 34 subjects completed the study
  - Female 21 (58.3%), Male 15 (43.7%)
  - White 27 (75.0%), Black 9 (25.0%)
  - Mean ± SD (range) age: 33 ± 7.0 yr (19 to 45 yr)
  - Mean ± SD (range) weight: 71.9 ± 10.97 kg (50.8 to 92.7 kg)

Figure 1. RPV Pharmacokinetics (n=34)

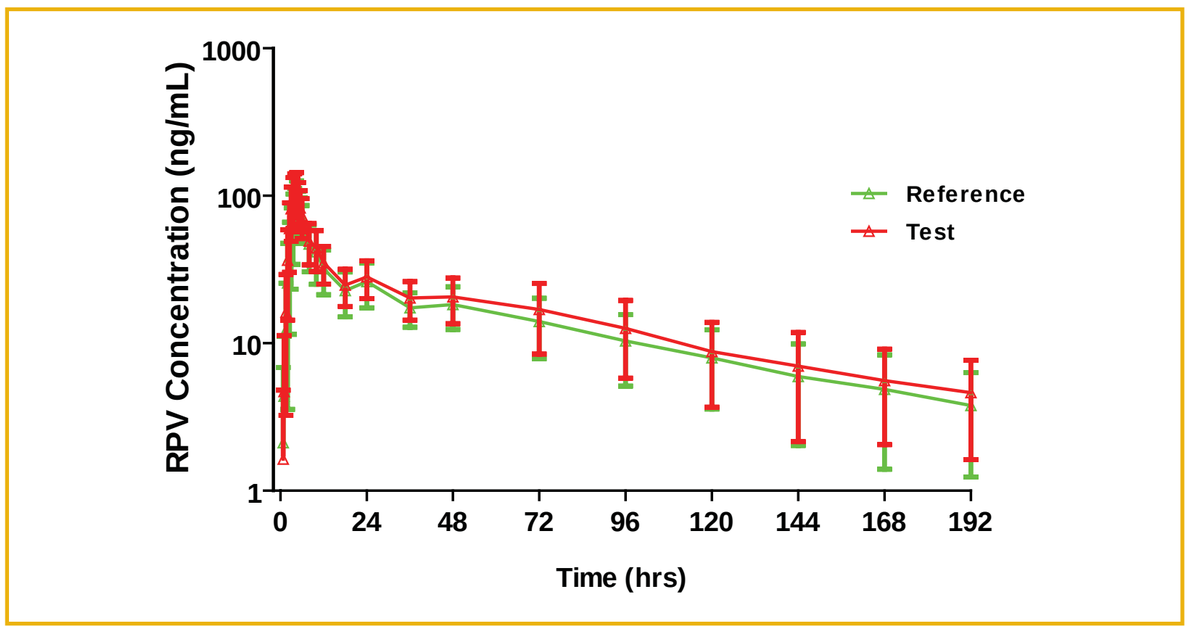
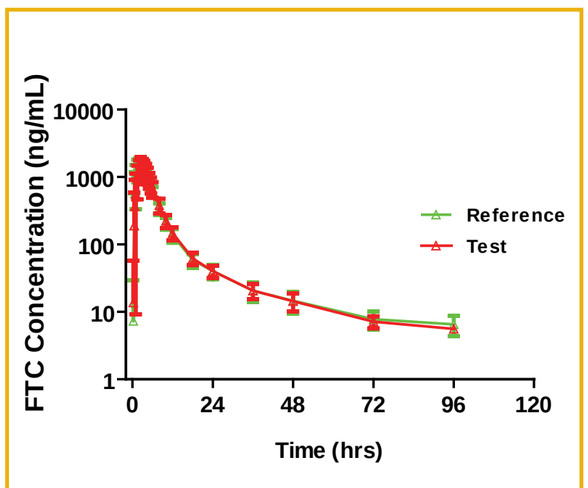
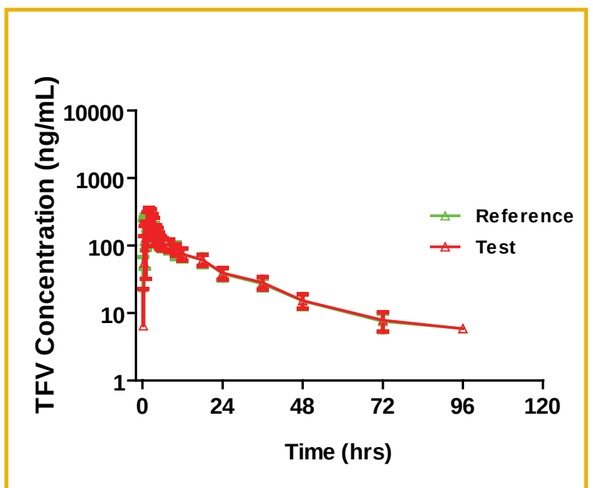


Figure 2. FTC Pharmacokinetics (n=34)



No measurable FTC concentrations were observed after 96 hours

Figure 3. TFV Pharmacokinetics (n=34)



No measurable TFV concentrations were observed after 96 hours

Results (cont'd)

Table 1. Pharmacokinetic Parameters of RPV (n=34)

PK Parameters	Test (FTC/RPV/TDF)	Reference (FTC+RPV+ TDF)	% GMR (90% CI)
C_{max} (ng/mL)	116 (29.6)	99.8 (30.5)	116 (108, 124)
AUC_{last}(ng·hr/mL)	3010 (34.5)	2600 (32.5)	116 (109, 123)
AUC_{inf} (ng·hr/mL)	3390 (39.4)	2920 (38.6)	116 (109, 123)
$T_{1/2}$ (hr)	54.2 (39.0, 62.9)	53.1 (40.2, 65.5)	–

Data presented as arithmetic mean (%CV) and as three significant figures
$T_{1/2}$: median (Q1, Q3)

Table 2. Pharmacokinetic Parameters of FTC (n=34)

PK Parameters	Test (FTC/RPV/TDF)	Reference (FTC+RPV+ TDF)	% GMR (90% CI)
C_{max} (ng/mL)	1750 (23.6)	1650 (21.9)	105 (100, 111)
AUC_{last}(ng·hr/mL)	9420 (14.3)	9420 (13.9)	99.9 (97.8,102)
AUC_{inf} (ng·hr/mL)	9640 (14.1)	9640 (13.6)	99.9 (97.7,102)
$T_{1/2}$ (hr)	18.3 (14.3, 20.2)	19.0 (14.4, 20.8)	–

Data presented as arithmetic mean (%CV) and as three significant figures
$T_{1/2}$: median (Q1, Q3)

Table 3. Pharmacokinetic Parameters of TFV (n=34)

PK Parameters	Test (FTC/RPV/TDF)	Reference (FTC+RPV+ TDF)	% GMR (90% CI)
C_{max} (ng/mL)	325 (26.0)	291 (26.4)	111 (104, 118)
AUC_{last}(ng·hr/mL)	3110 (21.1)	3040 (21.3)	102 (99.0, 105)
AUC_{inf} (ng·hr/mL)	3310 (19.7)	3250 (19.7)	102 (99.1, 105)
$T_{1/2}$ (hr)	18.1 (16.6, 19.5)	18.1 (16.8, 19.4)	–

Data presented as arithmetic mean (%CV) and as three significant figures
$T_{1/2}$: median (Q1, Q3)

- The 90% CI for the ratio of the geometric least-squares means of C_{max}, AUC_{last} and AUC_{inf} for the single tablet regimen versus the individual dosage forms were contained within 80% to 125% for FTC, RPV and TFV

Safety Results

- All treatments were generally well tolerated
- Most AEs were mild, transient and consistent with known FTC, RPV and TDF safety profiles
- Drug related treatment-emergent AEs (Grade 1) were experienced in 2/35* subjects (Reference) and 2/34 subjects (Test)
  - included diarrhea, musculoskeletal pain, pain in extremity, headache, dysuria, testicular pain, papular rash, and hot flashes
- Fasting hypercholesterolemia (Grade 1) was the most frequent treatment-emergent graded laboratory abnormality reported in 6/34 subjects (Reference) and 1/34 subjects (Test) respectively

*One of the two subjects who discontinued contributed to the adverse event dataset on Reference Treatment

Conclusions

- **The FTC/RPV/TDF single tablet regimen is bioequivalent to concurrent administration of the individual components**
- **This tablet is a next-generation, once-daily single-tablet antiretroviral regimen for the treatment of HIV-1 infection**
- **FTC/RPV/TDF single tablet regimen may offer an attractive treatment option to patients wishing to avoid efavirenz-containing regimens due to tolerability concerns and/or potential reproductive risks**

References

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3. Pozniak AL, et al. "Efficacy and safety of TMC278 in antiretroviral-naive HIV-1 patients: week 96 results of a phase IIb randomized trial." AIDS 2010; Jan 2; 24(1):55-65.