

A Comparison of the Single Dose Bioavailability of a Ritonavir Tablet Formulation Relative to the Ritonavir Soft Gelatin Capsule in Healthy Adult Subjects

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Abstract

Background: A ritonavir tablet formulation is being developed which does not require refrigeration. The bioavailability of a new tablet formulation, which may have improved physical stability compared to previous pilot formulations, was compared to the marketed soft gelatin capsule (SGC) in this Phase 1, open-label, randomized, crossover study.

Methods: Twenty-four subjects participated in a randomized, two-period, single-dose, open-label study to receive a 100 mg dose of ritonavir test tablet or the marketed SGC after a moderate-fat meal. Serial blood samples were collected for 36 hours after dosing in each period. The pharmacokinetic parameters of ritonavir were determined using non-compartmental methods, including area under the plasma concentration time curve (AUC) and maximum plasma concentration (C_{max}). The bioavailability of the tablet formulation relative to the SGC was assessed by the two one-sided tests procedure via 90% confidence intervals. Safety was assessed throughout the study.

Results: Ritonavir AUC and C_{max} were approximately 12% and 21% higher, respectively, after administration of the ritonavir tablets compared to administration of the marketed SGCs. The point estimates for ritonavir C_{max} and AUC after administration of the ritonavir tablet are lower than those observed for ritonavir after administration of the lopinavir/ritonavir tablet. The point estimate for ritonavir AUC was 20% higher and C_{max} was 35% higher after administration of the lopinavir/ritonavir tablet compared to the SGC. Both regimens were generally safe and well tolerated.

Conclusions: Ritonavir AUC after administration of the tablet was bioequivalent to the marketed SGC. The ritonavir C_{max} upper bound of the 90% confidence interval exceeded 1.25, which may be due, in part, to more efficient absorption of the tablet formulations. Further formulation refinements were made and the results of the pivotal biostudy will be presented at this conference. [Session #THAB04] The higher C_{max} of ritonavir tablet is unlikely to impact the safety profile or pharmacokinetic enhancing profile compared to the ritonavir SGC.

Introduction

- Ritonavir (marketed as Norvir®) has received regulatory approval worldwide and is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection.
- Due to its cytochrome P450 inhibition properties, ritonavir dosed 100 mg once daily (QD) to 200 mg twice daily (BID) is often used as a pharmacokinetic (PK) enhancer of other antiretroviral agents including protease inhibitors.
- A tablet formulation of lopinavir/ritonavir (LPV/r) was recently approved in many countries throughout the world. This tablet formulation does not require refrigeration. Using the same technology, a new tablet formulation of ritonavir is being developed.
- This pilot study was designed to compare the bioavailability of a single 100 mg dose of a test ritonavir tablet with that of a reference ritonavir soft gelatin capsule (SGC) under non-fasting conditions.

Objective

- Compare the bioavailability of a single 100 mg dose of a test tablet of ritonavir with that of a reference ritonavir SGC under non-fasting conditions.

Study Methods and Design

- Healthy HIV-negative adults (N=24) were enrolled into this single-dose, non-fasting, open-label, two-period, randomized, crossover design study if they met the following criteria:
 - General good health
 - No concomitant medication
 - Body mass index was between 18 and 29 kg/m²
- Subjects received a 100 mg dose of ritonavir following a moderate-fat breakfast
- Subjects were randomized to receive one of two sequences (marketed SGC in Period 1 and test tablet in Period 2 or test tablet in Period 1 and marketed SGC in Period 2)
- Twenty-two (22) subjects were included in the PK analyses (Table 1)
 - Two subjects discontinued prior to dosing in Period 2, both due to withdrawal of consent

Study Methods and Design cont.

Table 1. Demographics of Subjects Included in PK Analyses (N=22)

	Mean ± SD (N=22)	Min. – Max.
Age (years)	39.0 ± 10.52	23 – 55
Weight (kg)	71.0 ± 8.62	53 – 89
Height (cm)	167.7 ± 8.97	145 – 182
Sex	9 Males (41%), 13 Females (59%)	
Race	19 White (86%), 3 Black (14%)	

Pharmacokinetic Analysis

- Blood samples were collected for ritonavir assay at pre-dose (0 hour) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 18, 24, 30 and 36 hours after dosing on Study Day 1 in each period.
- Drug concentrations for ritonavir were measured by validated LC/MS/MS methods with a lower limit of quantitation (LLOQ) of 1.00 ng/mL.
- Ritonavir PK parameters were calculated with standard non-compartmental analysis using WinNonlin v. 5.0.1 software (Pharsight Corp., Mountain View, CA) to estimate the maximum observed concentration (C_{max}), time to the maximum observed concentration (T_{max}), apparent terminal phase elimination rate constant (β), terminal phase elimination half-life ($t_{1/2}$), area under the plasma concentration time curve from time 0 to the last measurable concentration (AUC_t) and AUC from time 0 to infinite time (AUC_{∞}).

Statistical Analysis

- Analysis of variance (ANOVA) was performed for T_{max} , C_{max} and AUC. Two one-sided tests via 90% confidence intervals were used to compare the pilot ritonavir 100 mg tablet to the marketed ritonavir 100 mg SGC.

Safety Analysis

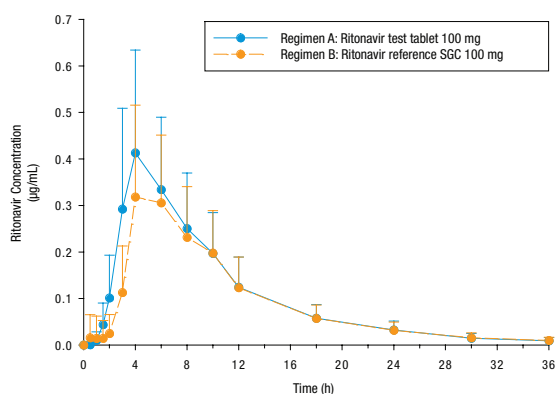
- Safety and tolerability were assessed throughout the study based on reported adverse events (AEs), vital signs and clinical laboratory measurements.

Results

Pharmacokinetics

- The observed plasma concentration versus time profiles for the ritonavir tablet and SGC are shown in Figure 1.

Figure 1. Ritonavir Plasma Concentration-Time Profile



- The ritonavir pharmacokinetic parameters are presented in Table 2.

Table 2. Ritonavir Pharmacokinetic Parameters

Pharmacokinetic Parameters (units)	Regimens [‡]	
	A: Test Tablet (N=22)	B: Reference SGC (N=22)
T_{max} (h)	4.1 ± 0.9*	5.6 ± 2.0
C_{max} (µg/mL)	0.44 ± 0.22*	0.38 ± 0.19
AUC_t (µg•h/mL)	3.67 ± 1.74*	3.25 ± 1.34
AUC_{∞} (µg•h/mL)	3.77 ± 1.82*	3.35 ± 1.41
$t_{1/2}$ (h)	5.78 ± 0.97*	6.18 ± 0.96

[‡] Both regimens were administered as a 100 mg single dose.

* Statistically significantly different from reference regimen (Regimen B, ANOVA, $p < 0.05$).

[‡] Harmonic mean ± pseudo-standard deviation; evaluations of $t_{1/2}$ were based on statistical tests for β .

Results cont.

- The relative bioavailability of the ritonavir test tablet compared to the marketed SGC is shown in Table 3.

Table 3. Relative Bioavailability of Ritonavir Pilot Tablet Versus Marketed SGC

Regimens Test vs. Reference	Pharmacokinetic Parameter	Central Value*		Relative Bioavailability	
		Tablet Test	SGC Reference	Point Estimate ⁺	90% Confidence Interval
Tablet vs. SGC	C_{max}	0.392	0.325	1.208	1.036 – 1.408
	AUC_0	3.283	2.934	1.119	1.040 – 1.204
	AUC_{∞}	3.363	3.020	1.114	1.037 – 1.196

* Antilogarithm of the least squares means for logarithms.

+ Antilogarithm of the difference (test minus reference) of the least squares means for logarithms.

- Ritonavir AUC met bioequivalence criteria.
- Ritonavir C_{max} was approximately 21% higher after administration of the ritonavir test tablets compared to administration of the marketed SGC.

Adverse Events

- The regimens were generally safe and well tolerated. No differences were seen between the tablet and SGC regimens for their adverse event profiles. The majority of AEs (6/7, 86%) were mild in severity.
 - One subject was dosed in both periods but discontinued from the study due to an SAE of acute confusional state in Period 2. Additional history obtained post event onset noted the subject had been saying inappropriate comments recently. The SAE was judged to be probably unrelated to the study drug.

Discussion

- The observed increase in C_{max} is consistent with the earlier T_{max} of the tablet formulation.
- The point estimates for ritonavir C_{max} and AUC after administration of the ritonavir test tablet are less than those observed for ritonavir after administration of the lopinavir/ritonavir tablet where the safety profile of the tablet and SGC were similar, Figure 2 (Study M05-730).
 - In similar studies in healthy volunteers, the point estimates for ritonavir AUC and C_{max} were approximately 20% and 35% higher, respectively, after administration of the lopinavir/ritonavir tablet compared to the SGC.
 - Following multiple-dose administration to HIV-1 infected patients the point estimates for ritonavir AUC and C_{max} were 20% and 25% higher, respectively, after administration of the lopinavir/ritonavir tablet compared to the SGC.
 - These increases in ritonavir exposure were not associated with changes in safety or tolerability.

Figure 2a. Safety Parameters Observed in Study M05-730 (Related Moderate/Severe Adverse Events)

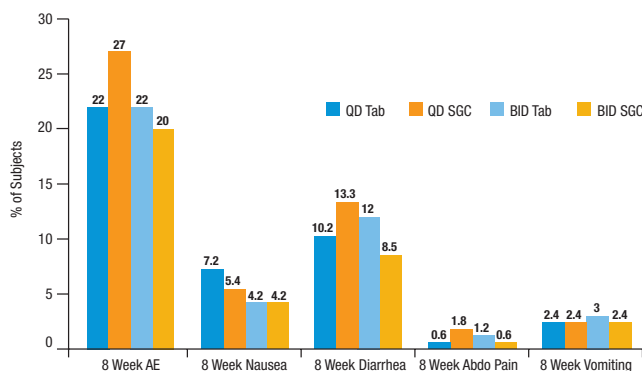
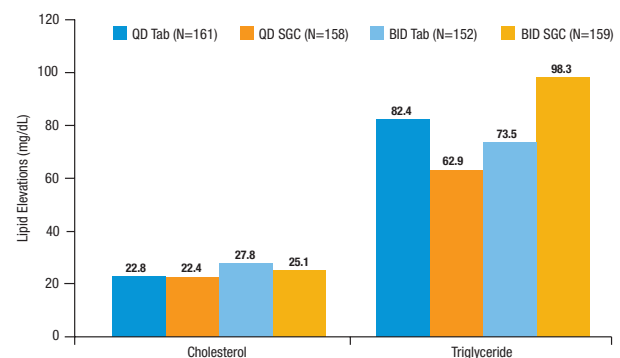


Figure 2b. Lipid Elevations Observed in Study M05-730 (Mean Change from Baseline)



- Adverse event (AE) profiles in Study M05-730 were similar across BID and QD, SGC and tablet treatment groups with respect to:
 - All AEs
 - Related, moderate or greater severity AEs
 - Gastrointestinal AEs
 - Discontinuations, SAEs, Grade 3+ laboratory abnormalities
- Lipid elevations at Week 8 were similar across treatment groups, and similar to those seen in prior lopinavir/ritonavir SGC studies.
- The increase in ritonavir exposure observed with the lopinavir/ritonavir tablet is not associated with a change in safety or tolerability, compared to the lopinavir/ritonavir SGC.
- The impact of higher ritonavir exposure on the pharmacokinetic enhancing profiles of co-administered protease inhibitors is shown in Table 4.

Discussion cont.

Table 4. Effect of Ritonavir Dose on Co-Administered Protease Inhibitors

Geometric Mean	Co-Administered PI		
	C_{max} (mcg/mL)	AUC _{tau} (mcg•h/mL)	C_{min} (mcg/mL)
Lopinavir – Arithmetic mean, single dose data were presented			
Lopinavir 400 mg + Ritonavir 100 mg	8.5	105.3	NA
Lopinavir 400 mg + Ritonavir 200 mg	8.3	121.9	NA
Fosamprenavir			
Fosamprenavir 1400 mg QD + Ritonavir 100 mg QD	7.9	66.4	0.86
Fosamprenavir 1400 mg QD + Ritonavir 200 mg QD	7.2	69.4	1.45
Atazanavir			
Atazanavir 400 mg QD + Ritonavir 100 mg QD	7.7	69.6	NA
Atazanavir 400 mg QD + Ritonavir 200 mg QD	7.1	69.1	NA
Tipranavir			
Tipranavir 500 mg BID + Ritonavir 100 mg BID	130.1	755	16.3
Tipranavir 500 mg BID + Ritonavir 200 mg BID	129.2	934	26.3
Darunavir – Arithmetic mean, single dose data were presented			
Darunavir 600 mg + Ritonavir 100 mg	5.6	92.3	NA
Darunavir 800 mg + Ritonavir 600 mg	6.2	102.0	NA

Reference: Lopinavir: Study M96-552; Fosamprenavir: Lexiva® USPI; Atazanavir: Bristol-Meyers Squibb Study AI424028; Tipranavir: Boehringer Ingelheim Study 1182.5; Darunavir: Tibotec Study TMC114-C105 and TMC114-C114.

- The maximum pharmacokinetic enhancement of sensitive CYP3A substrates occurs at the ritonavir dose of 100 mg.
- More than two-fold increases in the C_{max} and AUC of ritonavir (by doubling the dose to 200 mg) is not likely to result in clinically meaningful increases in exposure of co-administered protease inhibitors.
 - The increase in ritonavir C_{max} observed for the ritonavir tablet formulation compared to the SGC is substantially less than that observed after doubling the ritonavir dose from 100 to 200 mg.
- Therefore, the increased C_{max} observed with the ritonavir tablet does not alter the pharmacokinetic enhancing profile of ritonavir.

Conclusions

- Ritonavir AUC after administration of the pilot tablet formulation was bioequivalent to the marketed SGC.
- The upper bound of the 90% confidence interval for ritonavir C_{max} exceeded 1.25. This may be due, in part, to more efficient absorption of the tablet formulation compared to the SGC. Further formulation refinements were made and the results of the pivotal biostudy will be presented at this conference. [Session #THAB04]
- The higher C_{max} of the ritonavir tablet is unlikely to impact the safety profile or pharmacokinetic enhancing profile compared to the ritonavir SGC.

References

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5. Lexiva® package insert, March 2008
6. Bristol-Meyers Squibb Study AI424028 (Atazanavir/ritonavir)
7. Boehringer Ingelheim Study 1182.5 (Tipranavir/ritonavir)
8. Tibotec Study TMC114-C105 and Study TMC114-C114 (Darunavir/ritonavir)