CROI 2010, Abstract S-197

17th Conference on Retroviruses and Opportunistic Infections
February 16-19, 2010
San Francisco, CA

A Pharmacokinetic Comparison of Adult and Pediatric Formulations of Raltegravir (RAL) in Healthy Adults

DM Brainard,[1] IN Gendrano III,[1] B Jin,[1] WW Lewis,[2] LA Wenning,[1] JA Wagner,[1] M Iwamoto[1]

[1]Merck & Co., Inc., Whitehouse Station, NJ; [2]Covance Clinical Research Unit, Dallas, TX

Diana M. Brainard, MD
RY34-A500
Merck & Co., Inc.
126 E. Lincoln Avenue
Rahway, NJ 07065

Phone: 732-594-5558
diana_brainard@merck.com

Abstract

Background: RAL is a HIV-1 integrase strand transfer inhibitor approved for treatment of HIV-1 in combination with other antiretrovirals in adults. Infection is not limited to adults, thus pediatric development of this compound is warranted and underway. Two pediatric formulations have been developed: the chewable ethylcellulose (EC) formulation and an oral granule (OG) formulation for suspension. The current study evaluated the safety and tolerability of these pediatric formulations and compared their plasma pharmacokinetic profiles after single doses of 400 mg to that obtained after a single dose of the marketed poloxamer (POL) tablet formulation. In addition, the effect of a high-fat meal on the pharmacokinetics of the EC formulation was assessed.

Methods: Open label, 4-period, randomized, crossover study in 12 adults. Treatment A: 400 mg RAL POL x 1. Treatment B: 400 mg RAL EC x 1. Treatment C: 400 mg RAL OG in suspension x 1. Treatment D: 400 mg RAL EC x 1 following a high-fat meal. There was a 4 day washout between each period.

Results: No serious adverse experiences (AEs) were reported and there were no discontinuations due to drug related clinical or laboratory AEs. The geometric mean (GM) C_{12hr} of 400-mg RAL OG, EC and POL formulations was similar with an estimated geometric mean ratio (GMR) for OG/POL of 1.09 with 90% CI of (0.84, 1.41), and for EC/POL of 0.90 (0.70, 1.18). OG demonstrated a 2.6-fold and 4.6-fold higher $AUC_{0-\infty}$ and C_{max}, respectively, compared to POL. EC demonstrated a 1.8-fold and 3.2-fold higher $AUC_{0-\infty}$ and C_{max}, respectively, compared to POL. Both EC and OG formulations had earlier median T_{max} values compared to POL (0.5 and 1.0 hours for EC and OG, respectively, compared to 4.0 hours for POL). For EC, compared to administration in the fasted state, administration with a high-fat meal led to an increase in C_{12hr} [GMR (90% CI) for fed/fasted = 2.88 (2.21 , 3.75)], a decrease in C_{max} [GMR (90% CI) = 0.38 (0.28 , 0.52)], a delay in T_{max} [median 0.5 hr in the fasted state and 1.0 hr in the fed state], and a similar $AUC_{0-\infty}$ [GMR (90% CI) = 0.94 (0.78 , 1.14)].

Conclusions: Overall, the C_{12hr} was similar for all three formulations. Both pediatric formulations demonstrated moderately higher $AUC_{0-\infty}$ and C_{max} values as compared to the POL formulation. A high-fat meal slowed the rate of absorption from the EC formulation, with no statistically meaningful change in extent of absorption. These data support further clinical investigation of the OG and EC pediatric formulations.

Background

- RAL is a novel HIV-1 integrase strand transfer inhibitor indicated for the treatment of HIV-1 infection in adults.
- HIV-1 infection is not limited to adults, thus pediatric development of this compound is underway.
- Two pediatric formulations have been developed:
  - Chewable ethylcellulose tablet (EC) formulation.
  - Oral granules (OG) formulation for suspension.
- A clinical study was conducted to:
  - Assess the safety and tolerability of these pediatric formulations following single dose administration.
  - Compare the plasma pharmacokinetic profiles of the pediatric formulations after single doses of 400 mg to that obtained after a single dose of the marketed poloxamer (POL) tablet formulation.
  - Assess the effect of a high-fat meal on the pharmacokinetics of the EC formulation.

Study Design

4-Period Randomized, Crossover Study in 12 Healthy Adult Male and Female Subjects

Number of Subjects	Period 1	Period 2	Period 3	Period 4
N=12	RAL 400 mg POL (1 x 400 mg)	RAL 400 mg EC (4 x 100 mg)	RAL 400 mg OG Liquid suspension	RAL 400 mg EC (4 x 100 mg) with a high-fat meal

Methods

Safety Assessment

- Safety and tolerability were assessed by measurements of physical examinations, vital signs, ECG, and laboratory safety tests (CBC, chemistry panel, urinalysis).
- Adverse experiences were evaluated as to their intensity, seriousness, and relationship to study drug.

Analytical and Pharmacokinetic

- Plasma samples for RAL assay were collected predose and at the following times post-dose: 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 32, 48, 72 hours.
- Plasma samples were analyzed for RAL concentration using a validated HPLC–MS/MS assay with a lower limit of quantitation of 4.5 nM (2 ng/mL).[1]
- C_{12hr}, C_{max}, and T_{max} were determined by inspection.
- $AUC_{0-\infty}$ was calculated using linear up/log down trapezoidal method.

Statistical Analysis

- A linear mixed-effects model was used with fixed effect of treatment and period and a random subject effect.
- Natural-log transformation was performed for C_{12hr}, $AUC_{0-\infty}$, and C_{max} and before analysis.
- Two-sided 90% confidence intervals (CI) for the true mean difference in RAL C_{12hr} $AUC_{0-\infty}$, and C_{max} on the log scale were calculated and then exponentiated to obtain a CI for the true geometric mean ratio (GMR).
  - OG formulation vs. POL formulation
  - EC formulation vs. POL formulation
  - Food effect was analyzed in a similar fashion (high-fat meal/fasted).
- Summary statistics and between-treatment comparisons were provided for T_{max}.

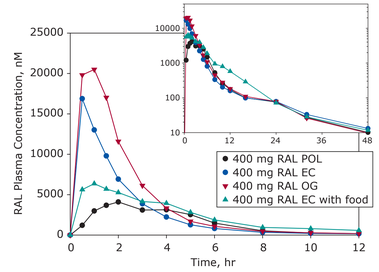
Subjects and Disposition

- Randomized:
  - Total (mean; age range): 12 (40 yrs; 26 to 552 yrs)
    - Male (mean; weight range) 9 (83 kg; 63 to 95 kg)
    - Female (mean; weight range) 3 (62 kg; 54 to 73 kg)
- Completed: 12
- Discontinued: 0

Results

Pharmacokinetics

Mean Plasma Concentration-Time Profiles for RAL Following Single-Dose Administration of the RAL OG Formulation, the RAL POL Formulation, and the RAL EC Formulation in Healthy Adult Male and Female Subjects (N=12) (Inset = Semilog scale)

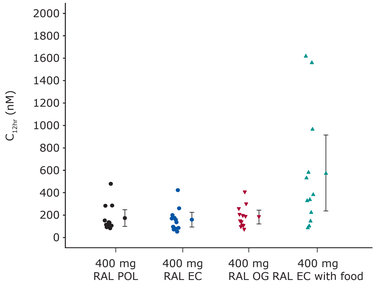


Summary Statistics of RAL Plasma Pharmacokinetics Following 400 mg Single-Dose Administration of the RAL OG Formulation, the RAL POL Formulation, and the RAL EC Formulation in 12 Healthy Adult Male and Female Subjects in the Fasted and Fed State

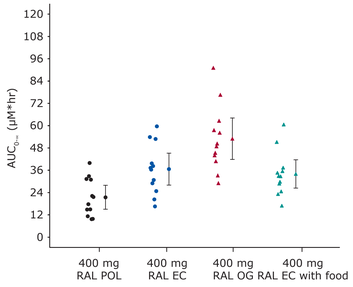
Pharmacokinetic Parameter (Units)	RAL POL	RAL EC	RAL OG	RAL EC FED	Comparison	GMR (90% CI)
	GM (%CV)	GM (%CV)	GM (%CV)	GM (%CV)		
C_{12hr} (nM)§	149 (58.0)	134 (65.7)	162 (55.0)	387 (122.5)	OG/POL	1.09 (0.84, 1.41)
					EC/POL	0.90 (0.70, 1.18)
					EC FED/EC FASTED	2.88 (2.21, 3.75)
AUC_{0-t} (μM•hr)§	19.2 (52.4)	34.2 (40.8)	50.4 (33.3)	32.3 (34.9)	OG/POL	2.62 (2.17, 3.17)
					EC/POL	1.78 (1.47, 2.15)
					EC FED/EC FASTED	0.94 (0.78, 1.14)
C_{max} (μM)§	5.00 (77.2)	16.1 (46.7)	23.2 (34.1)	6.14 (49.0)	OG/POL	4.64 (3.41, 6.30)
					EC/POL	3.22 (2.37, 4.38)
					EC FED/EC FASTED	0.38 (0.28, 0.52)
T_{max} (hr)#	4.0	0.5	1.0	1.0		
$t_{1/2l}$ (hr)¶	1.5 (0.3)	1.7 (0.2)	1.6 (0.3)	2.0 (0.6)		
$t_{1/2T}$ (hr)¶	9.0 (5.9)	9.3 (5.1)	10.0 (3.2)	9.2 (3.8)		

§ Back-transformed least squares mean and confidence interval from mixed effects model performed on the natural log-transformed values.
# Median values presented for T_{max}.
¶ Harmonic mean (jack-knife standard deviation) values presented for $t_{1/2l}$ and $t_{1/2T}$. For $t_{1/2T}$, the N's for POL, EC, OG, and EC FED are 11, 12, 12, and 10, respectively.

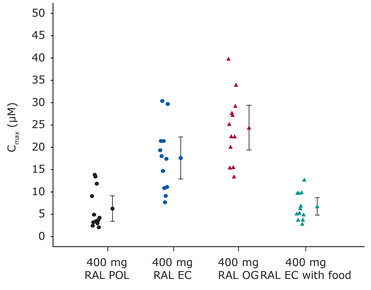
Scatter Plot of Individual C_{12hr} (nM) Values, Geometric Means, and 95% Confidence Intervals Following Single-Dose Administration of the RAL POL Formulation, the RAL OG Formulation, and the RAL EC Formulation (Fasted and Fed) in Healthy Adult Male and Female Subjects (N=12)



Scatter Plot of Individual $AUC_{0-\infty}$ (μM*hr) Values, Geometric Means, and 95% Confidence Intervals Following Single-Dose Administration of the RAL POL Formulation, the RAL OG Formulation, and the RAL EC Formulation (Fasted and Fed) in Healthy Adult Male and Female Subjects (N=12)



Scatter Plot of Individual C_{max} (μM) Values, Geometric Means, and 95% Confidence Intervals Following Single-Dose Administration of the RAL POL Formulation, the RAL OG Formulation, and the RAL EC Formulation (Fasted and Fed) in Healthy Adult Male and Female Subjects (N=12)



Summary of Pharmacokinetics

- The geometric mean C_{12hr} of both 400 mg RAL OG and EC formulations were similar to that obtained with the RAL POL formulation.
- The geometric mean $AUC_{0-\infty}$ of both 400 mg RAL OG and EC formulations were moderately higher (2.6- and 1.8-fold, respectively) than that obtained with the RAL POL formulation.
- Both the EC and OG formulations had earlier median T_{max} values compared with the POL (0.5 and 1.0 hours for the EC and OG formulations, respectively, compared to 4.0 hours for the POL).
- Compared to administration of the EC formulation fasting, administration with a high-fat meal led to an increase in C_{12hr}, a decrease in C_{max}, a delay in T_{max}, and a similar $AUC_{0-\infty}$. Intersubject variability for C_{12hr} was increased in the presence of food.

Safety

- Single dose administration of each of the 400 mg RAL formulations was generally well tolerated in healthy adult male and female subjects.
- No serious clinical or laboratory adverse experiences were reported; no subject discontinued because of an adverse experience.
- Six (6) subjects reported a total of 9 different nonserious clinical adverse experiences, 1 of which (somnolence) was judged by the investigator to be possibly related to study drug.
- All adverse experiences reported were transient and rated as mild in intensity.
- There were no laboratory adverse experiences reported in this study.

Reference
[1]Merschman, SA, Vallano PT, Wenning, LA, Matuszewski BK, Woolf EJ. Determination of the HIV integrase inhibitor, MK-0518 (raltegravir), in human plasma using 96-well liquid–liquid extraction and HPLC-MS/MS. *J Chromatog B* 2007; 857: 15-19.

Acknowledgments

The authors would like to thank:

- The subjects who participated in this study.
- Clinical research unit staff.
- Jon Stek and Michele McColgan for their assistance with the creation of this poster.

Conclusions

- Single doses of 400 mg RAL POL formulation, EC formulation (administered in the fed and fasted states), and OG in a liquid suspension were generally well tolerated.
- After single dose administration of RAL, the geometric mean C_{12hr} values were similar for all three formulations whereas the geometric means for $AUC_{0-\infty}$ and C_{max} of both the EC and OG formulations were moderately higher than that of the RAL POL formulation.
- Both EC and OG formulations demonstrated lower variability (% CV) with respect to $AUC_{0-\infty}$ and C_{max} as compared to the POL formulation.
- Administration of RAL EC formulation with a high-fat meal slows the rate of absorption, without a clinically meaningful change in the extent of absorption.

stekjo_2010_0134_01.indd 2/09/10 CROI, 4x8, Scale 200%