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

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Abstract

Background: RAL is a novel integrase strand transfer inhibitor approved for the treatment of HIV-1 infection in combination with other antiretroviral agents. Development of pediatric formulations is underway. The current study evaluated the safety and tolerability of these pediatric formulations. Scattered plots are provided. The geometric mean (GM) Cmax and Cmin values were compared to the PO formulation.

Methods: Adults (N=12) were randomized to 1 of 4 treatments: Treatment A: 400 mg RAL OG x 1 following a high-fat meal; Treatment B: 400 mg RAL EC x 1 following a high-fat meal; Treatment C: 400 mg RAL OG x 1 in the fasted state; Treatment D: 400 mg RAL EC x 1 in the fasted state. There was a 14-day washout between each treatment phase.

Results: No serious adverse experiences (AEs) were reported and there were no discontinuations due to drug-related clinical laboratory AEs. The geometric mean (GM) Cmax of RAL OG, EC, and PO formulations was similar with an averaged ratio of 1.08 (0.99, 1.14). AUC0-12hr of EC and PO formulations were comparable (1.00, 0.94, 1.10). The GM Cmax of OG formulation was higher than EC and PO formulations, respectively, by a factor of 3.99 (1.70, 8.30). The main precaution observed was somnolence, which (somatic) was judged by the investigator to be possibly related to study drug.

Analytical and Pharmacokinetic

• Plasma samples for RAL were collected pre-dose and at the following time points: 0, 0.5, 1, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 72, 96 hours.

Statistical Analysis

• A linear mixed-effects model was used with fluid effect of treatment and period and a random subject effect.

Safety

• No serious clinical or laboratory adverse experiences were reported; no subject discontinued due to an adverse experience. There were no deaths.

Conclusions

• Both EC and OG formulations were generally well tolerated. A lower mean plasma exposure of RAL was observed with the OG formulation compared to EC formulation.

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Results

Mean Plasma Concentration-Time Profiles for RAL OG Formulation, RAL EC Formulation, and the RAL EC Pediatric Formulation in Each Treatment Period

Scatter Plot of Individual Cmin (µM) Values, Geometric Means, and 65% Confidence Intervals Following Single-Dose Administration of the RAL OG Formulation, the RAL OG Formulation, and the RAL EC Formulation in Healthy Adult Male and Female Subjects (N=12)

Scatter Plot of Individual AUC0-12hr (µM*hr) Values, Geometric Means, and 65% Confidence Intervals Following Single-Dose Administration of the RAL OG Formulation, the RAL OG Formulation, and the RAL EC Formulation in Healthy Adult Male and Female Subjects (N=12)

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• Single doses of 400 mg RAL OG formulation, EC formulation (administered in the fed and fasted states), and OG in a lipid suspension were generally well tolerated.

• The geometric mean AUC12hr for OG and EC formulations were comparable; however, the geometric mean Cmax values of OG formulation were reported to be 3.99 times higher than those of EC formulation. The OG formulation was demonstrated to have a lower variability (%CV) compared to EC formulation with respect to AUC12hr.

Conclusions

1. Safety

• A single dose administration of each of the 400 mg RAL formulations was generally well tolerated. There were no serious clinical or laboratory adverse experiences reported; no subject discontinued due to an adverse experience. There were no deaths. No serious clinical or laboratory adverse experiences were reported; no subject discontinued due to an adverse experience.

• There were no laboratory adverse experiences reported. All adverse experiences were related to treatment and are consistent with the known safety characteristics of RAL.

2. Pharmacokinetic

• Both EC and OG formulations demonstrated lower variability (%CV) with respect to AUC12hr and Cmax as compared to the PO formulation.

• Administration of RAL EC formulation with a high-fat meal slowed the rate of absorption, without a clinically meaningful change in the extent of absorption.