

# The Effect of Moderate- and High-Fat Meals on the Bioavailability of Dolutegravir/Rilpivirine Fixed-Dose Combination Tablet

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**Abstract:** Dolutegravir 50 mg (DTG) and rilpivirine 25 mg (RPV) are a newly approved 2-drug regimen for the treatment of HIV in virally suppressed patients. A 2-part study evaluated the relative bioavailability and food effect of five experimental fixed-dose combination (FDC) tablet formulations of DTG/RPV. When given with a moderate- or high-fat meal, the absorption of both DTG and RPV was increased, resulting in higher exposures. As per product labelling, DTG/RPV FDC should be taken with a meal.

**Keywords:** food effect, pharmacokinetics, dolutegravir, rilpivirine

Juluca<sup>®</sup>, (ViiV Healthcare) the 2-drug regimen (2-DR) of dolutegravir 50 mg (DTG) and rilpivirine 25 mg (RPV), administered once daily with a meal has been approved in many countries for the treatment of HIV-1 infection in virologically suppressed patients. The approvals were based on the results of two Phase 3 trials (SWORD 1 and 2) which demonstrated non-inferior efficacy and safety of DTG + RPV once daily with a meal when compared to current 3-drug antiretroviral therapy,<sup>1</sup> and a pivotal bioequivalence (BE) study in fed condition which demonstrated that a fixed-dose combination tablet (DTG/RPV) was bioequivalent to the single entity tablets.<sup>2</sup>

During the course of drug development, a relative bioavailability (BA) study was conducted to evaluate the pharmacokinetics of multiple experimental fixed-dose combination (FDC) formulations in both the fasted and fed states in order to select the best FDC tablet formulation and to estimate food effect.<sup>3</sup> This communication will report the effect of food (moderate- and high-fat/calorie meals) on the pharmacokinetics of one of the DTG/RPV fixed-dose combination tablets: Formulation AM. Formulation AM was compositionally identical to the formulation evaluated in the pivotal BE study and eventually marketed product (DTG/RPV FDC) Juluca<sup>®</sup>, except had a different color film coat and no debossing. The relative bioavailability and food effect comparisons for the other formulations were previously presented<sup>3</sup> and will not be repeated here.

Study 201674 (NCT02373930) was a 2-part single-dose study to evaluate the relative bioavailability and food effect of five experimental FDC tablet formulations of DTG/RPV. Part 1 was a randomized, open-label, 3-way crossover, incomplete block, Youden square design in 24 healthy adult subjects with a 10-day between-treatment washout. All doses were administered 30 min after consumption of a high-fat meal (approximately 900 total calories: 17% protein, 28% carbohydrates, and 56% fat).<sup>4</sup> Part

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**Table 1** Effect of Moderate- or High-Fat Meals on the Pharmacokinetics of a Dolutegravir/Rilpivirine Fixed-Dose Combination Tablet (Formulation AM) in Healthy Subjects

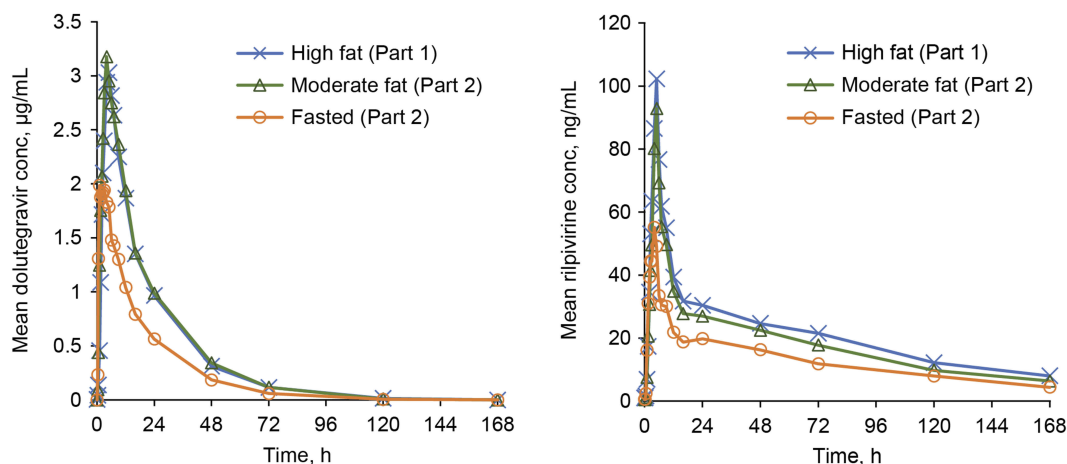
Drug	PK Parameter	Geometric Mean (CV%)		Ratio of Geometric Least Squares Means (90% Confidence Interval) Fed vs Fasted
		Fed N=12	Fasted N=12	
<b>Moderate-Fat Meal<sup>a</sup> (Part 2) vs Fasted (Part 2) Crossover Comparison</b>				
Dolutegravir	AUC(0-∞) (μg.h/mL)	64.62 (20.7)	34.64 (57.1)	1.865 (1.542, 2.257)
	C <sub>max</sub> (μg/mL)	3.40 (21.2)	1.94 (63.2)	1.749 (1.403, 2.181)
	T <sub>max</sub> (h) <sup>c</sup>	3.51 (1.0, 5.0)	2.25 (1.0, 5.0)	N/A
Rilpivirine	AUC(0-∞) (ng.h/mL)	3508 (37.8) <sup>d</sup>	2236 (67.6) <sup>d</sup>	1.569 (1.244, 1.980) <sup>d</sup>
	C <sub>max</sub> (ng/mL)	95.08 (35.9)	50.29 (92.2)	1.891 (1.339, 2.669)
	T <sub>max</sub> (h) <sup>c</sup>	5.00 (2.0, 5.0)	4.01 (2.0, 5.0)	N/A
<b>High-Fat Meal<sup>b</sup> (Part 1) vs Fasted (Part 2) Parallel Cohort Comparison</b>				
Dolutegravir	AUC(0-∞) (μg.h/mL)	60.75 (25.6)	34.64 (57.1)	1.873 (1.533, 2.289)
	C <sub>max</sub> (μg/mL)	3.36 (18.6)	1.94 (63.2)	1.718 (1.411, 2.092)
	T <sub>max</sub> (h) <sup>c</sup>	4.00 (2.0, 6.0)	2.25 (1.0, 5.0)	N/A
Rilpivirine	AUC(0-∞) (ng.h/mL)	3743 (34.1) <sup>d</sup>	2236 (67.6) <sup>d</sup>	1.716 (1.360, 2.164) <sup>d,e</sup>
	C <sub>max</sub> (ng/mL)	107.9 (45.7)	50.29 (92.2)	2.168 (1.619, 2.902)
	T <sub>max</sub> (h) <sup>c</sup>	4.00 (2.5, 5.0)	4.01 (2.0, 5.0)	N/A

**Notes:** <sup>a</sup>Moderate-fat breakfast contained ~625 total calories: 125 calories from protein, 300 calories from carbohydrate, and 200 calories from fat. <sup>b</sup>High-fat breakfast contained ~900 total calories: 150 calories from protein, 250 calories from carbohydrate, and 500 calories from fat. <sup>c</sup>T<sub>max</sub> presented as median (range); T<sub>max</sub> was not formally compared (N/A). <sup>d</sup>Approximately 20% of PK profiles across the study had AUC(0-∞) with % extrapolated >20%. <sup>e</sup>(n=11); 1 subject (fed) was excluded from the statistical analysis of AUC(0-∞) because % extrapolated >40% and lambda z time duration <2× calculated t<sub>1/2</sub>.

I evaluated four different formulations (AS, AM, AQ, AK) and a reference which was 1 tablet each of DTG (Tivicay<sup>®</sup>) and RPV (Edurant<sup>®</sup>) taken concurrently. Part 2 was a randomized, open-label, 3-way crossover with a 10-day between-treatment washout in 3 distinct cohorts each with 12 subjects. Two experimental tablets from Part 1 (AK and AM) and one previously untested experimental tablet (AU) were selected for evaluation in Part 2. All doses were administered

in the fasted state or 30 min after a moderate-fat meal (approximately 625 total calories: 20% protein, 48% carbohydrates, and 32% fat) in Part 2.

During both Parts 1 and 2, serial plasma PK samples were taken from 0 hours (predose) up to 168 hours after dosing and a variety of safety assessments were conducted. DTG and RPV plasma concentrations were measured by validated LC/MS/MS assays<sup>5,6</sup> and PK parameters were estimated by

**Figure 1** Mean plasma concentration–time profile of dolutegravir (left) and rilpivirine (right) following a single oral dose of dolutegravir/rilpivirine fixed-dose combination tablet (Formulation AM) in healthy subjects.

noncompartmental methods using Phoenix WinNonlin (Certara, Princeton, NJ, USA). For each primary PK parameter evaluated [AUC(0-∞) and C<sub>max</sub>], the point estimates and corresponding 90% CI were constructed for the ratio of the geometric least squares (GLS) means to compare the DTG and RPV PK parameters in the fed vs fasted state. The effect of a moderate-fat meal was derived from the PK results for Formulation AM from Part 2 (within-subject comparison between fasted and moderate-fat fed) and the effect of a high-fat meal on the systemic exposure of DTG and RPV was derived from cross-cohort comparisons of Formulation AM PK between Part 1 (high fat) and Part 2 (fasted).

This study was conducted in accordance with ICH GCP and the ethical principles outlined in the Declaration of Helsinki, 2013. The protocol and informed consent were approved by the Midlands Independent Review Board (Overland Park, KS, USA). Written informed consent was obtained from each subject prior to the performance of any study-specific procedures.

DTG and RPV exposures were higher when the DTG/RPV FDC was administered after consumption of a moderate- or high-fat meal than when administered in the fasted state (Table 1; Figure 1). Co-administration of DTG/RPV FDC with a moderate-fat meal increased DTG AUC(0-∞) and C<sub>max</sub> by 87% and 75%, respectively, and RPV AUC(0-∞) and C<sub>max</sub> by 57% and 89%, respectively. Co-administration of the DTG/RPV FDC with a high-fat meal increased DTG AUC and C<sub>max</sub> by 87% and 72%, respectively, and RPV AUC and C<sub>max</sub> by 72% and 117%, respectively. The study was not designed to directly compare different meal types and any apparent differences may be attributed to methodology used in comparisons (within-subject crossover for moderate fat versus cross-cohort for high fat).

In both parts of the study, drug-related adverse events (AEs) were mostly mild (abdominal pain, diarrhea, headache). Only three AEs were reported as moderate intensity (tooth abscess, headache) and no serious AEs were reported during the study. No clinically relevant findings in vital signs, ECGs, or clinical laboratory tests were reported. There were two non-serious AEs, both considered not related to study drug, leading to withdrawal from study, which included the above tooth abscess and ALT increase.

In conclusion, data collected in this relative bioavailability and food effect study allowed us to characterize the effect of moderate- and high-fat meals on the PK of the DTG/RPV FDC (Formulation AM). As expected, when the DTG/RPV fixed-dose combination tablet was taken with a meal, the

absorption of both dolutegravir and rilpivirine was increased, resulting in higher DTG and RPV exposures. The magnitude of food effect was consistent with what was previously observed for the DTG and RPV single entity products<sup>7,8</sup> and with other DTG- or RPV-containing fixed-dose combination products.<sup>9,10</sup> While DTG is approved to be taken with or without food, taking DTG/RPV FDC in fasted condition or with only a protein-rich nutritional drink may result in decreased plasma concentrations of rilpivirine, which could potentially reduce the therapeutic effect of DTG/RPV FDC.<sup>7</sup> DTG/RPV FDC, similar to rilpivirine-containing medicinal products, must be taken with a meal to obtain optimal absorption of rilpivirine.

## Disclosure

Rashmi Mehta and Allen Wolstenholme are employees of GlaxoSmithKline. Caifeng Fu is an employee of PAREXEL International. Herta Crauwels is a full-time employee of Janssen Pharmaceutical Companies, which is owned by Johnson and Johnson, and stockholder of Johnson and Johnson, market authorisation holder of rilpivirine. Brian Wynne and Kimberly Adkison are employees of ViiV Healthcare. The authors report no other conflicts of interest in this work.

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