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Effect of Food on the Pharmacokinetics of the Integrase Inhibitor Dolutegravir

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Healthy subjects received dolutegravir at 50 mg in a single-dose crossover study while they were in the fasted state or with low-, moderate-, or high-fat meals. Food increased dolutegravir exposure and reduced the rate of absorption. The area under the concentration-time curve from 0 h to infinity ($AUC_{0-\infty}$) increased by 33%, 41%, and 66% when administered with low-, moderate-, or high-fat meals, respectively, compared with fasting. This increase in dolutegravir exposure is not anticipated to impact clinical safety, and therefore dolutegravir can be taken with or without food and without regard to fat content.

Dolutegravir (DTG; S/GSK1349572) is an integrase inhibitor for the treatment of HIV infection, does not require boosting with ritonavir, and possesses activity against raltegravir-resistant strains (3, 4). DTG is currently in phase III clinical development at a dose of 50 mg once daily in treatment-naive and integrase-naïve treatment-experienced subjects and at 50 mg twice daily in subjects with resistance to raltegravir or elvitegravir. The pharmacokinetic (PK) profile of DTG is characterized by achievement of high plasma drug exposures, a half-life of approximately 15 h, low to moderate intersubject variability, and a well-described PK/pharmacodynamic relationship (5, 6). The ability to administer antiretroviral medications with or without food is an important aspect of dosing convenience. Drugs that do not have food restrictions are preferred by patients and allow them to take their medications without regard to timing or content of meals. The objective of this study was to evaluate the effect of meals with various fat and calorie contents on the PK of DTG.

(These data were presented in part at the 12th International Workshop on the Clinical Pharmacology of HIV Therapy, Coral Gables, FL, April 2011.)

This was a two-part, single-center, randomized, open-label, crossover study of healthy adult male and female subjects. The sample size was 24 subjects in part 1 and 18 subjects in part 2. In part 1, 24 subjects received DTG at 50 mg as a single dose after an overnight fast of at least 6 h. Eighteen of these subjects were enrolled into part 2 and were randomized to receive a single 50-mg dose on three separate occasions with a low-fat (300 kcal, 7% fat), moderate-fat (600 kcal, 30% fat), or high-fat (870 kcal, 53% fat) meal. To avoid selection bias, the first 18 subjects who were enrolled in part 1 who still met all eligibility criteria continued to part 2. Serial blood samples for PK analysis were collected predosing and 1, 2, 3, 4, 5, 6, 8, 12, 24, and 48 h postdosing. There was a washout period of 7 days between doses. Safety evaluations included physical exam, vital signs, electrocardiograms, a full laboratory panel, and daily monitoring for adverse events (AEs). Subjects had a follow-up visit within 7 to 14 days after the last dose.

Subjects were judged to be healthy by physical exam, medical history, and laboratory testing. Exclusion criteria included a positive HIV or hepatitis C virus antibody result, a positive hepatitis B virus surface antigen result, a positive illicit drug or alcohol result, or use of any prescription or nonprescription drugs, including vitamins or herbal products, within 7 days before the first dose and throughout the study. Written informed consent was obtained from all subjects, and the protocol was approved by the institutional review board of the study site (IntegReview, Austin, TX [NCT 01098513]).

DTG plasma concentrations were determined using a previously described, validated, high-performance liquid chromatography–tandem mass spectrometry method (5). Noncompartmental PK analysis was performed with WinNonlin (version 5.2; Pharsight Corporation, St. Louis, MO) to generate estimated PK parameters, including the area under the concentration-time curve from 0 h to infinity ($AUC_{0-\infty}$), maximum concentration of drug in plasma (C_{max}), C_{24} (concentration at 24 h postdosing), and time to maximum concentration of drug in plasma (T_{max}). Geometric least squares mean ratios and 90% confidence intervals were generated by the mixed-effects model for within-subject treatment comparisons.

Twenty-four subjects (14 female and 10 male) were enrolled, and 18 completed all four arms of the study. The mean age (± standard deviation [SD]) was 38.6 (±14.6) years. The mean body mass index (± SD) was 24.8 (±2.6) kg of body weight/m^2. Twenty-two subjects were Caucasian, one subject was African American, and one subject was of Arabic/North African heritage.

Concentration-time profiles of DTG in the fasting state or with meals of various fat and calorie contents are shown in Fig. 1. Coadministration with food increased plasma DTG exposures and reduced the rate of absorption, as evidenced by a longer T_{max}. Pharmacokinetic parameters are presented in Table 1, and statistical comparisons of these PK parameters are shown in Table 2. The increases in exposure were modest and were observed with increasing fat content. The $AUC_{0-\infty}$ increased by 33%, 41%, and 66% when DTG was administered with low-, moderate-, and high-fat meals, respectively, compared with the fasting state. The plasma DTG C_{max} increased by 46%, 52%, and 67% when DTG was administered with low-, moderate-, and high-fat meals, re-

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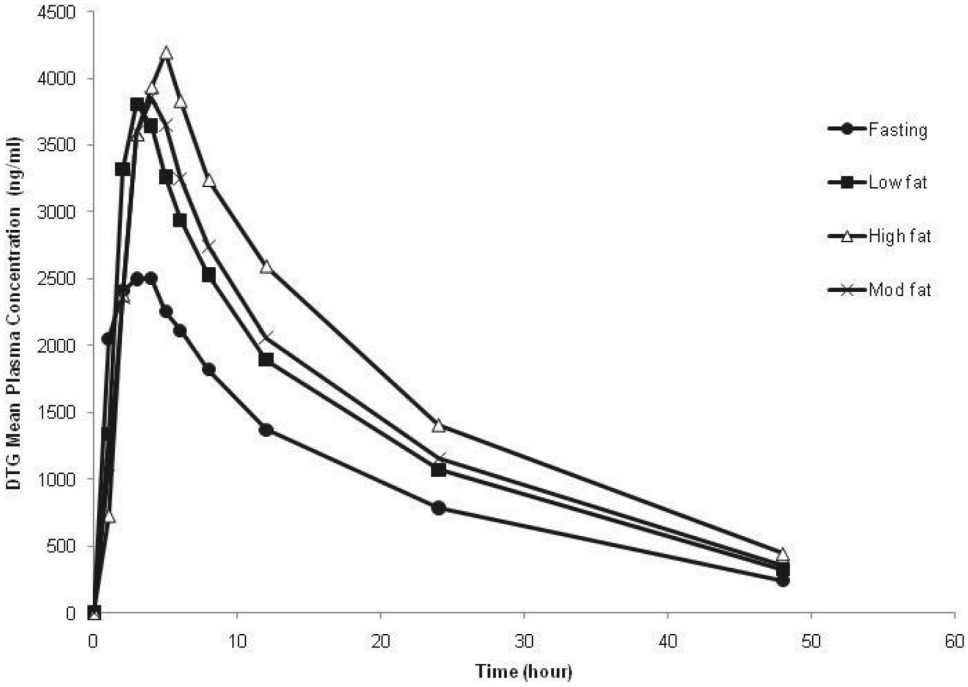

FIG 1 Mean concentration-time profiles of DTG administered in the fasting state or with meals with various fat contents.

spectively. When DTG was administered while subjects were fasting, the median T_{max} was 2.1 h. This increased to 3.0 h for a low-fat meal, 4.0 h for a moderate-fat meal, and 5.0 h for a high-fat meal. The elimination half-life was not affected by food.

DTG was well tolerated, with few AEs reported. No grade 3/grade 4 AEs or withdrawals due to AEs were reported. Two subjects reported gastrointestinal AEs (1 nausea, 1 vomiting; both grade 2) when DTG was administered under fasting conditions. Neither subject enrolled in part 2 of the study. There were no drug-related AEs when DTG was administered with food. Additionally, there were no clinically significant trends in clinical laboratory values, vital signs, or electrocardiograms.

Antiretroviral therapy has evolved to the point where many effective regimens can be administered once daily with one or two tablets or capsules per day. However, many of the most commonly used regimens still have food restrictions, requiring dosing with a meal or on an empty stomach (2, 8). Potent, once-daily antiretrovirals that allow dosing without regard to meals would be advantageous for patient convenience and adherence.

This study demonstrates that food modestly increases the exposure to DTG. The increases demonstrated in this study ranged from 33% to 66%, depending on the meal fat content, and are not anticipated to impact safety. In a treatment-naïve, phase IIb trial (SPRING-1), HIV-infected subjects who received DTG with or without food tolerated the drug well, as evidenced by the low rate of study withdrawal and favorable adverse event profile (9). In SPRING-1, subjects receiving DTG at 50 mg once daily had a mean (covariance [CV]) for C_τ (concentration at the end of the dosing interval) of 1.20 μg/ml (62%), which is similar to the exposure in this study for the subjects who received a high-fat meal (mean [CV] C_{24}, 1.30 μg/ml [47%]) (9). Furthermore, data from SPRING-1 demonstrated low to moderate variability in DTG exposures (C_τ CV range, 62 to 67%) across all DTG doses, suggesting that dosing without regard to food does not lead to unpredictable high exposures in clinical practice (9). Finally, an additional phase IIb study of integrase-resistant, treatment-experienced, HIV-infected subjects (VIKING) in which DTG was administered both at 50 mg once daily and as a twice-daily administration to sequential cohorts of subjects demonstrated comparable safety profiles across both dose groups, despite increases in DTG exposures (7). Thus, as dosing instructions without regard to food have not led to high variability in DTG exposures in patient studies and as increased exposures by dosing twice daily have not shown a different

TABLE 1 Pharmacokinetic parameters of DTG treatment administered in the fasting state or with food

Treatment	*N*	Geometric mean (% CV)				Median (range)
		C_{max} (μg/ml)	$AUC_{0-\infty}$ (μg · h/ml)	C_{24} (μg/ml)	$t_{½}$ (h)	T_{max} (h)
DTG, 50 mg, fasting	18	2.65 (28)	50.3 (27)	0.75 (34)	14.1 (22)	2.06 (1.0–5.0)
DTG, 50 mg, low-fat meal	18	3.88 (21)	66.7 (35)	1.00 (44)	13.4 (19)	3.00 (2.0–5.1)
DTG, 50 mg, moderate-fat meal	18	4.03 (19)	71.0 (31)	1.09 (39)	13.5 (19)	4.00 (2.0–6.0)
DTG, 50 mg, high-fat meal	18	4.44 (24)	83.6 (35)	1.30 (47)	13.4 (21)	5.00 (1.0–8.0)

TABLE 2 Treatment comparisons for effects of food on DTG pharmacokinetics

DTG PK parameter	Ratio of geometric least squares mean ratio (90% CI) for treatment group compared to fasted group[a]		
	DTG 50 mg + low fat ($N = 18$)	DTG 50 mg + moderate fat ($N = 18$)	DTG 50 mg + high fat ($N = 18$)
$AUC_{0-\infty}$	1.33 (1.21, 1.45)	1.41 (1.29, 1.55)	1.66 (1.52, 1.82)
C_{max}	1.46 (1.34, 1.60)	1.52 (1.39, 1.66)	1.67 (1.53, 1.83)
C_{24}	1.33 (1.20, 1.48)	1.45 (1.31, 1.61)	1.73 (1.56, 1.92)

[a] The fasted group (comparison group) also received DTG at 50 mg.

safety profile, DTG can be dosed with or without food, regardless of the fat content.

Increasing exposure was observed with increasing fat and calorie content, consistent with the solubility-limited absorption of DTG. The presence of food appears to aid in the solubilization of DTG, leading to an overall increase in exposure. However, the food effect with DTG is more consistent than that of the U.S. Food and Drug Administration-approved integrase inhibitor raltegravir. The AUC of raltegravir decreased by 46% with a low-fat meal, but it increased by 13% with a moderate-fat meal and increased more than 2-fold with a high-fat meal (1). Furthermore, the interpatient variability in drug exposure observed when subjects were dosed with food was considerably less with DTG than with raltegravir. Given the limitations of a cross-study comparison, the coefficient of variation with various types of meals ranged from 39 to 47% for DTG in this study, compared to previously reported values of 123 to 221% for raltegravir (1).

In summary, DTG is an investigational integrase inhibitor that is being administered in phase III clinical trials without ritonavir boosting and without regard to meals. Although the presence of food modestly increases the exposure to DTG, the effect is not considered clinically significant. Clinical experience from phase IIb trials further support this dosing recommendation. New agents with flexible and convenient dosing requirements can aid in the construction of efficacious regimens for treatment of patients with HIV infection.

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