CLINICAL PHARMACOLOGY REVIEW

NDA	206510
Original Submission Date	8 Apr 2014
Submission Type	505(b)(2), standard review
SDN	1, 5
Brand Name	DUTREBIS (proposed)
Generic Name	Lamivudine (3TC)/raltegravir (RAL) fixed-dose combination (MK-0518B)
Primary Reviewer	Leslie Chinn, Ph.D.
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OCP Division	DCP4
OND Division	Division of Antiviral Products
Applicant	Merck Sharp & Dohme Corp.
Strength and Formulation	Lamivudine 150 mg plus raltegravir 300 mg fixed-dose combination (FDC) oral IR tablet
Proposed Dosing Regimen	One tablet twice daily without regard to food
Proposed Indication	Treatment of HIV-1 infection, in combination with other antiretroviral agents, in adults and pediatric patients greater than 6 years of age and weighing at least 30 kg
Referenced Applications	NDA 22145 (raltegravir, ISENTRESS®), IND 113176 (3TC/RAL FDC)

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1. EXECUTIVE SUMMARY

Lamivudine (3TC, marketed in the US as Epivir®) is a nucleoside analog inhibitor of human immunodeficiency virus type 1 (HIV-1) reverse transcriptase that causes premature viral DNA chain termation. It was approved in the US for the treatment of HIV-1 infection in 1995.

Raltegravir (RAL or MK-0518, marketed in the US as Isentress®) is an integrase strand transfer inhibitor (InSTI) that prevents integration of the HIV-1 DNA into the host cell genome. It was approved in the US for the treatment of HIV-1 infection in 2009. The RAL/3TC fixed-dose combination (FDC) tablet currently under review contains a new formulation of RAL that has a (b) (4) (b) (4) The Applicant states that (b) (4) therefore, 300 mg of the reformulated RAL provides exposures as 400 mg of Isentress®.

The Applicant is seeking approval of the current NDA based on the results from the bioequivalence study P253, which will be evaluated by the Biopharmaceutics Reviewer. The Clinical Pharmacology Review includes an assessment of the results from the drug interaction study P214, in which the pharmacokinetics of RAL (administered as the RAL/3TC FDC) were evaluated in the presence or absence of etravirine, as well as the food effect study P254, in which the pharmacokinetics of the RAL/3TC fixed-dose combination (FDC) tablet following administration after a high-fat meal were evaluated. In addition, the Pharmacometrics Review contains an assessment of the clinical relevance of the RAL pharmacokinetic parameters that were not bioequivalent between the RAL tablet and the RAL/3TC FDC (C_{12}, C_{max}) as well as the appropriateness of the proposed dose in the pediatric population.

1.1 BACKGROUND

The option of taking a fixed-dose combination tablet in place of two or more components of an antiretroviral regimen is appealing to patients with a chronic medical condition such as HIV-1 infection that requires daily and lifelong medication use. By reducing the overall pill burden, FDC tablets may increase patient adherence with the potential for improved efficacy and decreased development of viral resistance.

For these reasons, the Applicant undertook development of the current RAL/3TC FDC. Per the Applicant, the RAL reformulation was developed to allow for use in fixed-dose combinations. The RAL/3TC FDC is a (b) (4), film-coated, (b) (4) tablet form containing the approved dosage of 3TC (i.e. 150 mg) and a lower dosage of RAL compared to the approved poloxamer formulation (i.e. 300 mg compared to 400 mg) for twice-daily administration.

The safety and efficacy of RAL coadministered with 3TC and other antiretroviral agents were established in multiple trials conducted during the Isentress® development program, all of which have previously been submitted to and reviewed under NDA 22145.

To support the current Application, the Applicant conducted Study P253 in order to evaluate the pharmacokinetics of a single dose of RAL and 3TC when administered as single agents (Isentress® 400 mg plus Epivir® 150 mg) or the FDC (RAL/3TC 300/150 mg) in the fasted state (both RAL and 3TC can be taken without regard to food). In pre-NDA correspondence (IND

113176 pre-NDA meeting minutes, 2 Dec 2013), the Division agreed with the Applicant's proposal that supportive safety and exposure-response data could be used to support the current NDA in the event that the FDC was not bioequivalent to the single agents.

The Applicant also conducted Studies P258 and P260, which were identical in design to Study P253, with the exception of the source of the 3TC single agent (P253: US, P258: European Union, P260: Canada). All three studies were conducted at the same study site (b) (4) within a timespan of three months (Sept-Nov 2011). Because of these similarities, the general results of all three BE studies were taken into consideration during the review process, although P253 was considered pivotal to this Application and was the only BE study that was evaluated by the Biopharmaceutics Reviewer and the only study for which site inspections were requested. A food effect study (P254) and a drug-drug interaction study with etravirine (P214) were also reviewed for this Application.

1.2 Summary of Clinical Pharmacology Findings

The pivotal BE study P253 was not reviewed by the Clinical Pharmacology Review Team. Please refer to the Biopharmaceutics Review by Dr. Okpo Eradiri for his evaluation of this study. Site inspections were requested by Dr. Eradiri; the results were pending at the time of this review.

Briefly, the three BE studies, P253, P258, and P260, appeared to demonstrate bioequivalence of 3TC. However, as described in Table 1, geometric mean RAL C_{max} values were slightly high in Study P258 (90% CI bounds of 107.9-141.7%) and geometric mean RAL C_{12h} values were slightly low in all three studies (90% CI ranging from 73.2-93.8%). These slight deviations from bioequivalence are not entirely surprising given the large intra- and interindividual variability in RAL pharmacokinetics (for RAL C_{12h}, intra- and intersubject CV values were approximately 122 and 212%, respectively; Clinical Pharmacology Review of NDA 22145), which is likely due to variability in UGT1A1 expression and activity, intestinal P-gp expression, and pH-dependent RAL solubility.

Table 1. Statistical results of the bioequivalence studies P253, P258, and P260 (source: adapted from Clinical Overview Table 2.5:4)

RAL PK Parameter	Study	GMR (RAL/3TC FDC:Isentress)	90% CI for GMR
AUC_{inf} h.ng/mL	P253	91.66	82.33-102.03
	P258	100.97	92.46-110.27
	P260	81.82	74.88-89.41
C_{max} ng/mL	P253	103.75	89.88-119.77
	P258	123.64	107.85-141.74
	P260	100.14	87.36-114.78
C_{12h} ng/mL	P253	85.87	78.62-93.79
	P258	85.12	78.69-92.07
	P260	78.92	73.20-85.08

Please refer to the Pharmacometrics Review by Dr. Fang Li (Section 3.1) for an evaluation of the findings from the BE studies, including the lower mean RAL C_{12} values and the higher mean RAL C_{max} values, in the context of the previously characterized RAL exposure-response relationship. Overall, the lower RAL C_{12} values are not expected to impact efficacy based on previous clinical trial data as well as PK/PD modeling and simulations provided by the Applicant. In addition, the higher RAL C_{max} values are not expected to impact safety based on observations from previous clinical studies that evaluated a dose of RAL 800 mg QD.

Please also refer to the Pharmacometrics Review (Section 3.1) for an assessment of the proposed use of the RAL/3TC FDC in adolescent patients 16 years of age and older and pediatric patients 6 to 16 years of age and weighing at least 30 kg. Overall, the RAL/3TC FDC is expected to be safe and effective in the proposed pediatric population based on RAL exposures observed in pediatric patients following Isentress® administration as specified in the approved prescribing information.

The results of the food effect study, P254, and the drug-drug interaction study with etravirine, P214, are described briefly below.

Study P254 was a randomized crossover study intended to assess the effect of food on a single dose of the RAL/3TC 300/150 mg FDC in 20 healthy volunteers. There were two treatments, with a 7-day washout between periods:

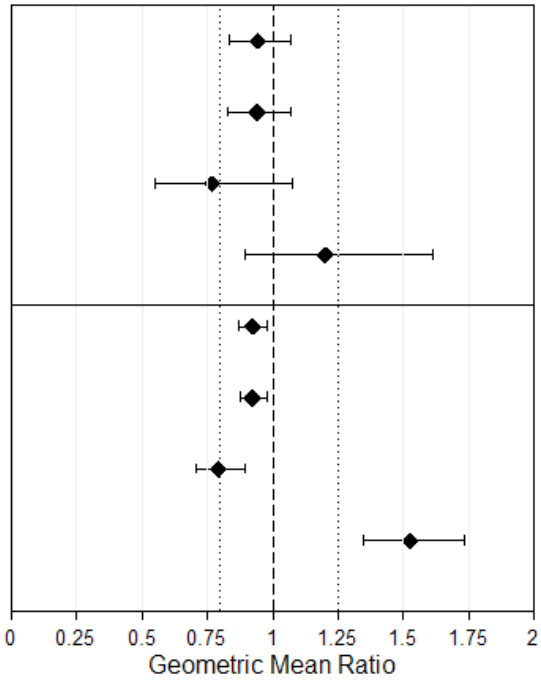
- A – RAL/3TC 300/150 mg FDC tablet, fasted
- B – RAL/3TC 300/150 mg FDC tablet, high-fat, high-calorie meal

Please refer to the individual study review (Section 3.2) for additional details about the study design and results.

Statistical analyses of RAL and 3TC PK parameters following administration of the RAL/3TC FDC under fed (high-fat, high-calorie meal [988 kcal, 56 g fat, 36 g protein]) or fasted conditions are displayed in Figure 2. Administration of the FDC following a high-fat meal appeared to result in delayed absorption and slightly lower maximal concentrations of both RAL and 3TC compared to administration in the fasted state (23 and 21% decreases for RAL and 3TC C_{max}, respectively), although overall systemic exposures (AUC) were not statistically significantly changed. Mean C_{12h} values for both analytes were slightly higher following fed administration compared to fasted (20 and 53% increases for RAL and 3TC C_{12h}, respectively).

Figure 1. Statistical comparisons of key raltegravir and lamivudine pharmacokinetic parameters following administration of the RAL/3TC 300/150 mg FDC with a high-fat meal compared to fasted administration of the FDC (source: Reviewer's analysis of CSR Tables 11.4.7-1 and 11.4.7-2)

Analyte	Parameter	GMR
Raltegravir	AUC12	0.945
	AUCinf	0.942
	Cmax	0.77
	C12	1.2
Lamivudine	AUC12	0.925
	AUCinf	0.924
	Cmax	0.794
	C12	1.53



The minor differences in systemic exposures and trough concentrations are within the magnitude of the food effects on the PK parameters of the single agents (which can both be administered without regard to food) as described in the approved Isentress® and Epivir® labels; the lower RAL C_{max} values and the higher RAL C_{12h} values following fed administration compared to fasted are not expected to influence safety or efficacy, respectively. Overall, the results of Study P254 suggest that fed and fasted administration of the RAL/3TC 300/150 mg oral FDC tablet provide comparable exposures of both analytes. The Reviewer concurs with the Applicant that these data support the use of the RAL/3TC FDC without regard to food.

Study P214 was an open-label fixed-sequence study intended to assess the effect of steady-state etravirine on RAL C_{12h} following single doses of the RAL/3TC 300/150 mg FDC in 18 healthy volunteers. There were two treatments, with no washout between periods:

- A – RAL/3TC 300/150 mg FDC tablet, single dose (Day 1 of Period 1)
- B – etravirine 200 mg BID (Days 1-14 of Period 2), coadministered with a single dose of RAL/3TC FDC tablet (Day 14 of Period 2)

Please refer to the individual study review (Section 3.3) for additional details about the study design and results.

The overall systemic exposures of RAL were comparable with or without etravirine (Table 2). Examination of RAL C_{12} revealed an approximately 14% decrease in the presence of etravirine at steady-state, with 90% CI (63.0-117%) within the predefined no-effect boundaries of 50-200%. The decrease in RAL C_{12h} is likely due to induction of UGT1A1 metabolism of RAL by etravirine.

Table 2. Statistical comparison of raltegravir pharmacokinetic parameters in the absence (Treatment A) or presence (Treatment B) of etravirine (source: CSR Table 11-2)

	Treatment B:Treatment A		Pseudo Within Subject %CV*
PK parameter	**GMR (%)**	**90% CI**	
C_{12}** (ng/mL)	85.81	63.04, 116.79	48.44
C_{max}** (ng/mL)	120.22	100.00, 144.53	29.09
AUC_{last}** (ng.h/mL)	108.32	95.03, 123.48	20.23
AUC_{inf}** (ng.h/mL)	108.30	95.25, 123.14	19.86

* Pseudo Within-Subject %CV= $100*(\sqrt{(\hat{\sigma}_A^2+\hat{\sigma}_B^2-2\hat{\sigma}_{AB})/2})$ where $\hat{\sigma}_A^2$ and $\hat{\sigma}_B^2$ are the estimated variances on the log scale for the two treatment groups, and $\hat{\sigma}_{AB}^2$ is the corresponding estimated covariance, each obtained from the linear mixed-effects model

* Back-transformed least squares mean and CI from mixed effects model performed on natural log-transformed values

In spite of the 14% decrease in mean RAL C_{12} values and the slight increases in RAL C_{max} and AUC, several factors support coadministration of the RAL/3TC FDC and etravirine without a dose adjustment: 1) the GMR and 90% CIs for C_{max} and AUC are higher than the corresponding values for RAL coadministered with etravirine listed in the Isentress® label; 2) previously characterized extensive variability in RAL trough concentrations; 3) the 1.2- to 1.6-fold increase in RAL trough concentrations at steady-state compared to after a single dose; and 4) higher absorption in patients with HIV infection due to the high prevalence of gastric achlorhydria (Barry M. et al. Clin Pharmacokinet 1997). For these reasons, this Reviewer concurs with the Applicant that the RAL/3TC 300/150 mg FDC oral tablet can be coadministered with etravirine with no dose adjustment.

1.3 RECOMMENDATIONS

The Office of Clinical Pharmacology (OCP) review team finds this application acceptable and recommends approval of the raltegravir/lamivudine 300/150 mg FDC tablet for the treatment of HIV-1 infection, in combination with other antiretroviral agents, in adults, adolescents (16 years of age and older), and pediatric patients (6 through 16 years of age and weighing at least 30 kg). In addition, the OCP review team also recommends the labeling changes described in Section 2 of this review.

1.4 POST-MARKETING COMMITMENTS OR REQUIREMENTS

There were no clinical pharmacology PMCs or PMRs at the time of completion of this review. Negotiations regarding the clinical recommendation regarding coadministration of the raltegravir/lamivudine 300/150 mg FDC tablet (b) (4)

(b) (4) as was stated during the preNDA meeting (IND 113176 preNDA meeting minutes, 2 Dec 2013) with the Applicant.

2. LABELING RECOMMENDATIONS

The following section describes labeling recommendations made by the Clinical Pharmacology review team based on our interpretation of the review issues at the time this review was filed. Internal labeling discussions are ongoing and negotiations with the Applicant are in progress; recommendations described in this section are subject to change.

Substantive clinical pharmacology changes were made to the label as follows:

- Table (b) (4) containing clinical recommendations regarding drug-drug interactions was updated to remove drugs for which no dose adjustment was needed; these drugs were added to the list of non-interacting drugs under the table
- Extraneous information (e.g. detailed ADME data) was removed throughout the prescribing information as it is already contained in the Epivir® and Isentress® prescribing information

3. APPENDICES

3.1 PHARMACOMETRICS REVIEW

The Pharmacometrics Review begins on page 8.

3.2 REVIEW OF STUDY P254

The review of Study P254 begins on page 30.

3.3 REVIEW OF STUDY P214

The review of Study P214 beings on page 38.

OFFICE OF CLINICAL PHARMACOLOGY:
PHARMACOMETRIC REVIEW

1 SUMMARY OF FINDINGS

1.1 Key Review Questions

The purpose of this review is to address the following key questions.

1.1.1 Is the lower raltegravir C_{12hr} from the lamivudine/raltegravir FDC tablet (MK-0518B) predicted to impact efficacy?

No, the lower raltegravir C_{12hr} concentrations after single dose administration of lamivudine/raltegravir FDC compared to ISENTRESS 400 mg tablet are not predicted to impact efficacy based on observations from previous clinical trials and PK/PD modeling and simulations provided by the sponsor.

In this submission, no clinical trials were conducted by the sponsor to evaluate efficacy and safety of the lamivudine/raltegravir FDC tablet. The sponsor conducted multiple BA/BE studies (P253, P258, and P260), and in all the trials the lamivudine component appeared to demonstrate bioequivalence (see Clinical Pharmacology Review, Section 1.2). However, the raltegravir component of the FDC exhibited lower C_{12hr} concentrations relative to ISENTRESS 400 mg in the single dose BA/BE studies (P253, P258, and P260; GMR of 0.79-086). Given that raltegravir C_{trough} has been shown to impact efficacy based on the inferior outcome of raltegravir 800 mg q.d. compared to raltegravir 400 mg b.i.d. (P071), an evaluation of the potential impact of this lower C_{12hr} of efficacy was evaluated by the sponsor using a population PK model for raltegravir based on data from the FDC tablet studies and a previously developed viral dynamic model (refer to Clinical Pharmacology Review NDA205786, Dr. Fang. Li November 2013). Given the totality of available information, the reviewer concludes that the lower C_{12hr} observed from the single dose BA/BE studies is not anticipated to impact efficacy.

First, steady state C_{12hr} predictions for the raltegravir component in the lamivudine/raltegravir FDC tablets values were projected to range between 214 to 232 nM based on the demographics in all three BA/BE studies and P071 (Table 2). They are higher than the C_{trough} with approved ISENTRESS dosing in adults. The exposure-response analysis with data from P071 identified a significant relationship between raltegravir C_{trough} and virologic response, and steady-state C_{12hr} of raltegravir should be $\geq$ 45 nM in order to reach the plateau of the C_{trough}-efficacy curve. (refer to Clinical Pharmacology Review for NDA 22145, Dr. Jenny Zhang and Pravin Jadhav; NDA206510; P071 Sponsor's PK/PD report). The raltegravir C_{12hr} after single and multiple doses of FDC tablets are predicted to be several-fold greater than 45 nM (Table 2) and will be on the plateau of the exposure-efficacy curve.

Table 1: **Observed and predicted raltegravir exposure in adults single-dose study P253, P258, and P260. The developed population PK model adequately predicts observed exposures of the FDC from the three BA/BE studies.**

Study	**P253 (US)**			**P258 (EU)**			**P260 (CA)**		
Dosing Regimen	**ISEN 400 mg**	**Ral in FDC 300 mg**		**ISEN 400 mg**	**Ral in FDC 300 mg**		**ISEN 400 mg**	**Ral in FDC 300 mg**	
	Obs. SD	**Obs. SD**	**Pred SD**	**Obs. SD**	**Obs. SD**	**Pred SD**	**Obs. SD**	**Obs. SD**	**Pred SD**
AUC_{0-12} (μM*h) Mean (90% CI)	**24.2** (5-49)	**19.2** (10-34)	**20.9** (9-40)	**22.3** (4-44)	**20.0** (10-31)	**20.0** (9-39)	**22.9** (7-38)	**17.1** (9-29)	**20.6** (9-40)
Cmax (μM) Mean (90% CI)	**8.2** (1.1-17)	**7.3** (2.7-13.3)	**7.9** (2.4-17.5)	**7.6** (0.9-16)	**8.0** (2.8-14.7)	**7.6** (2.4-16.8)	**5.7** (1.5-13.3)	**6.8** (2.4-13)	**7.8** (2.4-17.4)
C_{12hr} (nM)	**134**	**105**	**119**	**115**	**96**	**118**	**110**	**86**	**119**

SD: Single dose; MD: multiple doses;Pred.: predicted; ISEN: ISENTRESS: Ral: Raltegravir

Table 2: P**redicted steady-state C_{trough} of raltegravir in adult subjects of study P253, P258, P260 and P071**

Study	**P253 (US)**	**P258 (EU)**	**P260 (CA)**	**P071 (HIV Subjects)**		
Dosing Regimen	**Ral in FDC 300 mg**	**Ral in FDC 300 mg**	**Ral in FDC 300 mg**	**ISEN 400 mg BID**	**ISEN 800 mg, QD**	**Ral in FDC 300 mg, BID**
C_{12hr} (nM)	**226**	**214**	**218**	**257***	**40[#*]**	**232**

*# C_{trough} at 24 hours; *Observed value*

Source: Adapted from Table 13 on page 53 and Table 11 on page 47 of sponsor's clinical report 03TSW9; P071 data were adapted from Table 1 on page 14 of sponsor's clinical report 03N7N7.

Second, simulation results using a previously developed viral dynamic model indicate that the raltegravir component in lamivudine/raltegravir FDC tablet will achieve similar virologic response as that observed for already approved dosing in adults and children. The details of this assessment are described in additional detail in Section 3.4. As demonstrated in Figure 7 and Figure 8, the predicted proportions of patients with viral load < 40 copies/mL over 48 weeks of treatments were similar between ISENTRESS 400 mg b.i.d and raltegravir component of the FDC tablet.

Therefore, despite lower single dose C_{12hr} values observed with the raltegravir component in lamivudine/raltegravir FDC tablet after single dose administration in the BA/BE studies, the predicted C_{12hr} at steady state, viral dynamic simulations, and results from previous raltegravir studies all support that efficacy is not expected to appreciably be impacted.

1.1.2 Is the increased C_{max} for raltegravir from the lamivudine/raltegravir FDC tablet as observed in P258 expected to impact safety compared to raltegravir 400 mg q.d.?

No, a maximum of 42% higher C_{max} (upper bound of the 95% CI in P258) is not anticipated to impact safety associated with raltegravir given the results from previous clinical studies conducted with raltegravir 800 mg q.d. While there were no clinical studies conducted with lamivudine/raltegravir FDC tablet in adults or pediatric subjects, the potential safety impact of higher raltegravir exposures can be evaluated from the raltegravir 800 mg q.d. arm in study P071, which suggested that a 4-fold increase in raltegravir C_{max} did not substantially impact safety.

Study P071 (QDMRK) was a multicenter, double-blind, randomized, active-controlled study in treatment-naïve, HIV-1 infected adults to evaluate the long-term safety, tolerability, and efficacy of once-daily (q.d) raltegravir 800 mg PO compared with the approved twice daily (b.i.d) raltegravir 400 mg PO, when each was given in combination with TRUVADA (tenofovir disoproxil fumarate 300 mg + emtricitabine 200 mg) q.d. for up to 96 weeks. The film-coated tablet of raltegravir (ISENTRESS) approved for use in adults was used in both treatment arms. In the study, the pharmacokinetic data showed that raltegravir 800 mg q.d. resulted in approximately 4-fold higher C_{max}, 6-folder lower C_{trough}, and similar daily AUC (Table 12). While the raltegravir 800 mg q.d arm was not as effective as the 400 mg b.i.d arm due to the significantly lower C_{trough}, both regimens were considered safe. In addition, only flat exposure-response relationships were observed between safety adverse events of interest and C_{max} (Table 13 and Table 14), further suggesting that the C_{max} observed with raltegravir 800 mg q.d. did not result in increased safety risk.

As the raltegravir component of FDC tablet has a much lower C_{max} than raltegravir 800 mg. q.d, it is not expected that the more modest C_{max} increase with the FDC would impact safety in adults, either.

1.1.3 Is the proposed FDC regimen acceptable in pediatric subjects (greater than 6 years of age and weighing at least 30 kg) based on a comparison of predicted raltegravir PK from the FDC to observed data from the original raltegravir formulation?

The FDC tablet is expected to be effective and safe in pediatric subjects greater than 6 years of age and weighing at least 30 kg based on the population pharmacokinetic model developed for the FDC from the three BA/BE studies and previously observed pharmacokinetic, efficacy, and safety data with raltegravir in pediatrics subjects administered the approved ISENTRESS dosing regimen.

Table 3 and Table 4 summarize the predicted and observed raltegravir exposure with FDC tablets and ISENTRESS tablets, respectively, in adults and pediatrics subjects. The predicted raltegravir exposure after multiple dose of lamivudine/raltegravir FDC tablet in adults and pediatric subjects are compared with the observed exposure of raltegravir after administration of ISENTRESS tablets and chewable tablets in children (6-12 years, weighing at least 30 kg) and adolescences (12 to 18 years).

Raltegravir exposure by FDC tablets is predicted to be adequate in children ≥ 6 years and weighing at least 30 kg. The predicted mean C_{12hr} of the FDC tablets are in range of 317-390 nM, higher than the average exposure achieved by ISENTRESS in adults (161.6 nM), chewable ISENTRESS tablet in children 6-12 years (162.7 nM), and adult tablets in children 6-12 years (260.8 nM). Therefore, the efficacy of FDC tablet in children is not expected to be impacted compared to the approved ISENTRESS tablet and chewable tablet.

The maximum exposures of raltegravir in pediatric subjects 6 to 18 years receiving ISENTRESS adult tablets or chewable tablets as shown in study P022 (13.8 µM) were higher than the predicted average raltegravir exposure (ranging 8.5-13.2 µM) after multiple doses of the FDC tablets (Table 3). As such, the safety profile of the FDC tablets in children is unlikely to be impacted compared to the approved ISENTRESS tablets and chewable tablets. Overall, based on the predicted exposure, the lamivudine/raltegravir FDC is anticipated to be effective and safe in children ≥6 years and weighting at least 30 kg.

Table 3: **Predicted raltegravir exposure after multiple doses of lamivudine/raltegravir FDC tablets pooled adults and pediatric subjects**

Predicted Raltegravir Exposure of FDC	**AUC_{0-12} (90% CI) (µM*h)**	**C_{max} (90% CI) (µM)**	**C_{12hr} (90% CI) (nM)**
Adult Pooled	**22.2** (9.2-43.2)	**8.5** (2.6-19.5)	**232** (50-623)
Adolescents >=12 yrs; >=30 kg for 12-16 years	**26.8** (10.4-54.0)	**9.9**(2.9-22.8)	**317**(63.3-865.9)
Children of 6-11 yrs and >=30 kg	**35.0** (14.0-68.5)	**13.2** (4.0-29.9)	**390**(79.8-1052.3)

Source: Table 12 on page 48 of sponsor's clinical report 03TSW9

Table 4: Observed raltegravir (ISENTRESS) exposure in approved raltegravir dosing regimen in pediatric subjects (study P022) and adults

Approved Ral exposure	Cohort I (12y to 18y)	Cohort IIA (6y to 12y)	Cohort IIB (6y to 12y, 6mg/kg)	Adult 400 mg BID
N	21	15	9	6
AUC_{12} (µM*hr)	18.5	14.2	26.3	17.3
C_{12hr} (nM)	**527.8**	**260.8**	**162.7**	**161.6**
C_{max} (µM)	5.67	4.87	13.8	6.2

Cohort I: ≥12 to 19 years of age received adult tablets; Cohort IIA: ≥6 to < 12 years of age received adults tablets; Cohort IIB: ≥6 to < 12 years of age received chewable tablets.

Source: Clinical Pharmacology review for NDA205-786 (November 2013)

1.2 Recommendations

The Division of Pharmacometrics (Office of Clinical Pharmacology) has reviewed this application from a clinical pharmacology perspective and recommends approval of lamivudine/raltegravir (150 mg/300 mg) fixed dose combination tablet for the treatment of HIV-1 infection in combination with other antiretroviral agents in adults and pediatrics >6 years of age and weighing at least 30 kg. The reviewer agrees with the sponsor's conclusions from the population PK analyses and exposure-response analysis that the lower C_{12hr} and higher C_{max} values of the raltegravir component of the lamivudine/raltegravir FDC tablet is not expected to impact clinical efficacy and safety, respectively.

2 PERTINENT REGULATORY BACKGROUND

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. submitted the 505 (b) (2) NDA to seek approval for lamivudine and raltegravir 150 mg/300 mg (MK-0518B) fixed-dose combination (FDC) tablet for the treatment of HIV-1 infection in adults, adolescents (16 years of age and older), and pediatric patients (6 through 16 years of age weighing at least 30 kg). Both lamivudine and raltegravir are previously approved, potent antiretroviral agents that are commonly prescribed together in treatment-naïve and treatment-experienced HIV-1 infected patients. Lamivudine [EPIVIR® in US and EU, 3TC® in Canada] is a nucleoside reverse transcriptase inhibitor (NRTI) that consists of a dideoxy analog of cytidine. Raltegravir (MK-0518, ISENTRESS®) is an integrase strand transfer inhibitor. The purpose of the FDC combination is to provide a simplified dosing regimen that will provide a convenient backbone for antiretroviral therapy regimens that could improve patient compliance and satisfaction.

To support the proposed dosing regimen, the sponsor submitted eight Phase 1 studies conducted in healthy volunteers, including 3 bioavailability/bioequivalence (BA/BE) studies (P253, P258, and P260, with lamivudine sourced from U.S. EU, and Canada, respectively), to compare the exposures of lamivudine and raltegravir of the FDC tablet with those achieved by lamivudine [EPIVIR] and raltegravir[ISENTRESS] tablet.

The data submitted by the sponsor demonstrated that bioequivalence was achieved by lamivudine in all three BA/BE studies. However, raltegravir exposure by the FDC did not fall within the bioequivalence range of 80-125%. In particular, the raltegravir C_{12hr} of the FDC was lower than the low bound of 80% of the reference. The lower C_{12hr} in FDC may be clinically relevant because C_{12hr} is the PK parameter associated with clinical efficacy.

A population PK analysis was conducted to characterize raltegravir exposure from the lamivudine/raltegravir FDC tablet and to apply a previously developed viral dynamics model to predict clinical impact of these lower raltegravir C_{12hr} values. In addition, an exposure-response analysis for safety from study P071 was submitted to support safety of the FDC tablet given the potential for higher C_{max} values with the FDC (P258). Finally, exposures in pediatric subjects (12 to 16 years and 6 to 11 years [>30 kg]) were predicted

for raltegravir based upon the developed model for the FDC and compared with previously observed exposures for raltegravir administered as a separate therapy in children in order to support dosing recommendations of the FDC in pediatrics.

3 RESULTS OF SPONSOR'S ANALYSIS

3.1 Population PK Modeling

Objectives: The primary objectives of the PK and PKPD analyses were to:

- Develop a population PK model for the raltegravir component of lamivudine/raltegravir 150 mg/300 mg FDC tablet and determine the effect of relevant covariates on raltegravir exposure in lamivudine/raltegravir FDC tablet
- Use allometric scaling of weight on clearance and volume to project the PK of raltegravir component of lamivudine/raltegravir FDC tablet in children down to the age of 6 years and body weight of >30 kg
- Use the previously developed PK/PD viral dynamics model for raltegravir plus (1) the observed PK data from the final manufacturing image (FMI) relative bioavailability/bioequivalence (BA/BE) trials or (2) simulated PK in a representative population using the population PK model to project the efficacy of lamivudine/raltegravir FDC tablet versus the reference product formulations of ISENTRESS 400 mg tablets co-administered with EPVIR or 3TC 150 mg tablets and to assess the clinical significance of the deviations from relative BA/BE bounds observed in these studies.

Data: PK data from four Phases 1 BE/PC studies (P196, P253, P258, and P260) and one food effect study (P254) were pooled for the population PK dataset. The final population PK datasets contained 4052 PK samples from 366 healthy volunteers. There were 176 males and 190 females with the following median (range) demographic covariates: age 35 (18-55) years, body weight 73.1 (47.8-114.9) kg, and body mass index (BMI) 25.8 (18.7-32.0) kg/m^2. A summary of subject demographics is provided below in Table 5.

Table 5: Distribution of demographic information included in the Population PK analysis for raltegravir

Study		P196	P253	P258	P260	P254
Number of Subjects		24	108	108	108	20
Demographic Data						
Age (years)	Mean ± SD Range	36 ±9 23-51	36 ± 10 18 - 54	35 ± 10 18 - 54	35 ± 10 19 - 55	42 ± 8 24 - 53
Age Group	18 - 40 41 - 64	12 (50%) 12 (50%)	69 (63.9%) 39 (36.1%)	72 (66.7%) 36 (33.3%)	68 (63.0%) 40 (37.0%)	9 (45.0%) 11 (55.0%)
Sex	Male Female	14 (58.3%) 10 (41.7%)	57 (52.8%) 51 (47.2%)	53 (49.1%) 55 (50.9%)	46 (42.6%) 62 (57.4%)	8 (40.0%) 12 (60.0%)
Race	Asian Black White Other	1 (4.2%) 7 (29.2%) 16 (66.6%) 0 (0.0%))	17 (15.7%) 31 (28.7%) 60 (55.6%) 0 (0.0%)	15 (13.9%) 21 (19.4%) 72 (66.7%) 0 (0.0%)	21 (19.4%) 24 (22.2%) 61 (56.5%) 1 (0.9%)	2 (10.0%) 4 (20.0%) 14 (70.0%) 0 (0.0%)
Ethnicity	Hispanic/Latino	9 (37.5%)	35 (32.4%)	26 (24.1%)	24 (22.2%)	5 (25.0%)
Height (cms)	Mean ± SD Range	172.1 ± 6 157.5-183.0	169.9 ± 10.2 149.3-192.7	170.5 ± 9.1 152.2 - 191.3	167.7 ± 9.9 150.9 - 189.4	167.7 ± 8.1 154.0 - 181.8
Weight (kg)	Mean ± SD Range	79.8 ± 10 64.7-97.8	73.7 ± 12.2 49.7- 105.0	73.9 ± 13.0 47.8 - 107.1	73.6 ± 14.1 49.2 - 114.9	71.9 ± 11.3 50.3 - 94.3
BMI (kg/m^2)	Mean ± SD Range	26.9 ± 3 21.0-30.9	25.4 ± 2.6 19.7 - 29.9	25.3 ± 2.9 18.8 - 30.0	26.0 ± 3.5 18.7 - 32.0	25.5 ± 2.6 19.9 - 28.9

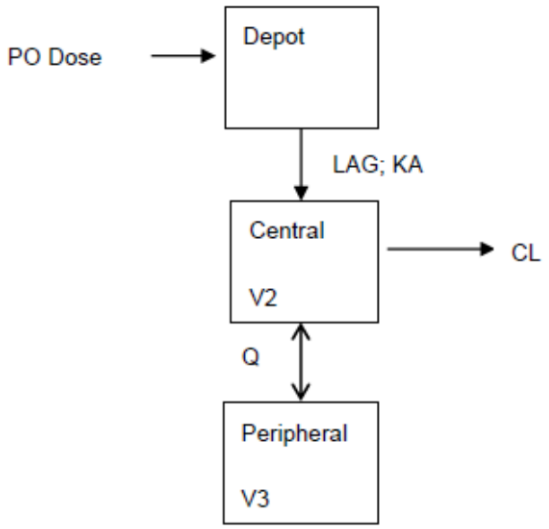
Source: Adapted from Appendix 2 of sponsor's population PK report

Population PK Models

Base Model

The base model selected to describe the PK of raltegravir in lamivudine/raltegravir FDC tablet was a two-compartment model with lag time for absorption and allometric scaling for body weight. The schematic of the base model is shown below in Figure 1.

Figure 1: Schematic of the best performing base model: 2- compartment PK model with lag time for absorption



Source: Figure 5 on page 32 of sponsor's population PK report

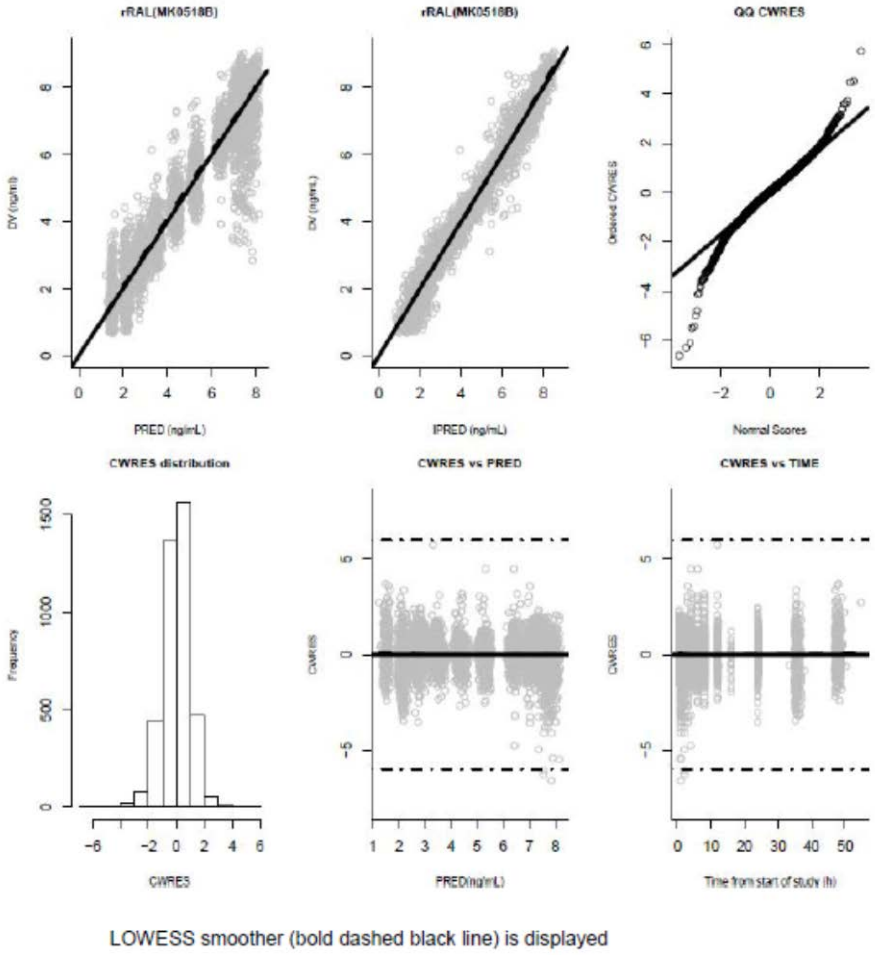
The parameter estimates for the base PK model are summarized in Table 6. The corresponding goodness-of-fit plots are shown in Figure 2.

Table 6: **Parameter estimates and standard errors from the Base Model for raltegravir component after administration of a single dose of lamivudine/raltegravir FDC tablet**

	Run 149: OFV = -712		
Parameter	**Estimate**	**RSE (%)**	**Shrinkage (%)**
Fixed effects			
CL/F (L/h)	39.5	2	
V2/F (L)	21	8.2	
KA (1/h)	0.645	1.6	
Q/F (L/h)	5.27	3.8	
V3/F (L)	89.4	4.7	
ALAG (h)	0.293	6.2	
F1	1 FIX	-	
Random effects			
IIV CL/F	28.6	16.4	19.9
IIV V/F	112.7	6.7	17.3
Correlation (CL-V)	27.9	17.1	-
IIV ALAG	38.6	15.2	37.1
IIV F1	38.6	22.4	21.6
Residual Error			
Proportional (%)	41	5.1	11.7

Source: Table 3 on page 32 of sponsor's population PK report

Figure 2: **Goodness of fit plots for the Base Model of raltegravir (run149)**



Source: Figure 6 on page 34 of sponsor's population PK report

Final Model

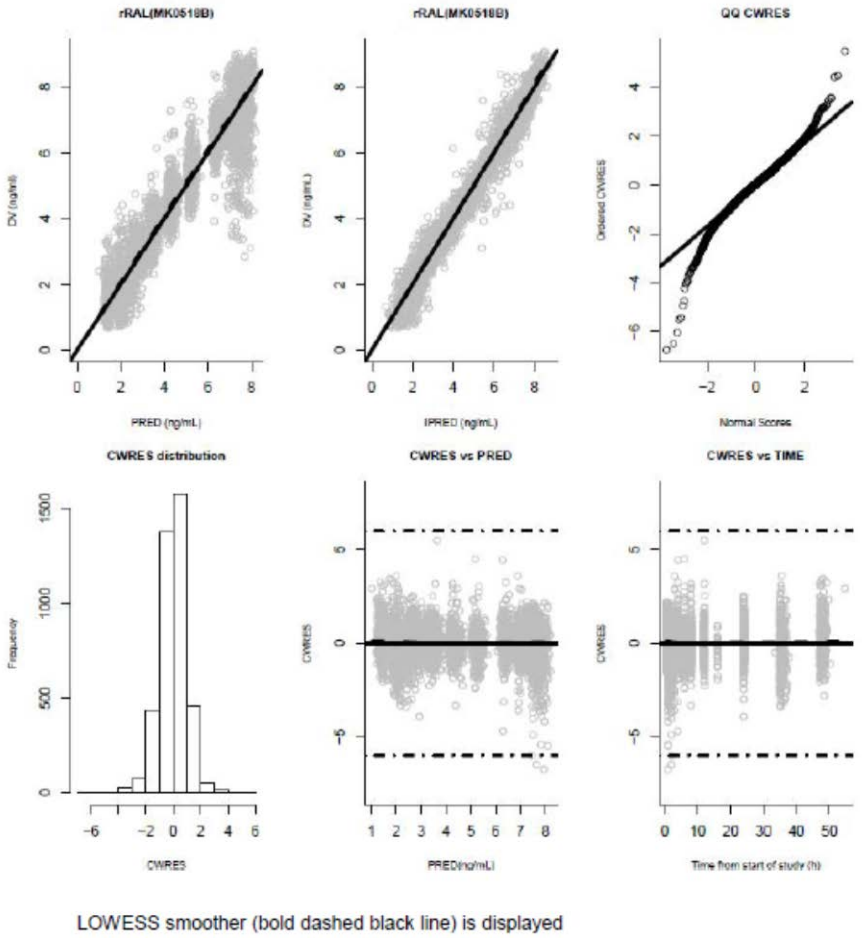
The full population PK model was constructed via forward inclusion of covariates of interest then a backward elimination step by removing covariates to check the minimum objective function value (MVOF). The resulted model was then refined to the final model. The parameter estimates of the final model were summarized as shown in Table 7. Additional covariates identified for the final model included race on clearance and race and gender on bioavailability. The magnitude of intersubject variability was large for Vc (115.8% CV), but was small for CL (24.9 %CV). The calculated η-shrinkage values were 22.5% for CL, 16.9% for Vc, and 25.1% for F1. The model was evaluated by goodness-of-fit plots as shown in Figure 3.

Table 7: **Parameters from the final population PK model for the raltegravir component of lamivudine/raltegravir FDC tablet**

	OFV = -787.92		
Parameter	**Estimate**	**RSE (%)**	**Remarks***
Fixed effects			
CL/F (L/h)	43.8	3.0	*CL* = Typical *CL/F* ×(BW/73.1) ^0.75
V_2/F (L)	21	9.3	*V2* = Typical V_2/F ×(BW/73.1)
KA (1/h)	0.643	1.6	
Q/F (L/h)	5.37	4.7	*Q* = Typical *Q/F* ×(BW/73.1) ^0.75
V_3/F (L)	90.8	5.4	*V* = Typical V_3/F ×(BW/73.1)
ALAG (h)	0.296	5.9	
F1	1 FIX	-	
CL-RACE (Black)	-0.289	16.3	
F1-RACE (Black)	-0.242	26.9	
F1-Gender (Males)	0.20	26.3	
Random effects			**Shrinkage (%)**
IIV CL/F	24.9	11.7	22.5
IIV V/F	115.8	6.1	16.9
Correlation (CL-V)	29.8	17.1	-
IIV ALAG	38.1	14.8	37.4
IIV F1	32.1	14.3	25.1
Residual Error (RUV)			
Proportional (%)	41.3	4	11.3

Source: Adapted from Table 7 on page 37 of sponsor's population PK report

Figure 3: **Goodness of fit plots for the final model (run 150)**



Source: Figure 8 on page 39 of sponsor's population PK report

Reviewer's Comment:

Based on the goodness-of-fit plots, the final model seems adequate in describing the observed data, and the estimated PK parameters appear reasonable.

The dataset for population PK analysis did not include any samples from pediatric subjects. The PK parameters of children were extrapolated using allometric scaling similar to the approach used in a previously developed model based on data from a chewable tablet formulation of raltegravir (with a PK profile reasonable similar to that obtained from raltegravir in lamivudine/raltegravir FDC tablet) in adults and children down to 2 years of age. That model was a 2-compartment model with first order absorption with weight included as a covariate on both clearance and volume (see Clinical Pharmacology Review, NDA205786, 203045 S009, NDA22145 S031.Dr. Fang .Li)

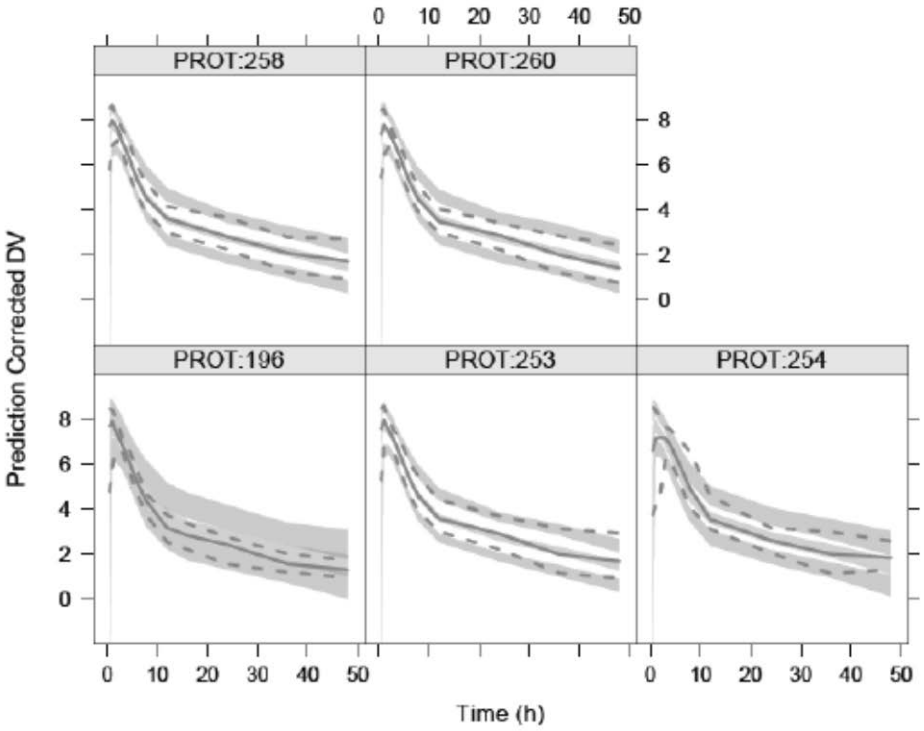
The model in this application used a similar structure and covariate relationships. This method is acceptable, and the reviewer concurs that the sponsors model validation assessments, shown above and in subsequent sections, support that the model can be used for simulation.

Model Validation

Several methods were used by the sponsor to validate the final model, including visual predictive check (Figure 4), bootstrap, comparison of observed versus predicted PK parameters (Table 8). The results are shown below.

Visual Predictive Check

Figure 4: Visual Predictive Check for the final covariate model (stratified on protocol)



Solid black and dashed line: indicate the 5th, 50th, and 95th percentiles of the observed data
Grey area: The shaded areas are the 95% confidence intervals of the corresponding percentiles of the simulated data.

Source: Figure 11 on page 45 of sponsor's population PK report

Table 8: **Comparison of the mean PK parameters calculated from observed data and model predicted PK profiles**

Study	Observed Mean						Simulated based on final Model (run150)					
	C_{max}		AUC_{last}		C_{12hr}		C_{max}		AUC_{last}		C_{12hr}	
Units	ng/ml	*µM*	ng.h/mL	*µm*hr*	ng/ml	*µM*	ng/ml	*µM*	ng.h/mL	*µm*hr*	ng/ml	*µM*
P196	3145.45	*7.08*	7652.81	*17.22*	28.62	*64.46*	3461.41	*7.79*	8879.97	*19.98*	51.75	*116.55*
P253	3148.81	*7.09*	8981.08	*20.21*	47.08	*106.04*	3229.38	*7.27*	8883.71	*19.99*	53.01	*119.39*
P258	3551.37	*7.99*	9541.92	*21.47*	42.32	*95.32*	3361.31	*7.56*	9139.33	*20.57*	52.73	*118.76*
P260	2986.40	*6.72*	8228.34	*18.52*	38.07	*85.74*	3367.14	*7.58*	9152.00	*20.59*	52.98	*119.32*
P254 (Fasted)	3409.30	*7.67*	9241.93	*20.80*	41.34	*93.11*	3369.75	*7.58*	9188.18	*20.68*	53.96	*121.53*
P254 (Fed)	2526.97	*5.69*	8808.22	*19.82*	58.12	*130.90*	3088.04	*6.95*	8750.09	*19.69*	55.06	*124.01*

Source: Table 10 on page 42 of sponsor's population PK report

Reviewer's comment: The results of visual predictive check showed a good consensus between the observed and model-estimated PK profiles of raltegravir in the FDC tablet.

In Table 10, the predicted values of AUC and C_{max} seems satisfactory, but the C_{12hr} was over predicted by up to 39% based on the observations from all three BA/BE studies (P253, P258, and P260). Please also note the units listed for C_{12hr} (µM) in Table 10 are incorrect and should instead be nM.

3.2 PK Simulations

Based upon the final population PK model, the sponsor simulated PK profiles for adults participating in the BA/BE studies (P253, P258, and P260), study P071, and pediatric subjects in study P1066/P022.

The projected PK parameters of raltegravir (AUC, C_{max}, and C_{12hr}) in adults after multiple doses of lamivudine/raltegravir FDC tablets were summarized in Table 9 and Table 10. The projected steady-state C_{12hr} after administration of lamivudine/raltegravir FDC tablets exceeded 45 nM.

Table 9: Comparison of PK data across BE studies and Phase III probability of Clinical Equivalence Assessment Using M&S

Parameter with 90% CI	P253: US sourced LAM BE			P258: EU sourced LAM BE			P260: Canadian sourced LAM BE		
	Reference Isentress (Obs.SD)	Experimental Treatment arm: RAL in FDC		Reference Isentress (Obs.SD)	Experimental Treatment arm: RAL in FDC		Reference Isentress (Obs.SD)	Experimental Treatment arm: RAL in FDC	
	400 mg	Obs. SD 300 mg	PK Model 300 mg	400 mg	Obs. SD 300 mg	PK Model 300 mg	400 mg	Obs. SD 300 mg	PK Model 300 mg
AUC_{0-12} (μM*h)	24.2 (5-49)	19.2 (10-34)	20.9 (9-40)	22.3 (4-44)	20.0 (10-31)	20.0 (9-39)	22.9 (7-38)	17.1 (9-29)	20.6 (9-40)
C_{max} (μM)	8.2 (1.1-17)	7.3 (2.7-13.3)	7.9 (2.4-17.5)	7.6 (0.9-16)	8.0 (2.8-14.7)	7.6 (2.4-16.8)	5.7 (1.5-13.3)	6.8 (2.4-13)	7.8 (2.4-17.4)
C_{12h} (nM)	134¥ (45-284)	105¥ (41-191)	226* (49-605)	115¥ (45-297)	96¥ (41-204)	214* (46-572)	110¥ (50-250)	86¥ (38-156)	218* (47-584)
% Patients With C12hr <45nM	6	9	6	5	10	3	6	13	5
ECC; nM (CV%) as input for viral model	532 (54)	450 (51)	369 (77)	500 (57)	412 (50)	385 (105)	520 (50)	392 (41)	381 (79)
Projected Difference Between Reference Arm and Experimental Arm % patients<40 copies/mL (95% Prediction Interval)	-	0.37% (-3.2, 4.2%)	1.48% (-2.2, 5.5%)	-	0.37% (-4.4, 3.3%)	1.85% (-2.3, 5.8%)	-	0.74% (-3.5, 4.6%)	1.11% (-2.7, 5.3%)

Source: Adapted from Table 13 on page 53 from sponsor's population PK report

Table 10: Projected PK values at steady state for AUC, C_{max} and C_{12hr} of the 300 mg raltegravir component of lamivudine/raltegravir FDC tablet in HIV infected subjects by subpopulation (HIV Infected Population Based on MK-0518 P071)

P071	Mean AUC_{0-12} (90% PI) (μM*hr)		Mean C_{max} (90% PI) (μM)		Mean *C_{12hr} (90% PI) (nM)	
Pooled	22.2	(9.2 - 43.2)	8.5	(2.6 - 19.5)	232	(50 - 623)
Gender effect						
Male	22.5	(9.4 - 43.5)	8.6	(2.6 - 19.3)	232	(50 - 619)
Female	21.3	(8.6 - 41.9)	8.0	(2.4 - 18.2)	235	(49 - 635
Race						
White	22.3	(9.2 - 43.3)	8.6	(2.6 - 19.3)	221	(48 - 589)
Black	21.9	(8.9 - 42.7)	7.6	(2.3 - 17.3)	303	(66 - 794)
Mixed Gender/Race						
Non-Black males + females	22.4	(9.3 - 43.5)	8.6	(2.6 - 19.3)	229	(49 - 613)
Black female gender	20.2	(8.2 - 39.3)	7.0	(2.1 - 15.9)	279	(62 - 744)

*C12hr levels are higher compared to the levels observed after single dose administration because the simulations of PN071 study were performed at steady state to mimic the clinical situation.

Source: Table 11 on page 47 of sponsor's population PK report

For pediatric subjects, full PK profiles were simulated at steady-state using demographics of study P022. The projected raltegravir exposure in pediatric subjects is summarized in Table 11. Again, the mean C_{12hr} value is predicted much higher than the minimum effective concentration of 45 nM.

Table 11: Projected PK values at steady state for AUC, C_{max} and C_{12hr} of the raltegravir component of lamivudine/raltegravir FDC tablets in children 6 through 11 years of age and ≥ 30 kg, adolescents ≥ 12 years of age (≥30 kg for 12-16) and adults

Simulations	*Mean AUC_{0-12} (90% PI) (μM*hr)*	*Mean C_{max} (90% PI) (μM)*	*Mean C_{12hr} (90% PI) (nM)*
Adult (pooled data)	22.2 (9.2 - 43.2)	8.5 (2.6 - 19.5)	232 (50 - 623)
Adolescents ≥ 12 yrs; ≥ 30 kg for 12 to 16 yrs	26.84 (10.42 - 53.97)	9.94 (2.85 - 22.79)	316.7 (63.3 - 865.9)
Children 6-11 yrs, ≥ 30 kg	35.02 (13.99 - 68.50)	13.17 (3.98 - 29.92)	389.6 (79.8 - 1052.3)

*C12hr levels are higher compared the levels observed after single dose administration because the simulations of PN071 study were performed at steady state to mimic the clinical situation.

Source: Table 12 on page 48 of sponsor's population PK report

3.3 PK/PD Model

A previously developed viral dynamic model was used to simulate efficacy of lamivudine/raltegravir FDC tablet. The model described the relationship between a derived raltegravir concentration, equivalent constant concentration (ECC), and percent of inhibition over dosing interval. The model was able to explain the results of P071 where ISENTRESS 800 mg q.d. failed to show non-inferiority to raltegravir 400 mg b.i.d.

The ECC values is believed to be better than AUC, C_{max}, and C_{trough} for efficacy simulation because it depends on the entire time-profile of a subject's PK. The schematic of the conversion of the raltegravir PK profile into an ECC value is shown in Figure 5.

Figure 5: Schematic of the Conversion of the Raltegravir Pharmacokinetic Profile into an Equivalent Constant Concentration (ECC) value Utilizing a Sigmoidal Emax Model for Viral Inhibition (400 mg BID Data Used as Example)

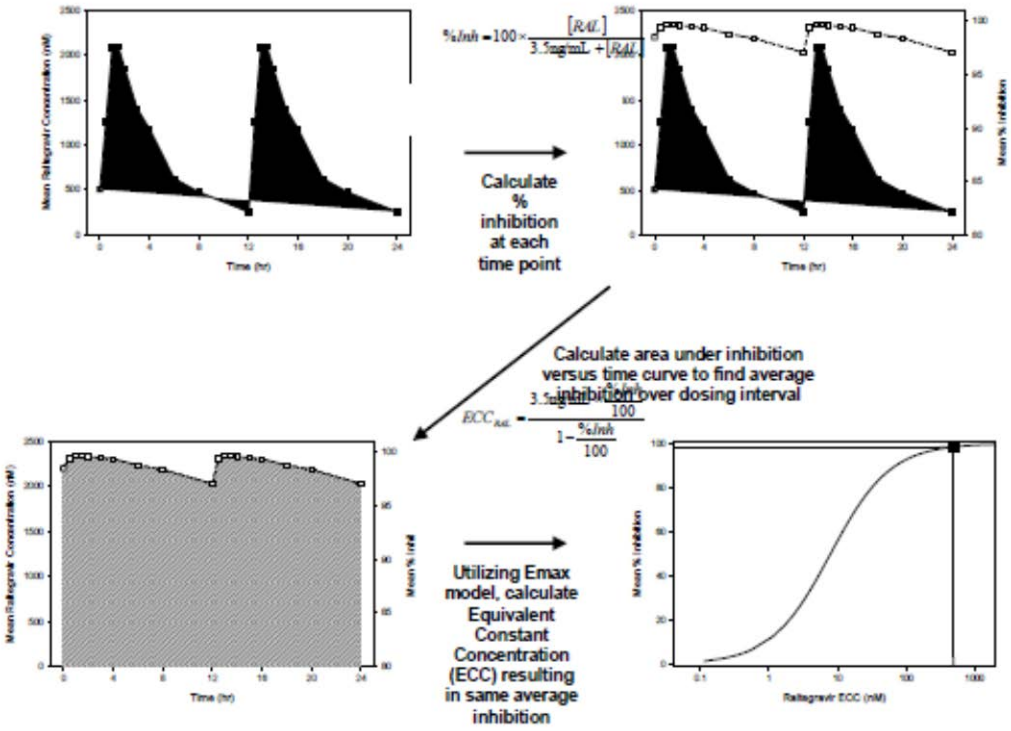
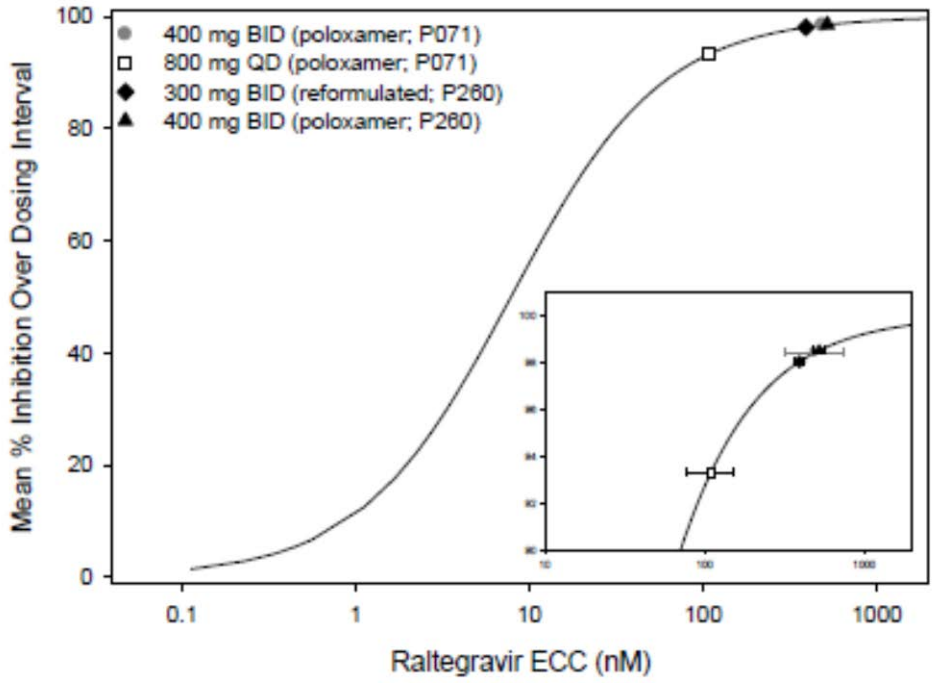


Figure 6: **Geometric mean ECC and % inhibition over the dosing interval for patients administered raltegravir as 400 mg BID (ISENTRESS as reference arm in P260 BA/BE study), 300 mg BID (raltegravir in lamivudine/raltegravir FDC tablet P260 BE study) or retrospective data from P071 for comparison; Inset: magnification of outer plot; error bars represent 95% confidence interval of ECC values using observed PK Data**

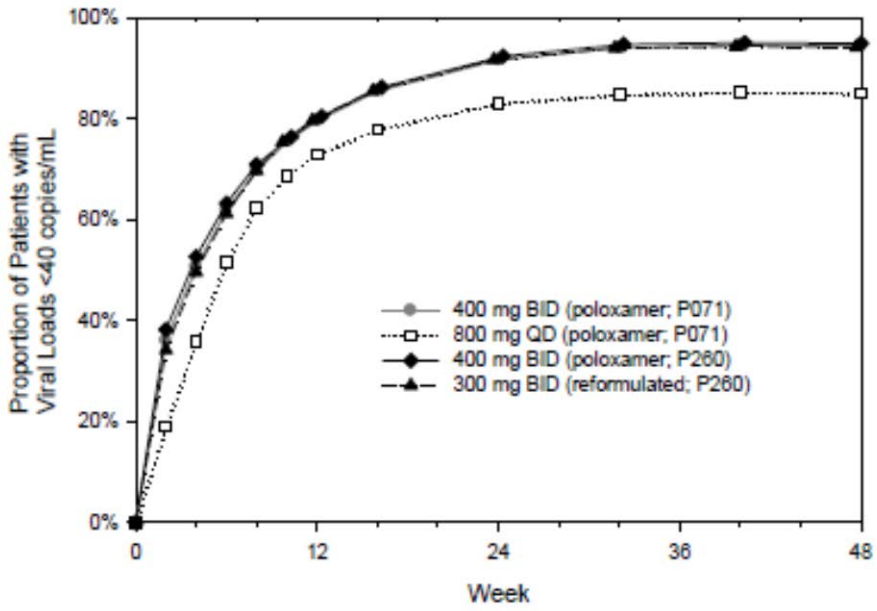


Source: Figure 16 on page 57 of sponsor's clinical report 03TSW9

3.4 Efficacy Simulation

With the previously developed viral dynamics model, the sponsor simulated efficacy outcomes for different raltegravir regimens. Proportions of adult HIV-patients with viral loads < 40 copies/mL over 48 weeks of treatment after administration with ISENTRESS 400 mg b.i.d versus those with ISENTRESS 800 mg q.d, and those in study P260 who administered lamivudine/raltegravir FDC tablet were compared in Figure 7. The projected efficacy with lamivudine/raltegravir FDC tablet in study P260 was similar to those with ISENTRESS 400 mg b.i.d.

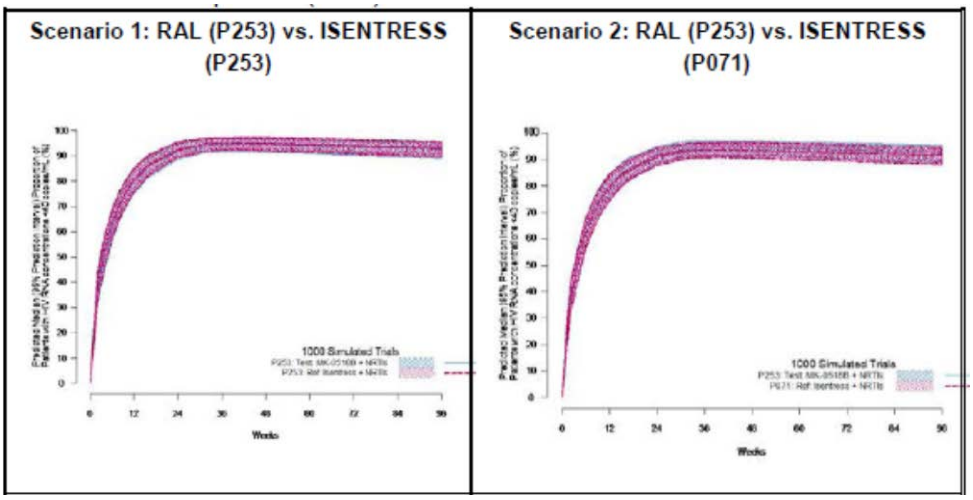
Figure 7: Simulated proportion of adult HIV-patients with viral loads < 40 copies/mL over 48 weeks of treatment for patients administered raltegravir as 400 mg BID (ISENTRESS as reference arm in P260) or retrospective data from P071 for comparison



Source: Figure 17 on page 57 of sponsor's clinical report 03TSW9

Additionally, the sponsor predicted the median and 95% confidence intervals for the proportions of patients with HIV RNA concentrations < 40 copies/mL as a function of treatment durations for several clinical scenarios. Scenario 1 compared the projected efficacy of raltegravir component of the FDC tablet with ISENTRESS 400 mg in healthy volunteers in study P253. Scenario 2 compared the projected efficacy of raltegravir component of the FDC tablet against ISENTRESS 400 mg in HIV-infected patients (P071). There was no evident difference between the predicted virologic response between tested and reference products (Figure 8).

Figure 8: **Clinical equivalence via viral dynamics model using observed PK data from BE studies (P253) and HIV-infected patients (P071)**



Source: Adapted from Figure 15 of sponsor's clinical report 03TSW9

3.5 Exposure-response analysis for safety

The exposure-response analysis for safety of raltegravir was conducted using clinical data from study P071-01 (QDMRK). The study was a multi-center, double-blind, randomized, active-controlled study in treatment-naïve, HIV-1 infected patients to compare the long-term safety, tolerability, and efficacy of once-daily (q.d.) raltegravir 800 mg PO compared with twice daily (b.i.d.) raltegravir 400 mg PO, when each was given in combination with TRUVADA (tenofovir disoproxil fumarate 300 mg + emtricitabine 200 mg) q.d. for up to 96 weeks. Sparse samples were collected in nearly all patients, and intensive PK profiles were collected in a subset of 20 patients in the b.i.d treatment arm and 22 patients in the q.d. treatment arm. C_{all} (defined as the geometric mean of all samples for a particular patient, regardless of time of collection) was deemed as the best available parameter for exposure-adverse AE analysis. Calculated PK parameters from sparse and intensive PK samples are summarized in Table 12. As expected, the C_{max} of the 800 mg q.d regimen were about 4-fold of the 400 mg b.i.d regimen. But the C_{trough} of the 800 mg .q.d (40 nM) was 84% less than the 400 mg b.i.d dosing regimen (257 nM).

Table 12: Summary statistics for raltegravir PK parameters from MK-0518 Protocol 071-01

Treatment	*N*	*Geometric Mean*	*%CV*	*Minimum*	*Median*	*Maximum*
C_{all} (nM)						
400 mg b.i.d.	384	455	92	42	446	6547
800 mg q.d.	380	196	176	11	185	11614
Maximum Sparse Concentration (μM)						
400 mg b.i.d.	384	1.99	128	0.16	1.80	22.76
800 mg q.d.	380	1.05	339	0.02	1.06	36.78
GM C_{trough} from Sparse PK (C_{12hr} for b.i.d. and C_{24hr} for q.d., nM)						
400 mg b.i.d.	304	380	126	17	373	10864
800 mg q.d.	245	83	140	7	77	9076
$AUC_{0\text{-}24hr}$ (μM·hr)						
400 mg b.i.d.	20	26.28	99	3.64	26.73	115.15
800 mg q.d.	22	30.87	70	7.27	36.75	89.96
C_{max} (μM)						
400 mg b.i.d.	20	3.38	135	0.45	3.47	20.11
800 mg q.d.	22	13.46	69	3.72	17.03	44.30
C_{trough} from Intensive PK (C_{12hr} for b.i.d. and C_{24hr} for q.d., nM)						
400 mg b.i.d.	20	257	167	32	171	2226
800 mg q.d.	22	40	111	5	39	329

Source: Table 1 on page 14 of sponsor's clinical report 03N7N7

No relationship between C_{all} and incidence of adverse events was observed following 48-week of treatment with raltegravir together with other antiretroviral therapy. There was no significant difference between the highest 25% of C_{all} values and the lower 25% of C_{all} values in patients with one or more adverse events for both 800 m.g q.d and 400 mg b.i.d dosing regimen (Table 13 and Table 14). The number of patients who discontinued study due to an adverse events was low for both dosing regimen suggesting that the 800 mg q.d was as tolerable as 400 mg b.i,d. even with a 4-fold C_{max}.

Table 13: **Clinical adverse experience summary by C_{all} Quartile in the 800 mg q.d. raltegravir treatment arm Protocol 071-01: week 0-48**

	C_{all} Quartile 1		C_{all} Quartile 2		C_{all} Quartile 3		C_{all} Quartile 4		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Patients in population	95		95		95		95		380	
with one or more adverse events	82	(86.3)	80	(84.2)	83	(87.4)	86	(90.5)	331	(87.1)
with no adverse event	13	(13.7)	15	(15.8)	12	(12.6)	9	(9.5)	49	(12.9)
with drug-related† adverse events	25	(26.3)	23	(24.2)	24	(25.3)	26	(27.4)	98	(25.8)
with serious adverse events	3	(3.2)	5	(5.3)	4	(4.2)	9	(9.5)	21	(5.5)
with serious drug-related adverse events	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.1)	1	(0.3)
who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued‡ due to an adverse event	0	(0.0)	2	(2.1)	0	(0.0)	2	(2.1)	4	(1.1)
discontinued due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	2	(2.1)	2	(0.5)
discontinued due to a serious adverse event	0	(0.0)	1	(1.1)	0	(0.0)	1	(1.1)	2	(0.5)
discontinued due to a serious drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.1)	1	(0.3)

† Determined by the investigator to be related to the drug.
‡ Study medication withdrawn.
Note: RAL 800 mg q.d. was administered with TRUVADA™

Source: Table 6 on page 22 of sponsor's clinical report 03N7N7

Table 14: Clinical adverse experience summary by C_{all} quartile in the 400 mg b.i.d raltegravir treatment arm Protocol 071-01: week 0 to 48

	C_{all} Quartile 1		C_{all} Quartile 2		C_{all} Quartile 3		C_{all} Quartile 4		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Patients in population	96		96		96		96		384	
with one or more adverse events	83	(86.5)	86	(89.6)	83	(86.5)	84	(87.5)	336	(87.5)
with no adverse event	13	(13.5)	10	(10.4)	13	(13.5)	12	(12.5)	48	(12.5)
with drug-related† adverse events	15	(15.6)	29	(30.2)	23	(24.0)	25	(26.0)	92	(24.0)
with serious adverse events	5	(5.2)	8	(8.3)	7	(7.3)	11	(11.5)	31	(8.1)
with serious drug-related adverse events	0	(0.0)	1	(1.0)	1	(1.0)	0	(0.0)	2	(0.5)
who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued‡ due to an adverse event	0	(0.0)	0	(0.0)	1	(1.0)	2	(2.1)	3	(0.8)
discontinued due to a drug-related adverse event	0	(0.0)	0	(0.0)	1	(1.0)	1	(1.0)	2	(0.5)
discontinued due to a serious adverse event	0	(0.0)	0	(0.0)	1	(1.0)	1	(1.0)	2	(0.5)
discontinued due to a serious drug-related adverse event	0	(0.0)	0	(0.0)	1	(1.0)	0	(0.0)	1	(0.3)

† Determined by the investigator to be related to the drug.
‡ Study medication withdrawn.
Note: RAL 400 mg b.i.d. was administered with TRUVADA™

Source: Table 7 on page 23 of sponsor's clinical report 03N7N7

Reviewer's Comment: The sponsor used C_{all} as the PK parameters to evaluate exposure-response relationship for safety. However, C_{all} is not strongly correlated with other PK parameters such as AUC, C_{max} , and C_{trough}. The sponsor admitted such limitations and warned that the interpretation to the results should be with caution. Despite this issue, the rate of subjects who discontinued treatment due to a drug-related adverse event or a serious adverse event was low in both treatment arms. Overall, both dosing regimen are well tolerated and were considered safe despite their significant difference in C_{max}

values. As no substantial differences in safety were observed for these two regimens with similar AUC despite markedly different C_{max} values (4-fold difference between 400 mg b.i.d. and 800 mg q.d.), it is not anticipated that a 1.4-fold increase in C_{max} as may occur with the FDC under b.i.d. administration would result in an increased safety concern either.

Study P254
MK-0518B Food Effect Study

Trial Period
24 Oct to 2 Nov 2012
Final report date: 17 Oct 2012

Trial Site
Pharma Medica Research, Inc., Toronto, Ontario, Canada

Trial Rationale
Raltegravir (RAL, ISENTRESS®) is an integrase strand transfer inhibitor (InSTI) approved in combination with other antiretroviral agents for the treatment of HIV-1 infection. Lamivudine (3TC, EPIVIR®) is a nucleoside analog reverse transcriptase inhibitor (NRTI) approved in combination with other antiretroviral agents for the treatment of HIV-1 infection. A fixed-dose combination (FDC) tablet formulation (for BID administration) is being developed to decrease pill burden and improve adherence, with a proposed indication for the treatment of HIV-1 infection in combination with other antiretroviral agents. The primary goal of this study was to evaluate the effect of a high-fat meal on the bioavailability of raltegravir/lamivudine (MK-0518B) 300/150 mg FDC tablets.

Trial Objectives
The primary objective of the trial was to:

- assess the effect of a high-fat meal on the in vivo performance of raltegravir/lamivudine (MK-0518B) 300/150 mg FDC tablets from Merck Sharp & Dohme Corp., USA after a single-dose administration in healthy subjects

Trial Design
This was an open-label, single-dose, randomized, two-period, two-sequence crossover food effect study with two treatments:

- Treatment A RAL/3TC (MK-0518B) 300/150 mg FDC tablets administered after an overnight fast of at least 10 h
- Treatment B RAL/3TC (MK-0518B) 300/150 mg FDC tablets administered after a high fat, high calorie breakfast

The washout period was 7 days. Subjects were confined to the clinic from at least 10.5 h prior to each drug administration until 24 h postdose.

Rationale for Dose Selection

The RAL dose of 300 mg and the 3TC dose of 150 mg are half of the proposed daily dose for reformulated RAL and the approved daily dose for 3TC for the treatment of HIV-1 and comprise one FDC tablet.

Drug Administration

Study drug was administered in the morning with 240 mL water by clinic staff. Subjects fasted overnight for at least 10 h prior to drug administration (or a high fat, high calorie [504 kcal, 50.6% fat content] breakfast, which was served 30 min prior to drug administration) and for at least 4 h following drug administration. Water was not allowed from 1 h prior to drug administration until 1 h after drug administration. Subjects remained seated for 4 h following drug administration.

Investigational Product

RAL/3TC (MK-0518B) 300/150 mg FDC tablets (Lot WL00049661/WL00049787) were supplied by the Sponsor.

Key Inclusion and Exclusion Criteria

Subjects were healthy nonsmoking males and females between 18 and 55 years of age with a BMI between 19 and 30 kg/m^2 with no clinically significant findings. Females of childbearing potential were surgically sterile, post-menopausal, abstinent from 21 days prior to study drug administration until 28 days after the end of the study, or willing to use two effective methods of birth control (condom, diaphragm, cervical cap, vaginal sponge, spermicide, IUD, tubal ligation, vasectomized partner, hormonal contraceptives) from 21 days prior to study drug administration until 28 days after the end of the study. Potential subjects were excluded if they were pregnant or lactating. Exclusion criteria also included known history or presence of any clinically significant medical condition, an estimated creatinine clearance of 80 mL/min or less (Cockcroft-Gault), positive test result for HIV-1 antibody, hepatitis C antibody, or hepatitis B surface antigen, or a positive urine screen for drugs of abuse.

Concomitant Medications

Concomitant medications, including prescription drugs (with the exception of hormonal contraceptives, non-systemic and/or topically applied products, and occasional use of common analgesics), herbal remedies, and nutritional supplements and vitamins, were prohibited from 14 days preceding study drug administration until completion of the study.

Grapefruit or products containing grapefruit were restricted from 14 days prior to study drug administration until completion of the study. Alcohol, caffeine, and xanthine were restricted from 48 h prior to study drug administration until the last sampling timepoint. Juices were restricted from 24 h prior to study drug administration until the last sampling timepoint.

Sample Collection

Blood was collected to assess RAL and 3TC concentrations in plasma predose and 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 36, and 48 h postdose in 6 mL K_2EDTA blood collection tubes.

Analytical Plan

Pharmacokinetic data

Raltegravir and lamivudine plasma C_{max}, t_{max}, C_{12}, AUC_{last}, AUC_{inf}, k_e, and apparent elimination half-life ($t_{1/2}$) were estimated using standard noncompartmental methods using SAS®. K_e, $t_{1/2}$, and AUC_{inf} were not estimated for RAL concentration-time profiles for which the terminal linear phase was not clearly defined. Statistical analyses of food effect on log-transformed RAL and 3TC PK parameters (AUC_{inf}, AUC_{last}, C_{12}, and C_{max}) used a linear mixed-effect model with period and treatment as fixed effects (b) (4)) to calculate the geometric mean ratios and corresponding 90% CI.

Trial Results

Bioanalytical methods

Concentrations of lamivudine in plasma samples were measured by LC-MS/MS by (b) (4) . Analysis was performed between 15 and 20 Nov 2012. The maximum storage sample time was 27 days, which is within the validated long-term frozen stability duration of 366 days in plasma containing MK-0518 (RAL). The calibration standards ranged from 10-2500 ng/mL and the quality control (QC) concentrations were (b) (4) All inter-assay accuracy and precision estimates were within the acceptable range (data not shown).

Concentrations of raltegravir in plasma samples were measured by LC-MS/MS by (b) (4) . Analysis was performed between 15 and 20 Nov 2012. The maximum storage sample time was 27 days, which is within the validated long-term frozen stability duration of 343 days in plasma. The calibration standards ranged from 2-1000 ng/mL and the quality control (QC) concentrations were (b) (4) . All inter-assay accuracy and precision estimates were within the acceptable range (data not shown).

Trial population

A total of 20 subjects were enrolled in and completed the study. A summary of subject demographics is displayed in Table 1.

Table 1. Demographic summary (source: Study Report Table 11.2-1)

		Statistical Dataset N = 20	Safety Dataset N = 20
Age (years)	**Mean ± SD** **Range**	42 ± 8 24 - 53	42 ± 8 24 - 53
Age Group	**< 18** **18 - 40** **41 - 64** **65 - 75** **> 75**	0 (0.0%) 9 (45.0%) 11 (55.0%) 0 (0.0%) 0 (0.0%)	0 (0.0%) 9 (45.0%) 11 (55.0%) 0 (0.0%) 0 (0.0%)
Sex	**Male** **Female**	8 (40.0%) 12 (60.0%)	8 (40.0%) 12 (60.0%)
Race	**Asian** **Black** **White** **Other**	2 (10.0%) 4 (20.0%) 14 (70.0%) 0 (0.0%)	2 (10.0%) 4 (20.0%) 14 (70.0%) 0 (0.0%)
Ethnicity	**Hispanic/Latino**	5 (25.0%)	5 (25.0%)
BMI	**Mean ± SD** **Range**	25.5 ± 2.6 19.9 - 28.9	25.5 ± 2.6 19.9 - 28.9
Height (cm)	**Mean ± SD** **Range**	167.7 ± 8.1 154.0 - 181.8	167.7 ± 8.1 154.0 - 181.8
Weight (kg)	**Mean ± SD** **Range**	71.9 ± 11.3 50.3 - 94.3	71.9 ± 11.3 50.3 - 94.3

Assessment of plasma raltegravir pharmacokinetics

The mean raltegravir concentration-time profiles following a single dose of the RAL/3TC 300/150 mg FDC oral tablet to healthy subjects in the fed (study drug administration after a high fat, high calorie meal) or fasted state are displayed in Figure 1. Raltegravir was absorbed more quickly (median t_{max}: 1 and 3 h in the fasted and fed states, respectively) and to a slightly greater extent (mean C_{max} was approximately 30% higher) in the fasted state compared to the fed state (Table 2). Overall systemic exposures were slightly influenced by fed vs. fasted administration (mean AUC_{inf} was approximately 6% higher in the fasted state compared to the fed state).

Figure 1. Mean ± SD raltegravir plasma concentration-time profiles by treatment (semi-log scale on the y-axis, with x-values offset for ease of visualization; source: Reviewer's analysis of RAW.xpt)

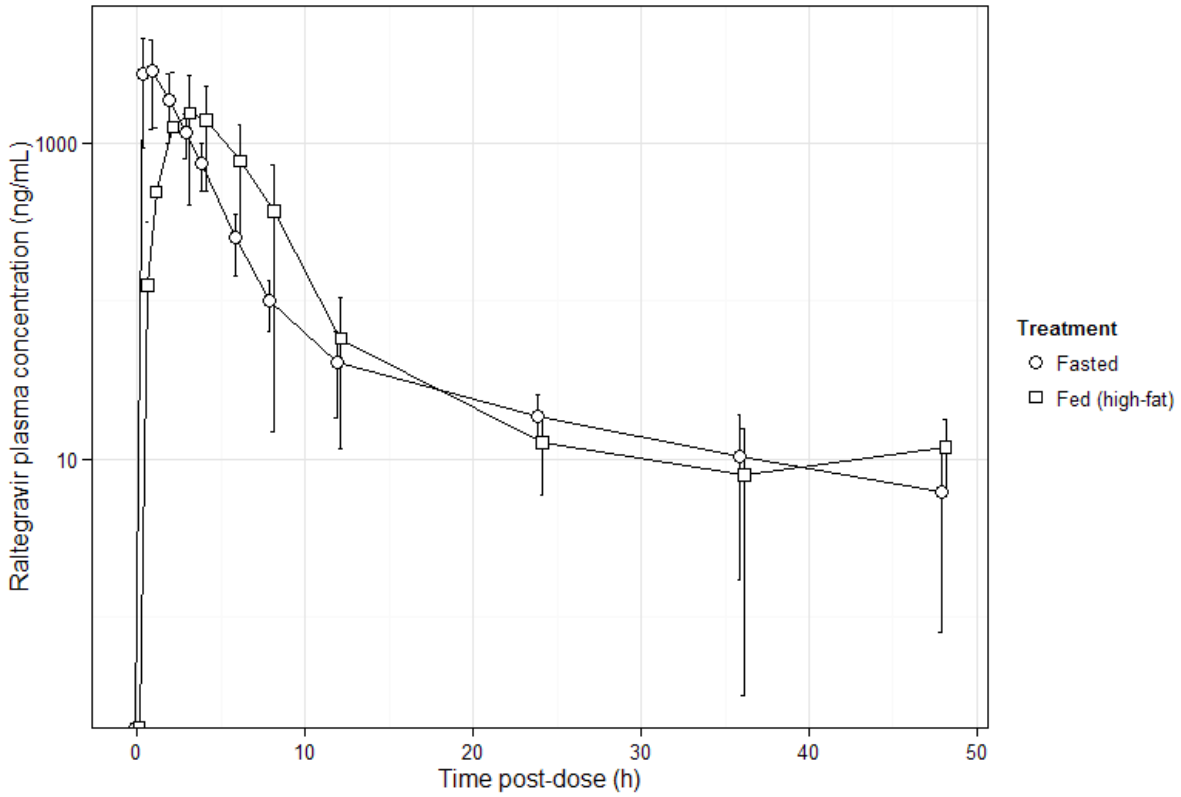


Table 2. Key raltegravir pharmacokinetic parameters (source: Study Report Table 11.4.7-1)

Based on Measured Plasma Raltegravir Concentrations								
Parameter	*Trt*	*n*	*GM*	*95% CI for GM*	*Contrast*	*GMR (%)*	*90% CI for GMR*	*Pseudo Intra-Sbj CV(%)**
AUC_{0-t}	A	20	8381.74	7036.95 - 9983.52	B vs. A	94.47	83.37 - 107.05	23
(h.ng/mL)	B	20	7918.47	7031.92 - 8916.80		-	-	-
AUC_{inf}	A	20	8603.28	7235.11 - 10230.16	B vs. A	94.22	82.93 - 107.05	23
(h.ng/mL)	B	19	8106.17	7138.50 - 9205.02		-	-	-
C_{max}	A	20	2874.04	2101.69 - 3930.22	B vs. A	76.99	55.16 - 107.46	61
(ng/mL)	B	20	2212.79	1705.78 - 2870.51		-	-	-
C_{12h}	A	20	37.31	30.33 - 45.90	B vs. A	120.14	89.48 - 161.30	54
(ng/mL)	B	20	44.82	31.99 - 62.80		-	-	-
			Median	*Range*				
T_{max}	A	20	1.0	0.5- 4.0				
(h)	B	20	3.0	2.0- 8.0				
			GM	*CV(%)***				
$t_{½}$	A	20	14.1	69.7				
(h)	B	19	13.0	88.9				

** Estimated based on the elements of the variance-covariance matrix from the linear mixed-effect model as: CV(%) = 100*sqrt[(σ^2_A + σ^2_B -2*σ_{AB})/2], where σ^2_A and σ^2_B are the estimated variances on the log scale for the two treatment groups, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed effects model.*
*** CV = 100 x sqrt(exp(s^2) - 1), where s^2 is the observed variance on the natural log-scale*
Treatment A: Fasted
Treatment B: Fed (high fat meal)

Assessment of plasma lamivudine pharmacokinetics

The mean lamivudine concentration-time profiles following a single dose of the RAL/3TC 300/150 mg FDC oral tablet to healthy subjects in the fed (study drug administration after a high fat, high calorie meal) or fasted state are displayed in Figure 2. Lamivudine was absorbed more quickly (median t_{max}: 2 and 4 h in the fasted and fed states, respectively) and to a slightly greater extent (mean C_{max} was approximately 26% higher) in the fasted state compared to the fed state (Table 3). Mean lamivudine trough concentrations were approximately 53% higher under fed conditions. Overall systemic exposures were slightly influenced by fed vs. fasted administration (mean AUC_{inf} was approximately 8% higher in the fasted state compared to the fed state).

Figure 2. Mean ± SD lamivudine plasma concentration-time profiles by treatment (semi-log scale on the y-axis, with x-values offset for ease of visualization; source: Reviewer's analysis of RAW.xpt)

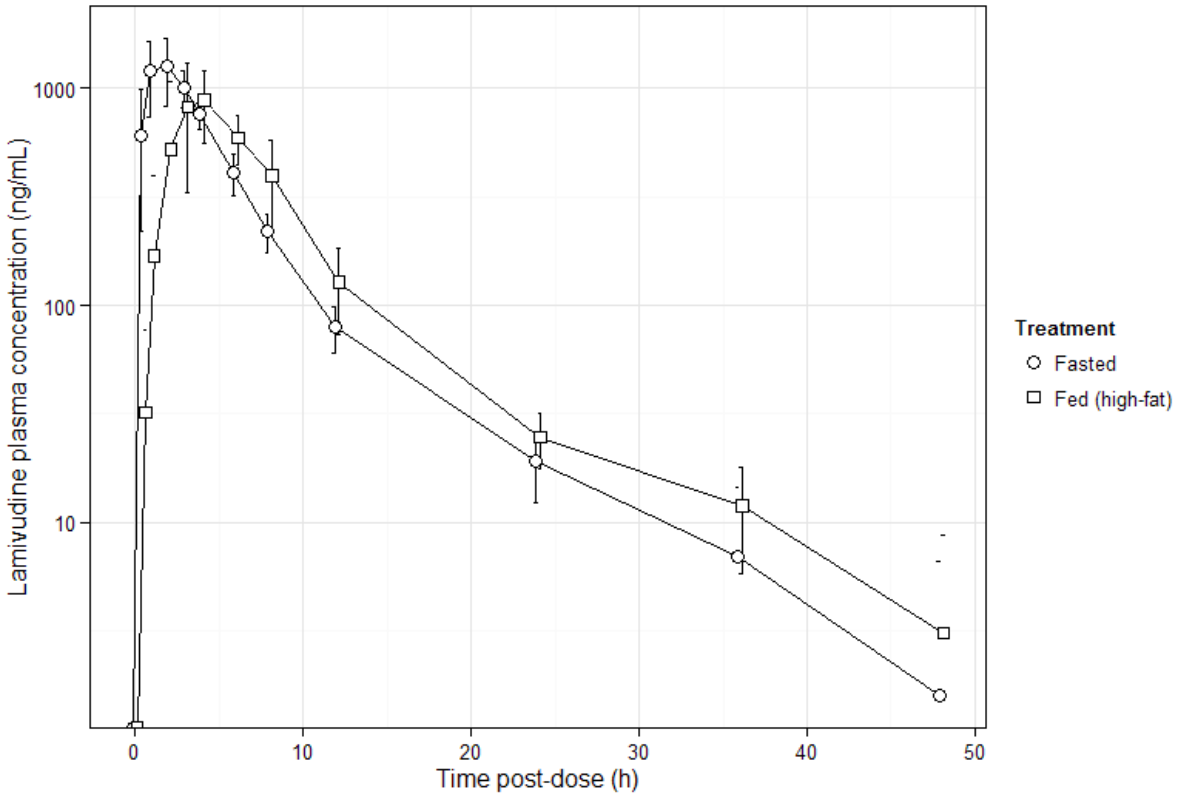


Table 3. Key lamivudine pharmacokinetic parameters (source: Study Report Table 11.4.7-2)

Based on Measured Plasma Lamivudine Concentrations								
Parameter	*Trt*	*n*	*GM*	*95% CI for GM*	*Contrast*	*GMR (%)*	*90% CI for GMR*	*Pseudo Intra-Sbj CV(%)**
AUC_{0-t}	A	20	6654.9	6081.8 - 7282.0	B vs. A	92.45	87.23 - 97.98	11
(h.ng/mL)	B	20	6152.5	5648.8 - 6701.2		-	-	-
AUC_{inf}	A	20	6834.0	6241.7 - 7482.6	B vs. A	92.43	87.51 - 97.63	10
(h.ng/mL)	B	20	6316.8	5786.3 - 6896.0		-	-	-
C_{max}	A	20	1358.0	1172.7 - 1572.6	B vs. A	79.43	70.73 - 89.20	21
(ng/mL)	B	20	1078.7	918.5 - 1266.7		-	-	-
C_{12h}	A	20	77.4	68.8 - 87.2	B vs. A	152.62	134.47 - 173.22	23
(ng/mL)	B	20	118.2	97.9 - 142.6		-	-	-
			Median	*Range*				
T_{max}	A	20	2.0	1.0- 3.0				
(h)	B	20	4.0	2.0- 8.0				
			GM	*CV(%)***				
$t_{½}$	A	20	6.8	64.4				
(h)	B	20	8.3	52.4				

** Estimated based on the elements of the variance-covariance matrix from the linear mixed-effect model as: $CV(\%) = 100*sqrt[(\sigma^2_A + \sigma^2_B - 2*\sigma_{AB})/2]$, where σ^2_A and σ^2_B are the estimated variances on the log scale for the two treatment groups, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed effects model.*
*** $CV = 100 \times sqrt(exp(s^2) - 1)$, where s^2 is the observed variance on the natural log-scale*
Treatment A: Fasted
Treatment B: Fed (high fat meal)

Results of safety analysis

There were eight adverse events reported during the study that were categorized as possibly related to study treatment (increased creatinine, headache, increased appetite, dizziness, somnolence, and dyspepsia); all were mild in severity. AEs were distributed evenly between treatments. No subjects discontinued study drug due to adverse events and no serious adverse events or deaths occurred during the study.

Trial Summary

In this study, the pharmacokinetics of raltegravir and lamivudine following a single dose of the RAL/3TC 300/150 mg FDC oral tablet in the fed (study drug administration after a high fat, high calorie meal) or fasted state were evaluated in healthy subjects. For both drugs, administration with a high fat meal appeared to result in delayed absorption and lower maximal concentrations of both raltegravir and lamivudine, although overall systemic exposures (AUC) were not statistically significantly changed. Overall, the results of this study support the administration of the RAL/3TC 300/150 FDC oral tablet without regard to food.

Study P214
A Study to Assess the Effect of Etravirine on MK-0518B Pharmacokinetics

Trial Period
11 Apr to 21 May 2012
Final report date: 18 May 2013

Trial Site
QPS Bio-Kinetic, Springfield, Missouri, USA

Trial Rationale
Raltegravir (RAL, ISENTRESS®) is an integrase strand transfer inhibitor (InSTI) approved in combination with other antiretroviral agents for the treatment of HIV-1 infection. Lamivudine (3TC, EPIVIR®) is a nucleoside analog reverse transcriptase inhibitor (NRTI) approved in combination with other antiretroviral agents for the treatment of HIV-1 infection. A fixed-dose combination (FDC) tablet formulation (for BID administration) is being developed to decrease pill burden and improve adherence, with a proposed indication for the treatment of HIV-1 infection in combination with other antiretroviral agents, such as the non-nucleoside reverse transcriptase inhibitor (NNRTI) etravirine (TMC125, INTELENCE®). The primary goal of this study was to evaluate the potential for a pharmacokinetic interaction between raltegravir, which is glucuronidated by UGT1A1, and etravirine, which induces UGT1A1, when etravirine is coadministered with raltegravir/lamivudine (MK-0518B) 300/150 mg FDC tablets. An earlier clinical study conducted with etravirine and raltegravir demonstrated that raltegravir AUC_{12}, C_{max}, and C_{trough} were reduced by approximately 10, 11, and 34%, but these changes were not considered clinically significant and no dose adjustments were recommended when raltegravir and etravirine are coadministered (P026).

Trial Objectives
The primary objective of the trial was to:

- assess the effect of etravirine on raltegravir C_{12} after administration of a single MK-0518B tablet

Trial Design
This was an open-label, fixed-sequence, two-period study with two treatments:

- Treatment A RAL/3TC (MK-0518B) 300/150 mg FDC tablet, single dose (Day 1 of Period 1)
- Treatment B etravirine 200 mg BID (Days 1-14 of Period 2), coadministered with a single dose of MK-0518B 300/150 mg FDC on Day 14 of Period 2

There was at least a two-day washout period between Treatments 1 and 2. Subjects were confined to the clinic the evening before RAL/3TC administration and for 24 h postdose.

Lamivudine was not expected to be a perpetrator or a victim in this drug interaction study; therefore, lamivudine PK was not characterized. In addition, etravirine concentrations were assessed predose on Days 1, 12, 13, and 14 in order to ensure that steady-state was achieved by Day 14, but etravirine PK was not otherwise characterized.

Rationale for Dose Selection

The RAL dose of 300 mg and the 3TC dose of 150 mg are half of the proposed daily dose for reformulated RAL and the approved daily dose for 3TC for the treatment of HIV-1 and comprise one FDC tablet. The etravirine dose of 200 mg BID administered with food is the approved dose of etravirine. The duration of dosing (14 days) was selected to allow etravirine to reach steady-state and to assure induction/inhibition of drug-metabolizing enzymes.

Drug Administration

For morning doses, study drugs were administered with 240 mL water by clinic staff following a meal. Evening doses of etravirine were self-administered. On Day 1 of Period 1 and Day 14 of Period 2, morning doses were administered with a standard light meal following a 4 hour fast.

Investigational Product

RAL/3TC (MK-0518B) 300/150 mg FDC tablets (Control No. WL00047553) were supplied by the Sponsor. Etravirine 200 mg tablets were commercially available (Lot BJL4G00).

Key Inclusion and Exclusion Criteria

Subjects were healthy nonsmoking males and females between 18 and 55 years of age with a BMI less than 32 kg/m^2 with no clinically significant findings. Females of childbearing potential were surgically sterile, post-menopausal, abstinent from screening until two weeks after the end of the study, or willing to use two effective methods of birth control (condom, diaphragm, cervical cap, vaginal sponge, spermicide, IUD, tubal ligation, vasectomized partner) from screening until two weeks after the end of the study. Potential subjects were excluded if they were pregnant or lactating. Exclusion criteria also included known history or presence of any clinically significant medical condition, an estimated creatinine clearance of 80 mL/min or less (Cockcroft-Gault), positive test result for HIV-1 antibody, hepatitis C antibody, or hepatitis B surface antigen, or a positive urine screen for drugs of abuse.

Concomitant Medications

Concomitant medications, including prescription drugs (with the exception of occasional use of common analgesics), herbal remedies, and nutritional supplements and vitamins, were prohibited from 14 days preceding study drug administration until completion of the study.

Grapefruit or products containing grapefruit were restricted from 14 days prior to study drug administration until completion of the study. Alcohol was restricted from 24 h prior to first dose of study drug until completion of Period 2 Day 14 procedures. Caffeine was restricted from 12 h prior until 12 h after study drug administration on Period 1 Day 1 and Period 2 Day 14.

Sample Collection

Blood was collected to assess RAL concentrations in plasma predose and 0.5, 1, 2, 3, 4, 6, 8, 12, 16, 24, 36, and 48 h postdose in K_2EDTA blood collection tubes. Blood was collected to assess etravirine concentrations in plasma predose on Days 1, 12, 13, and 14 in sodium heparin blood collection tubes.

Analytical Plan

Pharmacokinetic data

Raltegravir C_{12} values were log-transformed and evaluated using a linear mixed-effects model with a fixed effect term for treatment. A two-sided 90% CI for the GMR was compared against the prespecified bounds 0.5-2.00. Descriptive statistics were calculated for other RAL pharmacokinetic parameters.

Trial Results

Bioanalytical methods

Concentrations of raltegravir in plasma samples were measured by LC-MS/MS by (b) (4) Analysis was performed between 15 and 21 May 2012. The maximum storage sample time was 30 days, which is within the validated long-term frozen stability duration of 41 days in plasma containing 3TC and etravirine. The calibration standards ranged from 2-1004 ng/mL and the quality control (QC) concentrations were (b) (4). All inter-assay accuracy and precision estimates were within the acceptable range (data not shown).

Trial population

A total of 18 subjects were enrolled in the study, three of whom discontinued due to AEs (generalized rash) during Period 2 prior to RAL/3TC administration but following completion of Period 1. There were 18 subjects in the all subjects treated (AST) population and 15 in the per protocol (PP) population. A summary of subject demographics is displayed in Table 1.

Table 1. Demographic summary (source: Study Report Table 10-1)

Variable	Statistic or Category	AST population	PP population
Gender (n (%))	Male	10 (55.6)	9 (60.0)
	Female	8 (44.4)	6 (40.0)
Age (yrs)	Mean (SD)	33.8 (11.3)	34.5 (10.7)
Ethnicity (n (%))	Non hispanic	18 (100.0)	15 (100.0)
Race (n (%))	Black or African American	1 (5.6)	1 (6.7)
	White	17 (94.4)	14 (93.3)
Height (cm)	Mean (SD)	174.4 (8.7)	174.5 (9.3)
Weight (kg)	Mean (SD)	77.57 (15.05)	77.96 (15.32)
BMI (kg/m2)	Mean (SD)	25.33 (3.41)	25.43 (3.35)

Data Source: [14.2]

Assessment of plasma raltegravir pharmacokinetics

The mean raltegravir concentration-time profiles following a single dose of the RAL/3TC 300/150 mg FDC oral tablet to healthy subjects in the fed (study drug administration after a light meal) state are displayed in Figure 1. Geometric mean RAL $t_{1/2}$ was shorter in the presence of steady-state etravirine (6.47 h with etravirine compared to 8.34 h without etravirine) due to induction of UGT1A1 (Table 2). Overall systemic exposures of RAL were comparable with or without etravirine (Table 3). Examination of the primary PK parameter of RAL C_{12} revealed an approximately 14% decrease in the presence of etravirine at steady-state, with 90% CI (63.0-117%) within the predefined no-effect boundaries of 50-200% (Table 3).

Figure 1. Mean ± SD raltegravir plasma concentration-time profiles by treatment (semi-log scale; source: CSR Table 11-1)

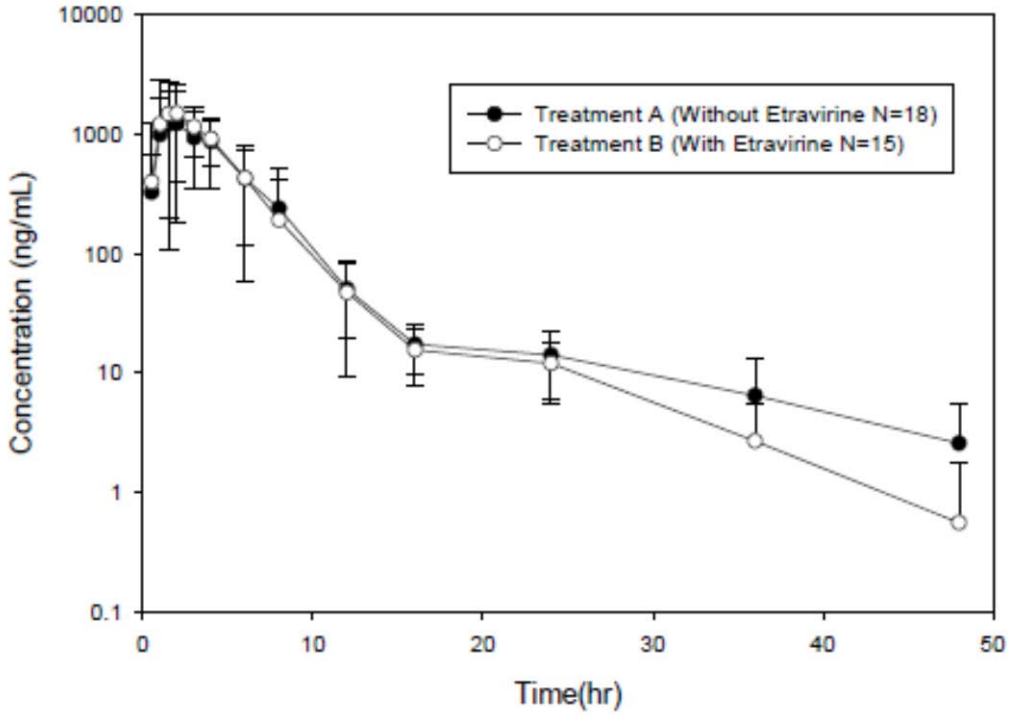


Table 2. Summary of raltegravir pharmacokinetic parameters in the absence (Treatment A) or presence (Treatment B) of etravirine (source: Study Report Table 11-1)

	Treatment A (N= 18)				Treatment B (N=15)			
Parameters	AM	SD	GM	GCV%	AM	SD	GM	GCV %
C_{max}, ng/mL	1800	1060	1550	62	2170	1260	1870	60
C_{12hr}, ng/mL	50.1	30.4	42.5	64	46.9	37.7	36.8	78
C_{24hr}, ng/mL	14.0	8.43	12.5	48	11.9	5.95	10.6	56
$AUC_{0\text{-last}}$, h·ng/mL	6160	1880	5870	33	6690	2500	6220	42
$AUC_{0\text{-}\infty}$, h·ng/mL	6220	1900	5920	33	6730	2480	6280	41
$t_{½}$, h	9.36	4.36	8.34	56	8.57	9.15	6.47	78
T_{max}, h*	3.50	[1.00	8.00]		2.00	[1.00	6.00]	

AM: Arithmetic Mean; SD: Standard Deviation; GM: Geometric Mean; * T_{max} expressed as median [Range]; GCV%: Geometric CV which is equal to 100 x sqrt(exp(s^2) - 1), where s^2 is the observed variance on the natural log-scale;
Treatment A: A single dose of MK-0518B (300-mg reformulated raltegravir/150-mg lamivudine) on Day 1.
Treatment B: 200 mg etravirine every 12 hours (q12h) for 15 days with a single dose of MK-0518B co-administered on the morning of Day 14.

Source [16.2.6.2]

Table 3. Statistical comparison of raltegravir pharmacokinetic parameters in the absence (Treatment A) or presence (Treatment B) of etravirine (source: Study Report Table 11-2)

	Treatment B:Treatment A		Pseudo Within Subject %CV*
PK parameter	GMR (%)	90% CI	
C_{12}** (ng/mL)	85.81	63.04, 116.79	48.44
C_{max}** (ng/mL)	120.22	100.00, 144.53	29.09
AUC_{last}** (ng.h/mL)	108.32	95.03, 123.48	20.23
AUC_{inf}** (ng.h/mL)	108.30	95.25, 123.14	19.86

* Pseudo Within-Subject %CV= $100*(\sqrt{(\hat{\sigma}_A^2+\hat{\sigma}_B^2-2\hat{\sigma}_{AB})/2})$ where $\hat{\sigma}_A^2$ and $\hat{\sigma}_B^2$ are the estimated variances on the log scale for the two treatment groups, and $\hat{\sigma}_{AB}^2$ is the corresponding estimated covariance, each obtained from the linear mixed-effects model

* Back-transformed least squares mean and CI from mixed effects model performed on natural log-transformed values

Source [16.2.6.2]

Because RAL pharmacokinetics have been characterized as highly variable (both between and within subjects), individual RAL C_{12} values in the presence of etravirine (Treatment B) were examined in order to compare trough concentrations to the PK target of 45 nM (21.7 ng/mL). The geometric mean C_{12} was 36.8 ng/mL (range: 13.8-135 ng/mL); three of 15 subjects had C_{12} values below 21.7 ng/mL. However, two factors suggest that RAL trough concentrations will be higher in clinical practice than those observed in the current study: 1) RAL trough concentrations are generally 1.2- to 1.6-fold higher at steady-state compared to after a single dose (ISENTRESS prescribing information); and 2) the high prevalence of gastric achlorhydria in patients with HIV infection, resulting in increased gastric pH (Barry M. et al. Clin Pharmacokinet 1997) and subsequently higher RAL absorption (ISENTRESS prescribing information). These factors, in addition to the 90% CI of the GMR of RAL C_{12} within the predefined no-effect bounds of 0.5-2.0 (and higher than the corresponding values in the ISENTRESS prescribing information [0.34-1.26]), support that no dose adjustment is necessary when the RAL/3TC FDC is coadministered with etravirine.

Results of safety analysis

There were 39 adverse events reported during the study that were categorized as possibly related to study treatment. One was reported during Period 1 (RAL/3TC FDC alone), 12 were reported during Period 2a (etravirine alone), and 1 was reported during Period 2b (RAL/3TC FDC with etravirine). The most common drug-related AEs were Nervous System Disorders (headache), Gastrointestinal Disorders (dyspepsia, diarrhea), General Disorders (fatigue), and Skin and Subcutaneous Tissue Disorders (rash generalized). Three subjects discontinued study drug due rash during Period 2a (etravirine alone). No serious adverse events or deaths occurred during the study.

Trial Summary

In this study, the pharmacokinetics of raltegravir following a single dose of the RAL/3TC 300/150 mg FDC oral tablet in the presence or absence of steady-state concentrations of etravirine (200 mg BID for 14 days) were evaluated in healthy subjects. As expected, RAL C_{12} values were decreased (by approximately 14%) in the presence of etravirine, presumably due to induction of UGT1A1; however, the 90% CI of the GMR of RAL C_{12} was within the predefined no-effect boundaries. In addition, the GMR of RAL C_{12} with to without etravirine and the corresponding 90% CI observed in the current study (85.8, 63.0-117) were higher than those reported in the ISENTRESS label (66, 34-126), in which no dose adjustment of either drug is recommended. Therefore, the RAL/3TC 300/150 mg FDC oral tablet can be coadministered with etravirine without dose adjustment.

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/s/

LESLIE W CHINN
12/31/2014

JEFFRY FLORIAN
12/31/2014
Signing for myself and Fang Li (Division of Pharmacometrics Reviewer, 12/31/2014).