CLINICAL PHARMACOLOGY REVIEW

NDA/SDN (supplement)	22145/1232 (S-36) 205786/247 (S-4) 203045/305 (S-13)
Submission Type	Efficacy supplement
Applicant Name	Merck
Submission Dates	7/27/2017
Generic Name	Raltegravir
Dosage Form (Strength)	NDA 22145: Tablet (400 mg and 600 mg) NDA 205786: Oral suspension (packet of 100 mg) NDA 203045: Chewable tablets (100 mg scored and 25 mg)
Indication	Treatment of HIV
Review Team	Mario Sampson, PharmD, Amal Ayyoub, PhD, Jeffry Florian, PhD, Islam R. Younis, PhD

1 Contents

2 Background

The applicant submitted this efficacy supplement to support proposed dosing of 1200 mg raltegravir QD, based upon the results of a single efficacy and safety study (Study PN292) where HIV-infected subjects were randomized to receive either raltegravir 400 mg BID (approved dose) or 1200 mg QD in combination with emtricitabine (FTC, 300 mg) and tenofovir disoproxil fumarate (TDF, 300 mg). The week 48 virologic response (HIV RNA <40 copies/mL) rate was 89% in the QD arm and 88% in the BID arm. In addition, clinical pharmacology studies with the 1200 mg QD dosing regimen were conducted to evaluate food effect (n=1), relative bioavailability of formulations (n=1), and drug interactions (n=3 to evaluate the effect of efavirenz (EFV), atazanavir (ATV), and metal-containing antacids). Finally, pediatric PK was simulated for the 1200 mg QD dosage regimen to support proposed labeling for use of 1200 mg QD in pediatric patients ≥40 kg. This review focuses on raltegravir exposure-response relationships, whether both the 400 mg and 600 mg strengths can be used to construct a 1200 mg QD regimen, acceptability of proposed pediatric QD dosing, and clinical pharmacology-related labeling recommendations concerning the QD regimen.

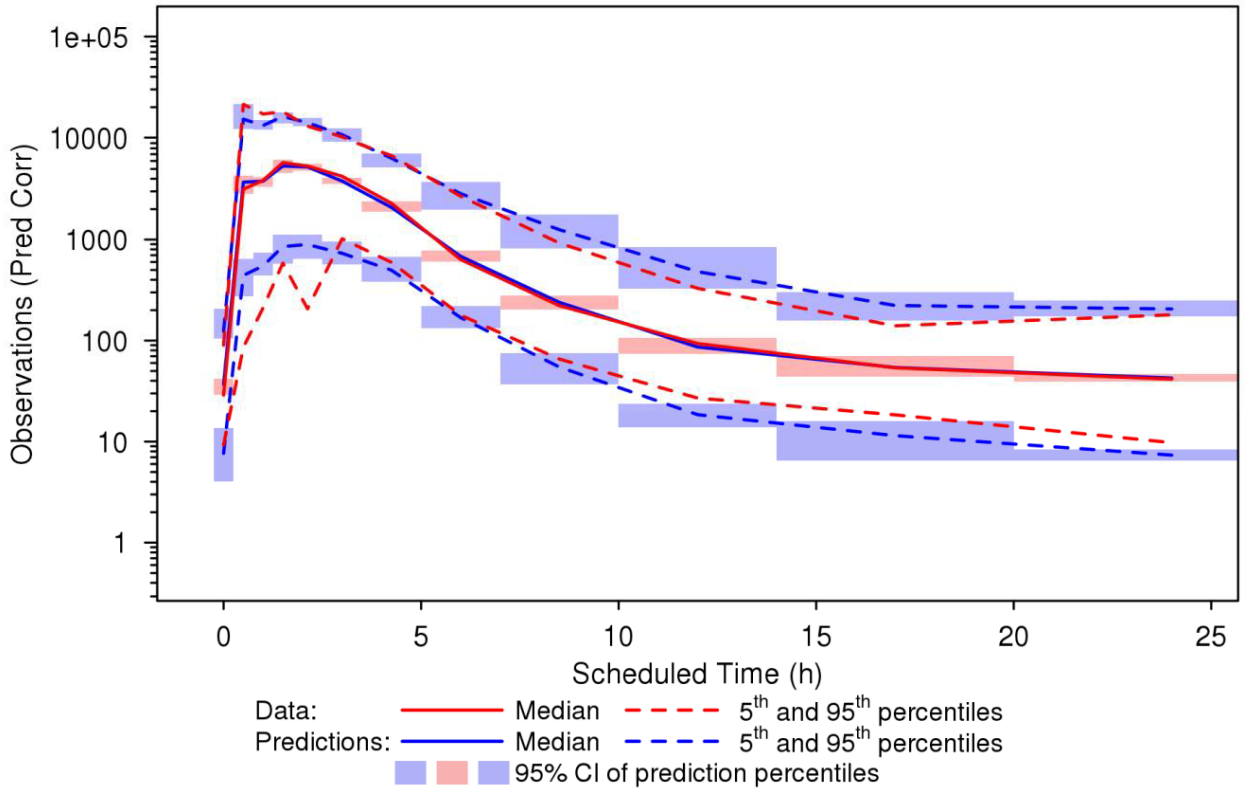
3 Summary of clinical pharmacology findings

3.1 Population PK model

The applicant developed a PK model based upon a dataset consisting of five phase 1 studies and the phase 3 study PN292. Only data from subjects administered raltegravir 1200 mg QD were included. The final 2-compartment model described raltegravir disposition via sigmoid absorption (fasted), lagged sigmoid absorption (fed), linear elimination, and covariate effects upon ka, duration of absorption, bioavailability, and CL.

The model adequately described the data as evidenced by precision of PK parameters, goodness-of-fit plots, and visual predictive check (Figure 1). A limitation of the model was the use of several fixed parameters. A sensitivity analysis requested by the review team showed that different values of the fixed parameters did not significantly impact posthoc PK parameters (Table 1). Overall, this model was sufficient to provide individual subject exposures for use in exposure-response analyses as well as for simulation of pediatric exposures upon 1200 mg QD dosing.

Figure 1. Prediction-corrected visual predictive check for the final phase 1-3 model.



Source: See section 6.2 (Link 1, page 221).

Table 1. Sensitivity analysis for the impact of fixed parameters on posthoc PK parameters.

Fixed Parameter	n	TV CL Coefficient	TV CL Race Effect	TV CL WTKG Exp	TV CL (L/h)	TV Vc (L)	CL (L/h)	Vc (L)	C24 (ng/mL)	Cmax (ng/mL)	AUC24 (ng*h/mL)
K_a (1/h)											
0.637[a]	524	0.6	-2.4	5.5	0.8	-13.6	0.5	-13.6	0.2	0.0	-0.1
0.741[b]	524	-0.8	-4.3	1.6	-0.6	17.0	-0.3	17.0	1.0	0.2	-0.6
Q (L/h)											
3.34[a]	524	-5.9	-2.6	4.2	-5.7	-4.0	-5.8	-4.0	0.1	0.4	0.3
4.59[b]	524	4.7	-2.4	3.0	4.8	1.9	4.6	1.9	1.2	-0.7	-1.0
V_p (L)											
56.1[a]	524	-4.4	-0.3	7.6	-4.3	0.1	-5.7	0.1	0.3	0.6	2.1
78.9[b]	524	2.8	-1.4	-0.9	2.9	-1.2	4.3	-1.2	-0.2	-0.5	-2.6
K_a (1/h) and Q (L/h)											
0.637 & 3.34[a]	524	-5.2	-2.9	6.3	-5.1	-14.0	-5.6	-14.0	-0.8	0.1	0.5
0.741 & 4.59[b]	524	3.5	3.4	-1.2	3.3	13.8	3.5	13.8	1.8	-0.5	-2.0

Abbreviations: AUC_{24}, individual model-predicted area under the raltegravir concentration-time curve from 0 to 24 hours; C_{24}, individual model-predicted raltegravir concentration 24 hours postdose (ng/mL); C_{max}, individual model-predicted maximum raltegravir concentration (ng/mL); CL, apparent clearance (L/h); Exp, exponent; K_a, absorption rate constant (1/h); n, number of subjects; Q, apparent intercompartmental clearance (L/h); TV, typical value; V_c, apparent central volume of distribution; V_p, apparent peripheral volume of distribution; WTKG, weight (kg).

[a] Lower limit of the 95% bootstrap confidence interval of the indicated fixed parameter value from the final raltegravir population pharmacokinetic model.

[b] Upper limit of the 95% bootstrap confidence interval of the indicated fixed parameter value from the final raltegravir population pharmacokinetic model.

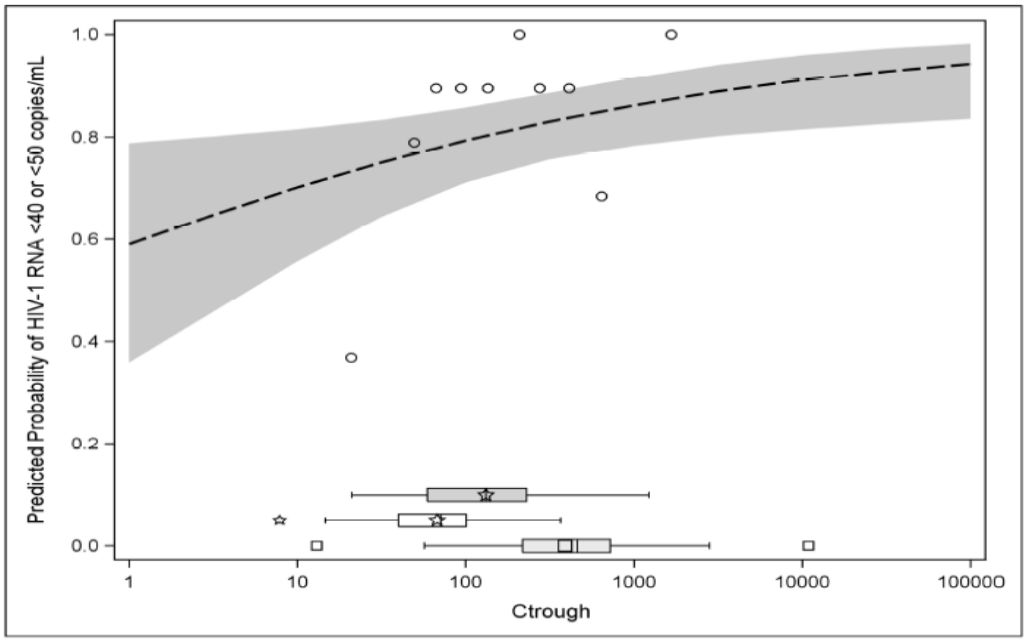
Source: See section 6.2 (Link 2, page 5).

3.2 Raltegravir exposure-response relationships

3.2.1 Exposure-efficacy

Using logistic regression, exposure-efficacy relationships were initially evaluated by the applicant using study PN292 data. Only Ctrough was used as an exposure metric. This is because a population PK model could not be developed for studies evaluating raltegravir 400 mg BID, and thus model-predicted Cmax and AUC values were not available for the BID arm. Across the range of exposures from 400 mg BID and 1200 mg QD, Ctrough was not associated with probability of virologic response. Screening viral load was a significant predictor of virologic response. We requested that the applicant include the 800 mg QD arm from study PN071 in this analysis because there was a somewhat lower response rate in this arm (~80% for 800 mg QD versus 88-89% for 400 mg BID and 1200 mg QD) and the additional data would be expected to help further inform the exposure-response efficacy relationship for raltegravir. This analysis found Ctrough was associated with response; screening viral load and baseline CD4 count were other significant predictors (Figure 2). In a published analysis of raltegravir PK/PD from study PN071, a Ctrough value <45 nM was identified as being associated with a lower probability of response (Figure 3). This value approximated the cutoff between the 1st and 2nd quartiles of Ctrough in the 800 mg QD arm of study PN071. In our analyses, we accepted this target of Ctrough >45 nM, while being aware that 1) there is not a steep drop in probability of response as Ctrough decreases below 45 nM and 2) the relationship between Ctrough and virologic response also depends on HIV viral load.

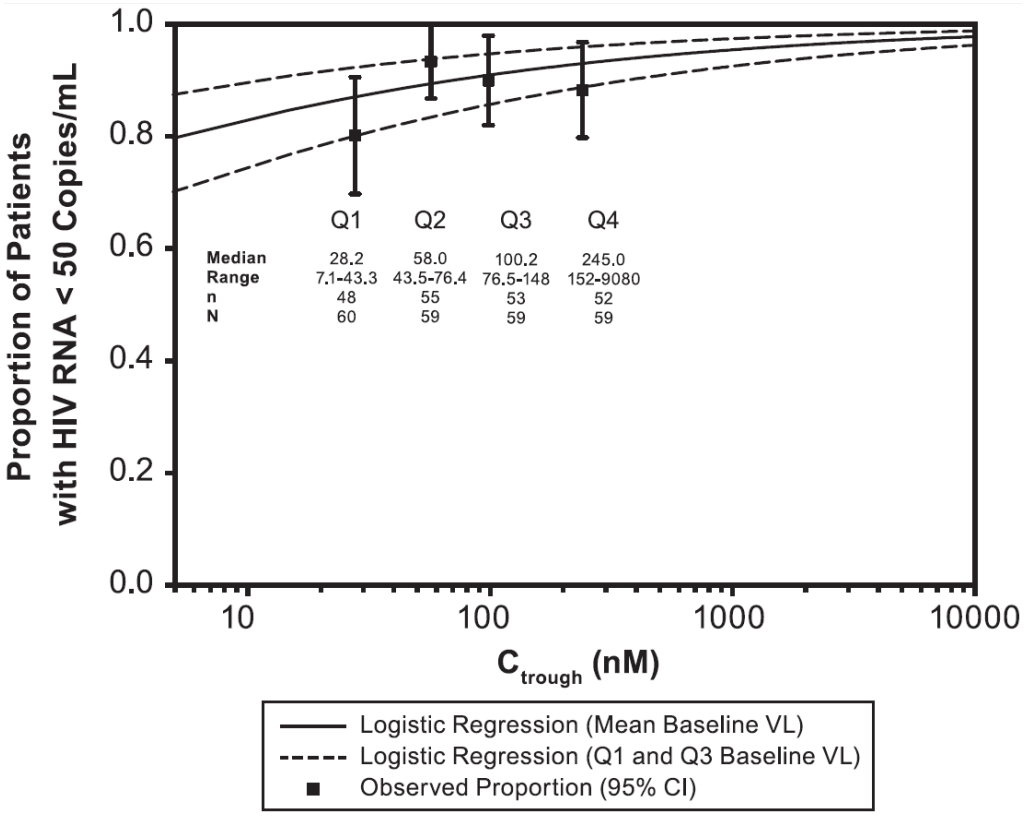
Figure 2. Predicted probability of response versus Ctrough for subjects with screening viral load >100,000 copies/mL and baseline CD4 count of 50-200 copies/mm3 from raltegravir 1200 mg QD, 800 mg QD, and 400 mg BID arms.



: Distribution of 1200 mg QD Ctrough, where stars show the mean and outliers of the PK boxplot
: Distribution of 800 mg QD Ctrough, where stars show the mean and outliers of the PK boxplot
: Distribution of 400 mg BID Ctrough, where squares show the mean and outliers of the PK boxplot
The observed Ctrough values were divided into 10 bins and the HIV-1 RNA <40 or <50 copies/mL occurrence rate was calculated for the patients in each bin.
The band shows the 95% CI of the predicted probability of achieving HIV-1 RNA <40 or <50 copies/mL.

Source: See section 6.3 (Link 4, page 13).

Figure 3. Probability of response versus Ctrough for study PN071 (400 mg BID versus 800 mg QD).



Source: Rizk et al, 2012, AAC.

We also requested that food effect be evaluated in the revised analysis because food effect differs between 400 mg BID (Ctrough increased 4-fold with a high fat meal relative to fasting) and 1200 mg (600 mg x 2) QD (Ctrough decreased 12% with a high fat meal) regimens/formulations. Meal type, defined for each subject as the most common meal throughout the study, was not found to be a significant predictor. However, this analysis was limited in that food intake information was only available on PK sampling visits and meal type often differed between visits for individual subjects.

3.2.2 Exposure-safety

Exposure-safety relationships were evaluated within study PN292 (1200 mg QD versus 400 mg BID). Of note, 1200 mg QD results in a ~6-fold higher Cmax and ~2-fold higher $AUC_{0\text{-}24h}$ relative to 400 mg BID in healthy adults. Despite the exposure differences between regimens, no differences in rates of AEs were identified between treatment regimens (see section 7.1). As no AEs were temporally associated with raltegravir administration (i.e. Cmax) and AUC reflects exposure over an entire dosing interval, AUC was selected by the applicant as the most relevant PK parameter for safety assessment.

3.3 Pediatric QD dosing

Twice-daily dosing of raltegravir is currently approved for pediatric patients weighing ≥3 kg. For the film-coated tablet, the adult dose of 400 mg BID is recommended for pediatric patients ≥25 kg. In this application, the applicant proposed dosing of raltegravir 1200 mg QD for pediatric patients weighing ≥40 kg. This proposal was based solely on predicted pediatric exposures upon 1200 mg QD dosing.

The applicant used the adult 1200 mg QD model (see section 6.2) to predict pediatric exposures upon 1200 mg QD dosing. A prior raltegravir pediatric PK study (P1066) was used to characterize the age-weight relationship in HIV-infected pediatric subjects and to then generate a virtual dataset of 1000 subjects for simulation. The weight cutoff for use of the adult dose in pediatrics was derived by identifying the lowest pediatric weight group where the geometric mean of the predicted pediatric exposure did not exceed the adult 95th percentile of AUC after 1200 mg QD dosing. Eight simulations were conducted to evaluate each combination of race (White/Asian or Black/other), FTC/TDF use (yes or no), and meal type (fasted or high fat meal). In the simulations, weight cutoffs ranged from 30-45 kg; 40 kg was selected by the applicant as the cutoff for the overall pediatric population.

Raltegravir is approved in pediatrics for BID dosing and no exposure-related safety concerns have been identified in adults. For this reason, the review team considered the proposal to provide pediatric labeling for 1200 mg QD based on simulated exposures alone. The key limitation of this approach, however, is that safety cannot be extrapolated from adults. In other words, pediatric subjects with comparable exposures to that expected from 1200 mg QD in adults would be needed to inform safety and support labeling of this regimen.

Upon request by the review team, the applicant provided safety data from six pediatric subjects in study P1066 weighing ≥50 kg and with AUC and Cmax values above the 5th percentile of simulated AUC and Cmax in pediatric subjects following administration of raltegravir 1200 mg QD. No safety concerns were reported for these six subjects. The median observed $AUC_{0\text{-}24h}$ from the six pediatric subjects (62 μM*h) was lower than the median simulated AUC in pediatric subjects 40-45 kg (95 μM*h) and 50-55 kg (86 μM*h) given 1200 mg QD and comparable to median observed AUC in adults given 1200 mg QD (50 μM*h) (Table 2). The AUC range from the six subjects was within the simulated pediatric and observed adult AUC range. Based on the significant overlap of exposures and limited safety data suggesting no safety concerns at exposures associated with 1200 mg QD in pediatric subjects ≥50 kg, the review team recommends dosing raltegravir 1200 mg QD for pediatric subjects ≥50 kg.

Table 2. Comparison of pediatric simulated (1200 mg QD), pediatric observed (300-600 mg BID), and adult raltegravir exposures (1200 mg QD).

Safety Threshold: Adult 95th percentile $AUC_{0-24,ss}$ exposure of **109 uM*h** in ONCEMRK

Group	Dosing	PK	AUC0-24h[2] (uM*h)	Cmax (uM)	AUC and Cmax Value type
Adults in ONCEMRK	1200 mg QD	Sparse; model-predicted exposures	50 (15, 336) 56 (27)	15 (2, 45) 16 (6)	Median (min, max) Mean (SD)
Healthy adults in relative BA study		Intensive	60 (27, 93) 60 (51, 69)	22 (8, 41) 21 (17, 25)	Median (min, max) Geometric mean (95% CI)
Simulated pediatrics 40-45 kg		Simulated from adult 1200 mg QD model scaled to pediatric	95 (53, 157)	27 (14, 44)	Average of median (5th, 95th) across eight covariate combinations (race, FTC/TDF use, food intake)[3]
Simulated pediatrics 50-55 kg			86 (45, 149)	23 (11, 37)	
6 pediatric subjects (51-63 kg[1]) with observed exposures >5th percentile of simulated exposures for 1200 mg QD	300-600 mg BID	Intensive	62 (50, 157) 80	14 (11, 18) 14	Median (min, max) Mean

[1]Median weight 58 kg
[2]For BID regimens, AUC0-24h = AUC0-12h x 2
[3]The sponsor provided simulated exposures for each of eight covariate combinations by pediatric weight range (for example, combo 1 for 40-45 kg: race = white/Asian; Truvada = yes; Food = fasted). We recorded the median (5th, 95th) for each of the eight scenarios. The average of the eight medians, 5th percentiles, and 95th percentiles was recorded in the table above.

Source: Reviewer's analysis with contribution of the Clinical reviewer (Sarita Boyd, PharmD).

3.4 Interchangeability of the 400 mg and 600 mg strengths for constructing a 1200 mg QD regimen

(b) (4)

Compared to the 400 mg BID regimen, administration of 400 x 3 mg QD produces a higher AUC and Cmax and lower Ctrough (Table 3). Relative to 400 mg BID, the reduction in Ctrough is similar for 400 mg x 3 and 600 mg x 2 (Figure 4). Despite being lower relative to 400 mg BID, the Ctrough values for the QD regimen were >45 nM for the majority of subjects and are not expected to affect efficacy. AUC and Cmax following 400 mg x 3 QD are lower relative to 600 mg x 2 and therefore safety of the 400 mg x 3 QD regimen is not a concern. In single dose food effect and formulation study PN290, the distributions of exposures were comparable across formulations and meal types, though variability was higher in the 600 mg x 2 group (Figure 5). Taken together, there was no indication of significant PK differences between a 1200 mg QD regimen constructed from two 600 mg tablets versus three 400 mg tablets that would appear to impact efficacy or safety.

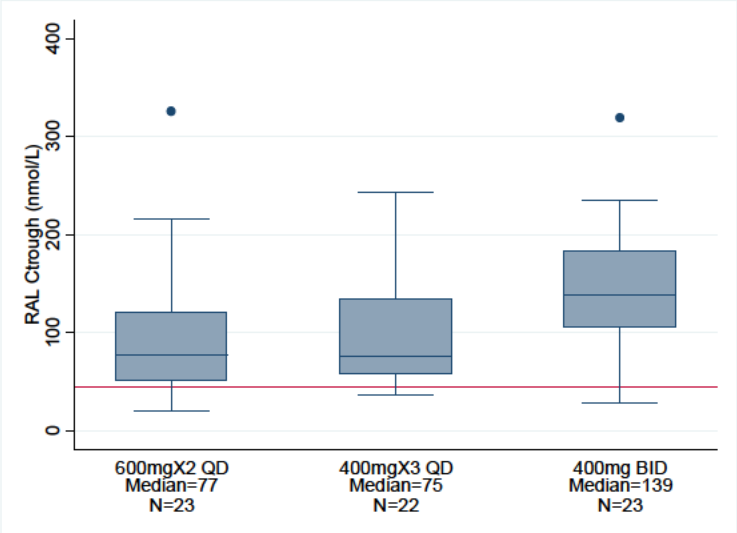
(b) (4)

Table 3. Geometric mean ratios of PK parameters from relative bioavailability study PN291.

Comparison	AUC	90% CI	Cmax	90% CI	Ctrough	90% CI
(600x2) QD vs. 400 BID	**2.34**	1.77-3.10	**6.02**	4.10-8.85	**0.62**	0.50-0.77
(400x3) QD vs. 400 BID	**1.93**	1.12-2.63	**4.14**	2.80-6.09	**0.64**	0.52-0.78
(600x2) QD vs. (400x3) QD	**1.22**	0.94-1.57	**1.46**	1.09-1.95	**0.97**	0.79-1.19

Source: Prepared by the reviewer based on the Study PN291 CSR, page 67.

Figure 4. Day 5 Ctrough comparison from multiple dose formulation study PN291 in healthy subjects.

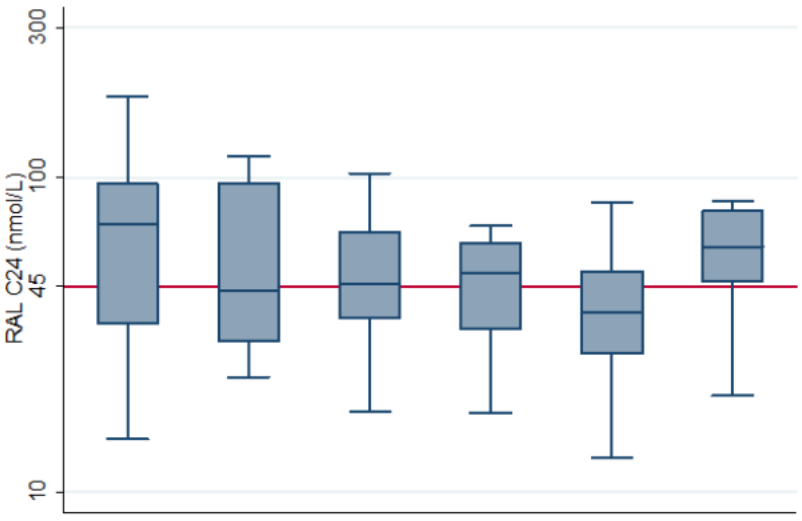


Source: plotted by reviewer.

Figure 5. Ctrough comparison from single dose food effect and formulation study PN290 in healthy subjects.

Treatments (n=16-18 per group)
A = 600 mg x 2 fasting
B = 600 mg x 2 low-fat
C = 600 mg x 2 high-fat
D = 400 mg x 3 fasting
E = 400 mg x 3 low-fat
F = 400 mg x 3 high-fat

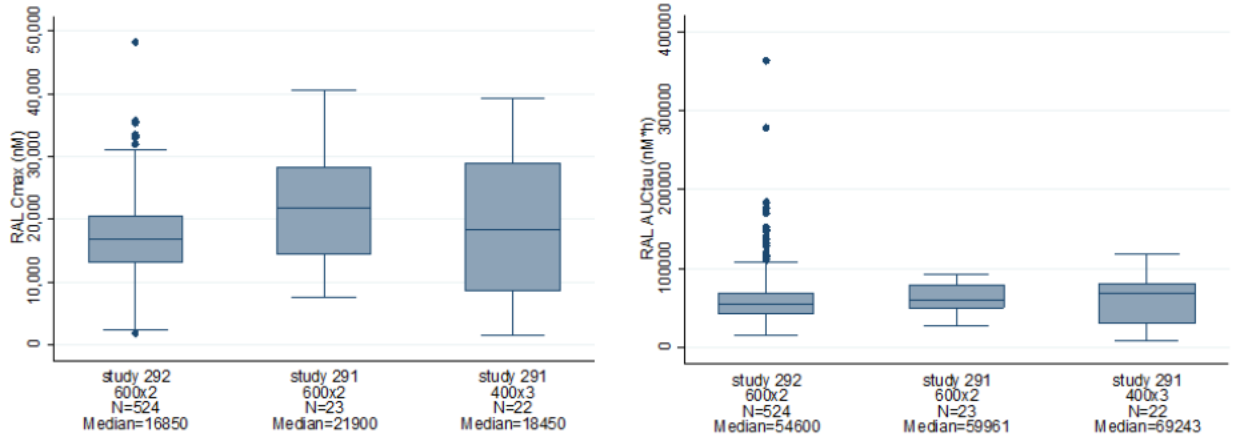
Crossover study
-subjects received treatments ABC or DEF



Median Ctrough (nM)	71	44	46	50	37	60

Source: plotted by reviewer.

Figure 6. Cmax and AUC from raltegravir 600 mg x 2 versus 400 mg x 3 in studies PN291 and PN292.



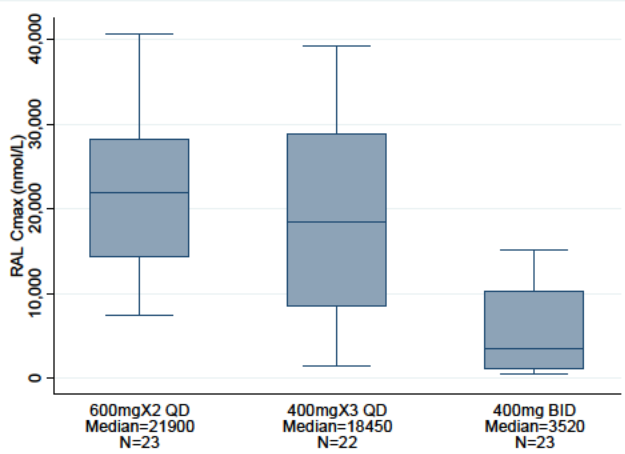
Study 292 = phase 3 study; study 291 = relBA study in healthy adults

Source: plotted by reviewer.

3.5 Switching from raltegravir 400 mg BID to 1200 mg QD and vice versa

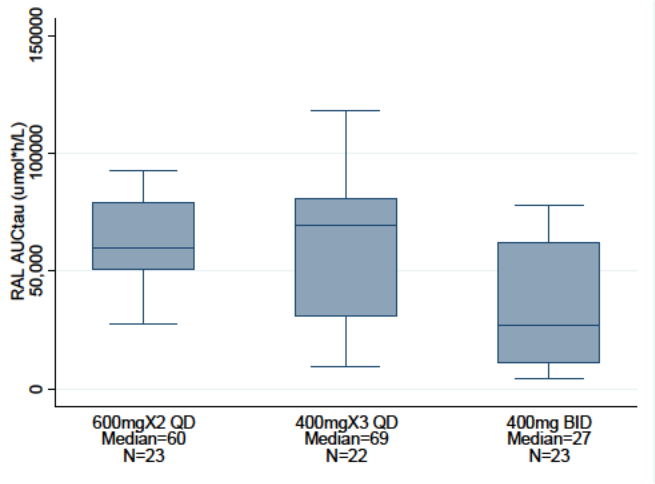
There were significant Cmax, AUC, and Ctrough differences between 1200 mg QD (400 mg x 3 or 600 mg x 2) and 400 mg BID regimens (Table 3, Figure 4, Figure 7, Figure 8). Overall efficacy results of study PN292 where the 1200 mg QD was non-inferior to the 400 mg BID arm suggests that these exposure differences are not clinically significant. In an exposure-response analysis of the 1200 mg QD and 400 mg BID arms of study PN292, Ctrough was not associated with virologic response. Exposure-response analyses focused on Ctrough because model-predicted Cmax and AUC values were unavailable for the 400 mg BID arm of phase 3 study PN292. In conclusion, the efficacy and exposure-response results from study PN292 suggest that virologic suppression should be unaffected by switching between QD and BID regimens.

Figure 7. Day 5 Cmax comparison from multiple dose formulation study PN291 in healthy subjects.



Source: plotted by reviewer.

Figure 8. Day 5 AUC comparison from multiple dose formulation study PN291 in healthy subjects.



Source: plotted by reviewer.

3.6 Drug interactions

Atazanavir (ATV) and ATV/ritonavir (ATV/r)

A prior drug interaction study evaluated the effect of ATV/r on raltegravir 400 mg BID. Raltegravir Cmax and AUC ratios were 1.24 and 1.41 when coadministered with ATV/r, respectively. No raltegravir dose adjustment is recommended in labeling.

In a raltegravir 1200 mg-ATV interaction study submitted in this supplement, raltegravir Cmax and AUC ratios in the presence of ATV were 1.16 and 1.67, respectively. (b) (4) iven raltegravir's relatively benign safety profile and lack of exposure-safety relationships, (b) (4)

Etravirine (ETR)

When raltegravir 400 mg BID was coadministered with ETR in a prior drug interaction study, raltegravir Ctrough was the most affected PK parameter; the Ctrough ratio was 0.66. The labeling recommendation is no dose adjustment for raltegravir.

(b) (4) . A further reduction in raltegravir Ctrough when given with ETR may be more likely to result in subtherapeutic concentrations for subjects on a 1200 mg QD regimen versus the 400 mg BID regimen. Our labeling recommendation is that raltegravir 1200 mg QD is not recommended to be coadministered with ETR.

Omeprazole

When raltegravir 400 mg was coadministered with omeprazole in healthy adults, raltegravir Cmax was increased ~4-fold and AUC ~3-fold. Current labeling for raltegravir 400 mg BID states there is no clinically significant interaction with omeprazole. The review team considered these raltegravir exposure changes to be potentially misleading because there is evidence that the effect of omeprazole on raltegravir PK is lessened in HIV-infected subjects. Relative to HIV-infected subjects not on a gastric pH-altering agent, Ctrough in subjects with a gastric pH-altering agent was 21% higher (Iwamoto et al, Clin Inf Dis, 2009). However, this report lacked Cmax and AUC values (these were more sensitive parameters) and did not describe the timing or duration of gastric pH-altering agent dosing relative to raltegravir dosing. Also, a Merck-coauthored abstract reported a raltegravir 400 mg BID-omeprazole drug interaction study in HIV-infected adults where raltegravir Cmax, AUC, and C12h ratios in the presence of omeprazole were 1.39, 1.51, and 1.24, respectively (Rhame et al, HIV medicine, 2009). To address the potential difference in interaction magnitude between healthy and HIV-infected subjects, we requested that the applicant provide more details for the studies in HIV-infected subjects. Review of this issue is ongoing and will be discussed in an addendum to this review.

Tipranavir/ritonavir (TPV/r)

When raltegravir 400 mg BID was coadministered with TPV/r, the raltegravir PK parameter most affected was Ctrough (ratio = 0.45). Current raltegravir 400 mg BID labeling states that no dose adjustment is required. As a justification for no dose adjustment, the raltegravir QBR says ~100 patients in phase 3 trials on TPV/r had comparable efficacy compared to those not on TPV/r. Because raltegravir Ctrough is ~30% lower for 1200 mg QD versus 400 mg BID, coadministration could result in further reduced Ctrough values that are subtherapeutic. For this reason we agree with the proposed labeling that raltegravir 1200 mg QD is not recommended to be coadministered with TPV/r.

Metal-containing antacids and efavirenz (EFV)

Raltegravir 1200 mg drug interaction studies were conducted metal-containing antacids and EFV. We agree with the applicant's labeling recommendations to 1) not recommend use of raltegravir with metal-containing antacids (section 6.8) and 2) there is no clinically significant interaction with EFV (section 6.6).

3.7 Hepatic and renal impairment

Current labeling for raltegravir 400 mg BID states no dose adjustment is necessary for patients with mild to moderate hepatic impairment or for renal impairment. This is based on raltegravir 400 mg single dose studies that found no significant differences in PK between subjects with moderate hepatic impairment versus healthy controls or between subjects with severe renal impairment versus healthy controls. On the basis of extrapolation from the 400 mg studies, the applicant proposes that no dose adjustment is necessary for (b) (4) patients with renal impairment taking raltegravir 1200 mg QD. We agree with the applicant with regard to extrapolating the recommendation for the 400 mg BID to 1200

mg QD for patients with renal impairment because only 9% of the raltegravir dose is excreted unchanged in urine. (b) (4) Instead we propose to state in labeling that no hepatic impairment study was conducted with raltegravir 1200 mg QD.

4 Recommendation

The application is recommended for approval from a clinical pharmacology perspective.

5 Labeling Recommendations

Labeling negotiations are ongoing. Clinical pharmacology-related topics where our labeling recommendation differs from the applicant includes:

(b) (4)

Final clinical pharmacology-related labeling recommendations will be described in an addendum to this review.

6 Study Reviews

6.1 Notes

Studies PN290 and PN291 were reviewed by Amal Ayyoub; all others were reviewed by Mario Sampson.

Bioanalytical method validation and sample analysis for all studies discussed below were acceptable (see Bioanalytical methods).

Raltegravir is also known as MK-0518.

6.2 Population Pharmacokinetics of Raltegravir Once Daily Program in Adults

Relevant links

Report title	Link
PopPK report [Link 1]	\\cdsesub1\evsprod\nda022145\0325\m5\53-clin-stud-rep\535-rep-effic-safety-stud\qd1200\5353-rep-analys-data-more-one-stud\04c39t\04c39t.pdf
Response to information request dated 2 10/2017 [Link 2]	\\cdsesub1\evsprod\nda022145\0341\m1\us\efficacy-information-amendment-10feb2017.pdf
PopPK key analysis files	Phase 1-3 dataset \\cdsesub1\evsprod\nda022145\0325\m5\datasets\04c39t\analysis\legacy\programs\poolpk8-nmdat.txt Control stream and output for final model with locked data Control stream: \\cdsesub1\evsprod\nda022145\0325\m5\datasets\04c39t\analysis\legacy\programs\final-ecld1-biolfmf-ccv-01-ctl.txt Report file: \\cdsesub1\evsprod\nda022145\0325\m5\datasets\04c39t\analysis\legacy\programs\final-ecld1-biolfmf-ccv-01-rpt.txt Table output: \\cdsesub1\evsprod\nda022145\0325\m5\datasets\04c39t\analysis\legacy\programs\final-ecld1-biolfmf-ccv-01-tbl.txt

The applicant's population PK modeling was limited to subjects administered raltegravir 1200 mg QD. Modeling was previously pursued for studies including the BID regimen and a model could not be developed. The goal was to use the 1200 mg QD model to obtain model-predicted PK parameters for subjects in phase 3 study PN292, which could then be used for E-R analyses. In addition, this model was allometrically scaled to pediatric subjects and simulations were performed to support a weight cutoff for dosing of 1200 mg QD to pediatric subjects (see Section 6.4).

Methods

Six studies were included in the model (1200 mg QD arms only); this included two relative BA studies, three drug interaction studies, and study PN292 (Table 4). Thirty-eight percent of the samples collected were excluded for various reasons (Table 5).

Table 4. Studies included in the 1200 mg QD popPK model.

Study	Description	Dosing	Population	Sampling	Subjects enrolled	Samples collected
PN290	Food effect study (fasted, low-fat, high-fat)	Single dose -Raltegravir 400 mg x 3 -Raltegravir 600 mg x 2	Healthy adults	Intensive to 48 h post-dose	18	648
PN291	Multiple dose study	5 days dosing -Raltegravir 400 mg x 3 -Raltegravir 600 mg x 2 -Raltegravir 400 mg x 2	Healthy adults	Intensive to 48 h post-dose	24	576
PN812	DDI with EFV	-Single dose raltegravir 600 mg x 2 on days 1 and 12 -EFV 600 mg QD on days 1-14	Healthy adults	Intensive to 72 h post-dose	21	581
PN823	DDI with ATV	-Raltegravir single dose of 600 mg x 2 with a moderate-fat meal on days 1 and 7 -ATV 400 mg QD on days 1-9	Healthy adults	Intensive to 72 h post-dose	14	378
PN824	DDI with metal-containing antacids	-Raltegravir 600 mg x 2 alone -Raltegravir 600 mg x 2 + Tums -Raltegravir 600 mg x 2 12 h after Maalox -Raltegravir 600 mg x 2 12 h before Tums	HIV-infected adults	Intensive to 24 h post-dose	22	1056
PN292	Phase 3, active-controlled study	-Raltegravir 600 mg x 2 QD + FTC/TDF background therapy -Raltegravir 400 mg x 1 BID + FTC/TDF background therapy	Treatment-naïve HIV-infected adults	-Predose on day 1, week 4, and week 24 -1-4 h postdose on weeks 2 and 16. -Anytime postdose on week 8	533	4264
Total					632	7503

Source: Reviewer's analysis. Only data from raltegravir 600 mg x 2 was included in the model. Data from arms where metal-containing antacids were given 12 h post-dose were excluded.

Table 5. Samples excluded from the popPK model dataset.

		Subjects	Samples	Percent of total samples
Total subjects enrolled and samples collected		**632**	**7503**	**100%**
	Subjects affected	Subjects excluded	Samples	Percent of total samples
Missing concentration value[1]	544	2	1244	16.6%
Pre-1st dose concentration BLQ	589	3	591	7.9%
Concomitant medication not included in the analysis	19	0	418	5.5%
Missing meal information (study PN292)	98	4	194	2.6%
Post-dose concentration BLOQ	66	0	178	2.3%
Drug never administered	2	2	96	1.3%
Phase 1 graphical outliers		2	73	1.0%
Phase 3 graphical outliers		0	53	0.7%
Other reasons		1	32	0.4%
Total excluded data		**14**	**2879**	**38.4%**
Total included in the model		**618**	**4624**	**61.6%**

Source: Link 1, page 63 and 263. [1]Includes placeholders for unscheduled blood draws.

UPLC-MS-MS method DM-712A (calibration range 2-1000 ng/mL) was used to determine raltegravir concentrations in all studies (see Bioanalytical methods). Nonmem 7.3 (FOCE method) was used for model development. Numerous intrinsic and extrinsic factors were evaluated as potential covariates for their effect upon PK parameters (Table 6).

Table 6. Investigation plan for covariates included in the analysis.

Covariates	Reason for Investigation	Variable Definitions	Parameter
Weight (kg)	CL/F and V/F are likely to be weight, height, or body mass index dependent; previously developed population PK model found weight to be a significant covariate on V/F and CL/F	NA	CL/F, V/F
Food Status/ Meal Type	Food was found to have a clinically relevant effect in modifying the overall exposure of raltegravir in a dedicated study	FED 0 = fasted, 1 = fed Meal Type 0 = fasted, 1 = low fat, 2 = moderate fat, 3 = high fat	k_a, relative BIO, ALAG, DUR
Race/Ethnicity	Potential racial and ethnic influence on PK; black race identified as a statistically significant (but not clinically important) covariate on BIO and CL/F in prior model	RACE 0 = white, 1 = black or African-American, 2 = Asian, 3 = American Indian or Alaska Native, 9 = other/unknown ETHNICITY 0 = not Hispanic/Latino, 1 = Hispanic/Latino, 2 = unknown	CL/F, V/F
Sex	Sex may influence distributional and PK characteristics	0 = Male 1 = Female	CL/F, V/F
HIV infection	HIV status may influence PK	0 = healthy volunteer, 1 = HIV positive	CL/F, V/F, k_a, relative BIO, DUR
DDI -inducers UGT1A1	Potent/modest inducers of UGT1A1 are expected to reduce raltegravir exposure; low probability to explore this effect in this analysis because rifampin, rifabutin, phenobarbital, and phenytoin are excluded from Phase 3	DDI CATEGORY 0 = no concomitant medication use, 1 = UGT inducer present, 2 = UGT inhibitor present, 3 = TUMS® administered concomitantly, 4 = Maalox® administered 12 hours postdose, 5 = TUMS administered 12 hours postdose, 6 = Phase 3 metal cation antacid present, 7 = Phase 3 gastric pH-altering medication present, 8 = Phase 3 metal cation antacid and gastric pH-altering medication present	CL/F
DDI-inhibitors UGT1A1	Potent inhibitors of UGT1A1 (for example, atazanavir) are expected to increase raltegravir exposure		CL/F
DDI- gastric pH altering	Drugs that are known to increase gastric pH (for example, proton pump inhibitors [omeprazole], H2 blockers [famotidine, ranitidine, cimitedine]) may affect solubility of raltegravir		k_a, relative BIO, ALAG, DUR
DDI-TUMS® (concomitant administration)	Coadministration of divalent metal cation antacids (for example, TUMS) may reduce raltegravir absorption by chelation		k_a, relative BIO, ALAG, DUR

Source: Link 1, page 59.

Results

The final 2-compartment model had sigmoid absorption (fasted), lagged sigmoid absorption (fed), linear elimination, and covariate effects upon k_a, duration of absorption, bioavailability, and CL. Several important parameters were fixed, including k_a, Q, and V_p (Table 7). Goodness-of-fit and visual predictive check plots were provided to support the ability of the model to describe the data (Figure 9, Figure 10). Due to the presence of several fixed parameters, we requested that the applicant perform a sensitivity analysis to evaluate the impact of different

values of the fixed parameters (lower and upper limit of bootstrap 95% confidence interval) on posthoc PK parameters (Table 8).

Table 7. Parameter estimates for the phase 1-3 final model.

Parameter	Final Parameter Estimate		Interindividual Variability / Residual Variability	
	Typical Value (BS 95% PI)[b]	%SEM	Magnitude[a] (BS 95% PI)[b]	%SEM
k_a: Absorption Rate Constant (1/h)	0.678 (0.637, 0.741)	FIXED	NE	NA
k_a: Proportional Change for UGT Inhibitor	-0.252 (NE)	FIXED		
CL: Apparent Clearance (L/h)	50.2 (47.6, 52.6)	3.31	Ph 1: 34.5 %CV (28.4, 41.1)	19.3
CL: Proportional Change for UGT Inhibitor	-0.186 (NE)	FIXED		
CL: Proportional Change for Race = Black and Other	-0.184 (-0.240, -0.130)	17.5	Ph 3: 39.3 %CV (34.4, 43.9)	11.1
CL: Power for Weight	0.400 (0.232, 0.580)	23.1		
V_c: Apparent Central Volume (L)	27.9 (23.7, 32.4)	10.3	71.7 %CV (59.2, 84.6)	21.0
Q: Apparent Intercompartmental CL (L/h)	3.92 (3.34, 4.59)	FIXED	67.0 %CV (57.5, 76.3)	16.0
V_p: Apparent Peripheral Volume (L)	66.5 (56.1,78.9)	FIXED	81.3 %CV (66.8, 96.3)	19.8
ALAG: Fasted Lag Time to Start of Input (h)	0	FIXED	NE	NA
ALAG: Fed Lag Time to Start of Input (h)	0.189 (0.128, 0.257)	FIXED	64.2 %CV (51.9, 82.1)	21.8
DUR: Fasted Duration of Sigmoid Input (h)	0.480 (0.374, 0.577)	8.61	Ph 1: 98.2 %CV (78.7, 119.1)	22.0
DUR: Proportional Change for Low- and Moderate-fat Meal	1.75 (1.28, 2.41)	11.8	Ph 3: 104 %CV (93.6, 118.2)	13.7
DUR: Proportional Change for High-fat Meal	5.56 (4.46, 7.58)	9.12		
BIO: Relative BIO for Low-fat Meal	-0.244 (-0.298, -0.186)	12.8	NE	NA
BIO: Relative BIO for UGT Inducer	-0.145 (-0.262,-0.0130)	FIXED		
BIO: Relative BIO for TUMS® Concomitant	-0.703 (-0.763, -0.649)	FIXED		
BIO: Relative BIO for TRUVADA®/Phase 3	0.121 (0.049, 0.205)	58.5		
BIO: Relative BIO for Moderate-fat Meal	-0.146 (-0.231, -0.066)	21.9		
cov(IIV in Q, IIV in CL)[c]	0.158 (0.093, 0.234)	23.4	NA	NA
cov(IIV in V_p, IIV in CL)[c]	0.132 (0.063, 0.204)	29.4		
cov(IIV in V_p, IIV in Q)[c]	0.416 (0.285, 0.571)	19.2		

Parameter	Final Parameter Estimate		Interindividual Variability / Residual Variability	
	Typical Value (BS 95% PI)[a]	%SEM	Magnitude (BS 95% PI)[a]	%SEM
Phase 1 Residual Variability: CV	0.177 (0.163, 0.191)	5.45	42.0 %CV (40.4, 43.7)	NA
Phase 3 Residual Variability: CV	0.387 (0.359, 0.414)	3.52	62.2 %CV (59.9, 64.3)	NA
Minimum value of the objective function = 60040.962 / Condition Number = 219				

Abbreviations: BIO, bioavailability; BS, bootstrap; CI, confidence interval; %CV, coefficient of variation expressed as a percentage; CV, coefficient of variation; IIV, interindividual variability; NA, not applicable; NE, not estimated; Ph, phase; PI, prediction interval; %SEM, standard error of the mean expressed as a percentage; UGT, uridine diphosphate glucuronosyltransferase.

[a] ETA shrinkage: Phase 1: CL-2.9012E+00 Q-7.8074E+00 Vp-5.5773E+00 Vc-1.7728E+01 ALAG-2.0777E+01 DUR-1.8786E+01 Phase 3: CL-1.0490E+01 DUR-2.6848E+01

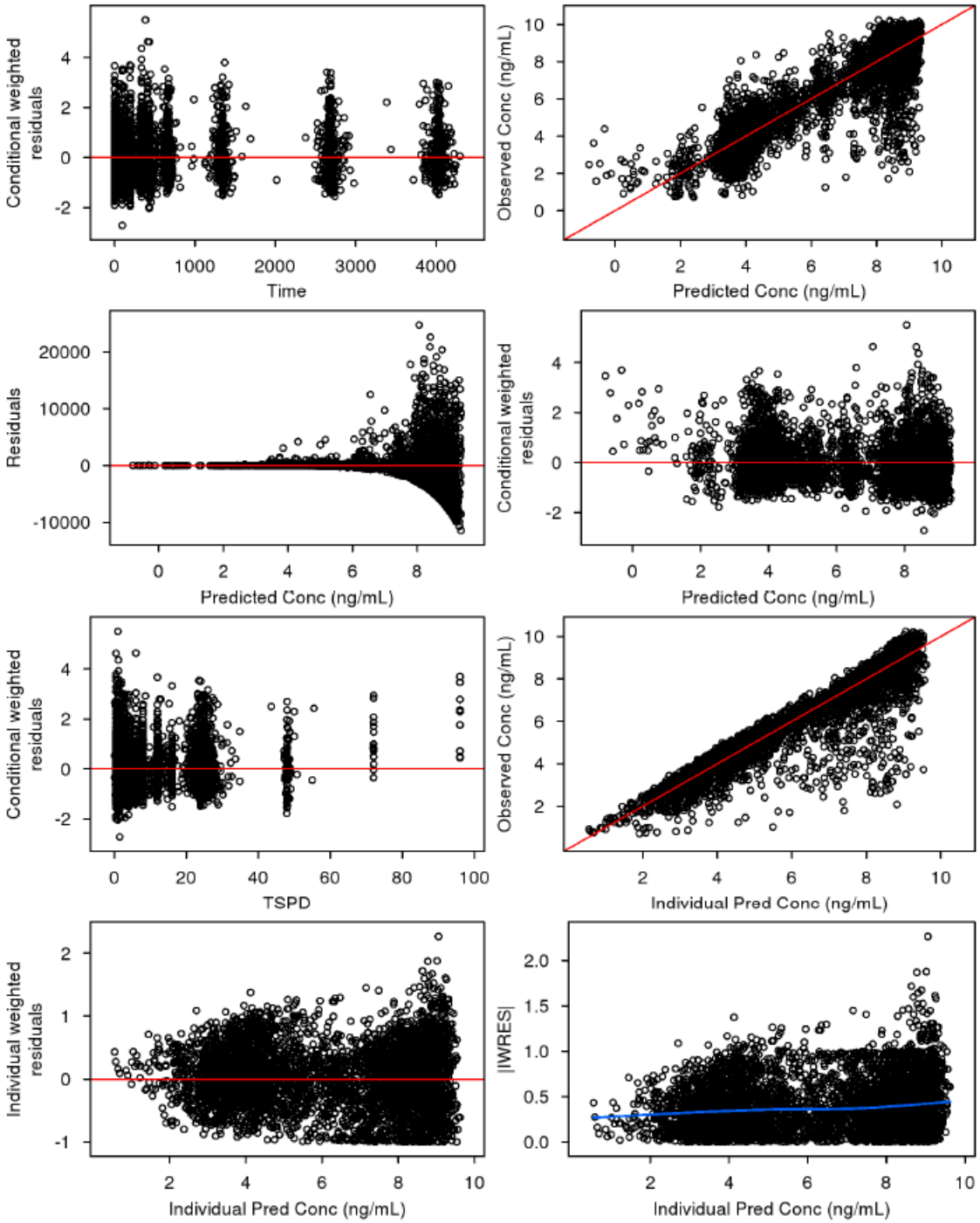
[b] Bootstrap results: 256 (51.2%) minimized successfully, 219 (43.8%) terminated with rounding errors, and 25 (5.0%) terminated for various other reasons. The bootstrap 95% PIs were calculated using the successful minimizations and those that terminated with rounding errors (95.0% of the bootstrap models).

[b] The calculated correlation coefficients (r^2) of the off-diagonal omegas were as follows: 0.464 for cov(IIV in Q, IIV in CL), 0.223 for cov(IIV in V_p, IIV in CL), 0.583 for cov(IIV in V_p, IIV in Q).

Source: d2pk\tables\doc\final-ecld1-biolfmf-ccv-01_r157775.docx and d2pk\sas\calc_bootstrap_pis.lst.

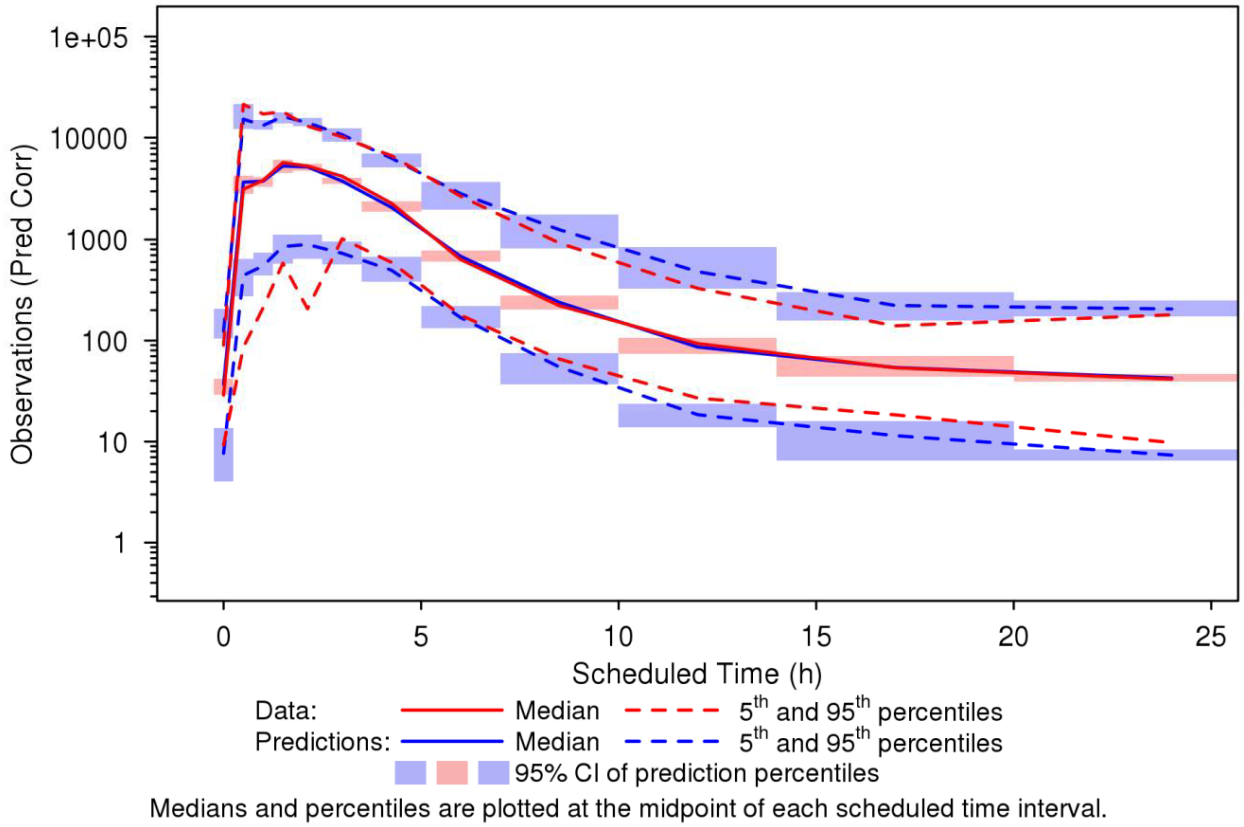
Source: Link 1, page 89.

Figure 9. Goodness-of-fit plots for the final phase 1-3 model.



Source: Link 1, page 204.

Figure 10. Prediction-corrected visual predictive check for the final phase 1-3 model.



Source: Link 1, page 221.

Table 8. Sensitivity analysis for the impact of fixed parameters on posthoc PK parameters.

Fixed Parameter	n	TV CL Coefficient	TV CL Race Effect	TV CL WTKG Exp	TV CL (L/h)	TV Vc (L)	CL (L/h)	Vc (L)	C24 (ng/mL)	Cmax (ng/mL)	AUC24 (ng*h/mL)
K_a (1/h)											
0.637[a]	524	0.6	-2.4	5.5	0.8	-13.6	0.5	-13.6	0.2	0.0	-0.1
0.741[b]	524	-0.8	-4.3	1.6	-0.6	17.0	-0.3	17.0	1.0	0.2	-0.6
Q (L/h)											
3.34[a]	524	-5.9	-2.6	4.2	-5.7	-4.0	-5.8	-4.0	0.1	0.4	0.3
4.59[b]	524	4.7	-2.4	3.0	4.8	1.9	4.6	1.9	1.2	-0.7	-1.0
V_p (L)											
56.1[a]	524	-4.4	-0.3	7.6	-4.3	0.1	-5.7	0.1	0.3	0.6	2.1
78.9[b]	524	2.8	-1.4	-0.9	2.9	-1.2	4.3	-1.2	-0.2	-0.5	-2.6
K_a (1/h) and Q (L/h)											
0.637 & 3.34[a]	524	-5.2	-2.9	6.3	-5.1	-14.0	-5.6	-14.0	-0.8	0.1	0.5
0.741 & 4.59[b]	524	3.5	3.4	-1.2	3.3	13.8	3.5	13.8	1.8	-0.5	-2.0

Abbreviations: AUC_{24}, individual model-predicted area under the raltegravir concentration-time curve from 0 to 24 hours; C_{24}, individual model-predicted raltegravir concentration 24 hours postdose (ng/mL); C_{max}, individual model-predicted maximum raltegravir concentration (ng/mL); CL, apparent clearance (L/h); Exp, exponent; K_a, absorption rate constant (1/h); n, number of subjects; Q, apparent intercompartmental clearance (L/h); TV, typical value; V_c, apparent central volume of distribution; V_p, apparent peripheral volume of distribution; WTKG, weight (kg).

[a] Lower limit of the 95% bootstrap confidence interval of the indicated fixed parameter value from the final raltegravir population pharmacokinetic model.

[b] Upper limit of the 95% bootstrap confidence interval of the indicated fixed parameter value from the final raltegravir population pharmacokinetic model.

Source: Link 2, page 5. Values are percent change in PK parameter for the value of the fixed parameter in the sensitivity analysis relative to the value of the fixed parameter in the final model.

Reviewer's assessment

The applicant developed a complex model to describe PK data from five phase 1 studies and phase 3 study PN292. This model adequately described the data as evidenced by precision of PK parameters, goodness-of-fit plots, and visual predictive check. Nearly identical model parameters were obtained when the applicant's final model was run at FDA. A limitation of the model was the presence of several fixed parameters. However, a sensitivity analysis showed that using the 5th and 95th percentiles of these fixed values did not significantly impact posthoc PK parameters. Overall, this model was sufficient to provide posthoc exposures for use in exposure-response analyses as well as for scaling to a pediatric population to provide predictions of pediatric exposures upon 1200 mg QD dosing.

6.3 Exposure-Efficacy Analysis Report for raltegravir Once Daily Program (QD)

Relevant links

Report title	Link
Exposure-Efficacy Analysis Report for raltegravir Once Daily Program (QD) [Link 3]	\\cdsesub1\evsprod\nda022145\0325\m5\53-clin-stud-rep\535-rep-effic-safety-stud\qd1200\5353-rep-analys-data-more-one-stud\04c3b0\04c3b0.pdf
Response to Information Request. Submitted 12/2/2016 [Link 4]	\\cdsesub1\evsprod\nda022145\0338\m1\us\efficacy-information-amendment-02dec2016.pdf
Response to Information Request. Submitted 2/10/2017 [Link 5]	\\cdsesub1\evsprod\nda022145\0341\m1\us\efficacy-information-amendment-10feb2017.pdf

The initially submitted exposure-efficacy analysis included data only from study PN292, which compared raltegravir 1200 mg QD versus 400 mg BID (Link 1). The efficacy endpoint was week 48 HIV RNA <40 copies/mL and response rates were 89% and 88%, respectively. Subjects in both arms had trough samples collected on day 1 and weeks 4 and 24. Additional samples on weeks 2 and 16 were 1-4 hours post-dose, and the week 8 sample was collected regardless of timing relative to dosing. The PK dataset for the analysis consisted of geometric mean concentration regardless of time point (Call_obs) as well as observed and model-predicted Ctrough (Table 9). Because Call_obs could not be readily compared between subjects, this parameter was ignored. AUC and Cmax were not evaluated because a population PK model could not be developed for studies using the 400 mg BID regimen.

Table 9. Available PK data used in the PN292 exposure-efficacy analysis.

PK metric	Definition	N QD arm	N BID arm
Call_obs	Geometric mean of all observed concentrations for each subject from weeks 2, 4, 8, 16, and 24	528	261
Ctrough	Geometric mean of week 4, 8, and 24 observed concentrations from samples collected 11-13 hours postdose (BID arm) or 22-26 hours postdose (QD arm) for each subject	389	148
Model-predicted Ctrough	Steady-state C24h was predicted for subjects in the QD arm using the population PK model (note there was no model for raltegravir BID)	524	0

N = number of subjects.

Logistic regression analysis was used to evaluate the relationship between PK endpoints and probability of response. Screening viral load, baseline CD4 count, and hepatitis B and/or C co-infection were evaluated as covariates. Screening viral load was the only significant covariate.

No relationship was found between exposure and probability of response within the 1200 mg QD arm or across the 1200 mg QD and 400 mg BID treatment arms (Table 10, Table 11).

Also in analysis of quartiles of Cmax, AUC, and Ctrough, there was no association between exposure and response within the 1200 mg QD arm (Table 12, Table 13).

Table 10. Logistic regression parameter estimates for exposure as a predictor of response within the 1200 mg QD arm.

PK parameter	Model Parameter	Parameter Estimate	Standard Error	P-value	95% CI	Bootstrap 95% CI
C24	Intercept	1.002	0.863	0.246	(-0.690, 2.693)	(-0.728, 2.521)
	C24	0.429	0.415	0.301	(-0.384, 1.241)	(-0.299, 1.238)
	Screening viral load (<=100,000 copies/mL)	0.341	0.298	0.253	(-0.244, 0.926)	(-0.242, 0.937)
C24_obs	Intercept	1.498	0.880	0.089	(-0.226, 3.223)	(-0.426, 3.153)
	C24_obs	0.111	0.407	0.785	(-0.686, 0.908)	(-0.574, 0.979)
	Screening viral load (<=100,000 copies/mL)	0.797	0.352	0.024	(0.107, 1.486)	(0.096, 1.489)
Call_obs	Intercept	1.122	1.018	0.270	(-0.873, 3.117)	(-1.500, 3.934)
	Call_obs	0.238	0.338	0.482	(-0.425, 0.900)	(-0.670, 1.133)
	Screening viral load (<=100,000 copies/mL)	0.379	0.294	0.198	(-0.197, 0.955)	(-0.322, 0.998)

Source: Link 3, page 29.

Table 11. Logistic regression parameter estimates for exposure as a predictor of response across the 1200 mg QD and 400 mg BID arms.

PK parameter	Model Parameter	Parameter Estimate	Standard Error	P-value	95% CI	Bootstrap 95% CI
C24_obs and C12_obs	Intercept	1.161	0.695	0.095	(-0.202, 2.523)	(-0.306, 2.557)
	C24_obs and C12_obs	0.337	0.297	0.257	(-0.245, 0.919)	(-0.201, 1.009)
	Screening viral load (<=100,000 copies/mL)	0.648	0.313	0.038	(0.035, 1.262)	(0.041, 1.332)
Call_obs	Intercept	0.933	0.883	0.291	(-0.798, 2.663)	(-1.400, 3.124)
	Call_obs	0.292	0.295	0.322	(-0.286, 0.870)	(-0.415, 1.092)
	Screening viral load (<=100,000 copies/mL)	0.487	0.241	0.043	(0.015, 0.960)	(-0.005, 0.961)

Source: Link 3, page 30.

Table 12. Response rates for 1200 mg QD as a function of AUC and Cmax.

Quartile	AUC values (μM*h)	Response rate	Cmax values (μM)	Response rate
1st	≤42250	90%	≤13100	90%
2nd	>42250 - ≤54600	85%	>13100 – ≤16850	87%
3rd	>54600 – ≤69000	91%	>16850 - ≤20500	86%
4th	>69000	92%	>20500	95%

Source: reviewer's analysis.

Table 13. Response rates for 1200 mg QD as a function of Ctrough.

1200mg QD quartile	1200 mg QD concentration range (nM)	Response rate
1st (n=131)	10.9 - ≤65.45	88%
2nd (n=132)	>65.45 - ≤100	88%
3rd (n=131)	>100 - ≤171	89%
4th (n=137)	>171 - 4000	92%

Source: reviewer's analysis.

In order to increase the chance of identifying the exposure threshold below which probability of response decreases, we requested the sponsor to repeat the analysis after adding data from the 800 mg QD arm of study PN071 (Information Request dated 11/16/16). In this study, raltegravir 800 mg QD was compared to 400 mg BID. Non-inferiority of 800 mg QD to the reference 400 mg BID was not established; response rates were 83% and 89%, respectively (IND 69928 Clinical Review dated 1/8/2013). In the response, Ctrough and Call_obs were defined as in the previous analysis (Link 2). PK samples were not collected around Cmax in PN071 (unlike PN292); thus Call_obs was not interpretable between studies and was ignored. With inclusion of data from the 800 mg QD arm, data from 1200 mg QD plus 800 mg QD totaled 634 subjects. With all three treatment arms in the analysis (1200 mg QD, 800 mg QD, 400 mg BID), significant predictors (p value <0.05) included Ctrough, screening viral load, and baseline CD4 count (Table 14, Figure 11). Based on the significant difference in predicted probability (shaded area) versus observed responses by deciles (circles) on Figure 11, we requested further documentation that the assumptions of logistic regression were met as well as evidence of model performance. In the applicant's response, this information was provided and supported the adequacy of the model (Link 3).

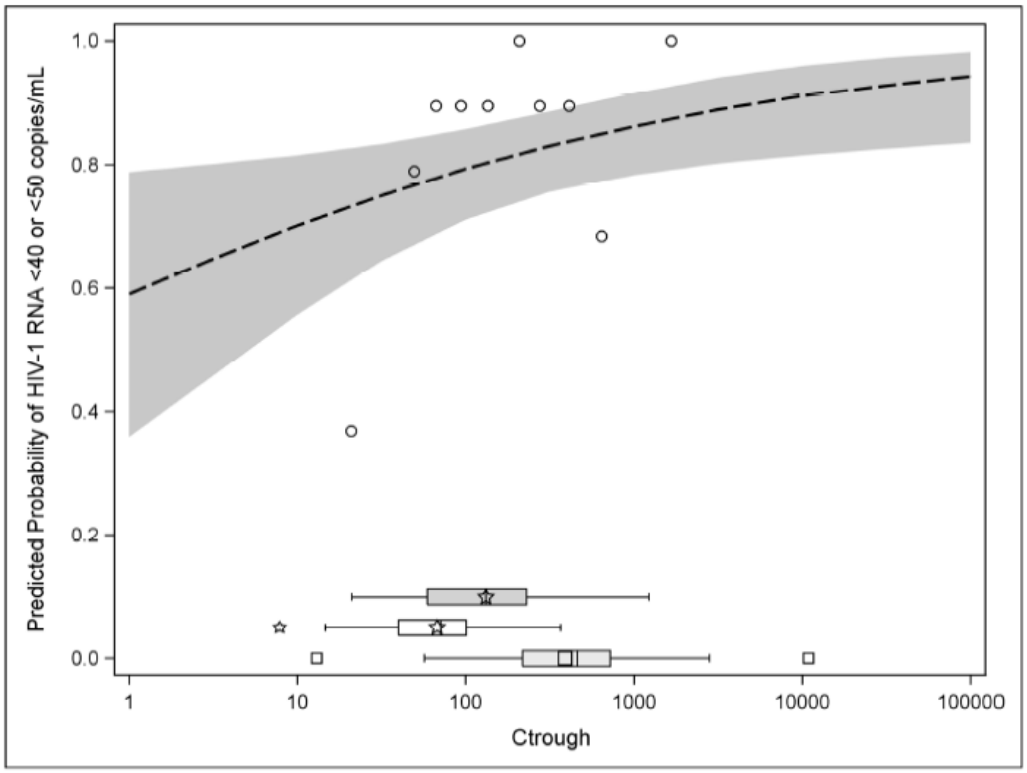
The applicant identified Ctrough <45 nM as being associated with a lower probability of virologic response. This value approximates the cutoff between the 1st and 2nd quartiles of Ctrough in the 800 mg QD arm of study PN071 (Rizk et al, 2012, AAC) (Figure 12). However, it is clear that baseline HIV RNA is also important (Figure 13).

Table 14. Final logistic regression model for HIV RNA <40 or <50 copies/mL from studies PN292 and PN071.

PK parameter	Model Parameter	Parameter Estimate	Standard Error	P-value	95% CI	Bootstrap 95% CI
Ctrough	Intercept	-0.477	0.596	0.424	(-1.640, 0.691)	(-1.680, 0.702)
	Log(Ctrough)	0.489	0.198	0.013	(0.102, 0.876)	(0.108, 0.896)
	Screening viral load (<=100,000 copies/mL)	0.495	0.214	0.021	(0.075, 0.914)	(0.112, 0.918)
	Baseline CD4 (>200 cells/mm3)	1.467	0.395	<0.001	(0.694, 2.241)	(0.704, 2.090)
	Baseline CD4 (>50 and <=200 cells/mm3)	0.842	0.422	0.046	(0.015, 1.670)	(0.076, 1.632)

Source: Link 4, page 11.

Figure 11. Predicted probability of response versus Ctrough for subjects with screening viral load >100,000 copies/mL and baseline CD4 count of 50-200 copies/mm^3 from raltegravir 1200 mg QD, 800 mg QD, and 400 mg BID arms.

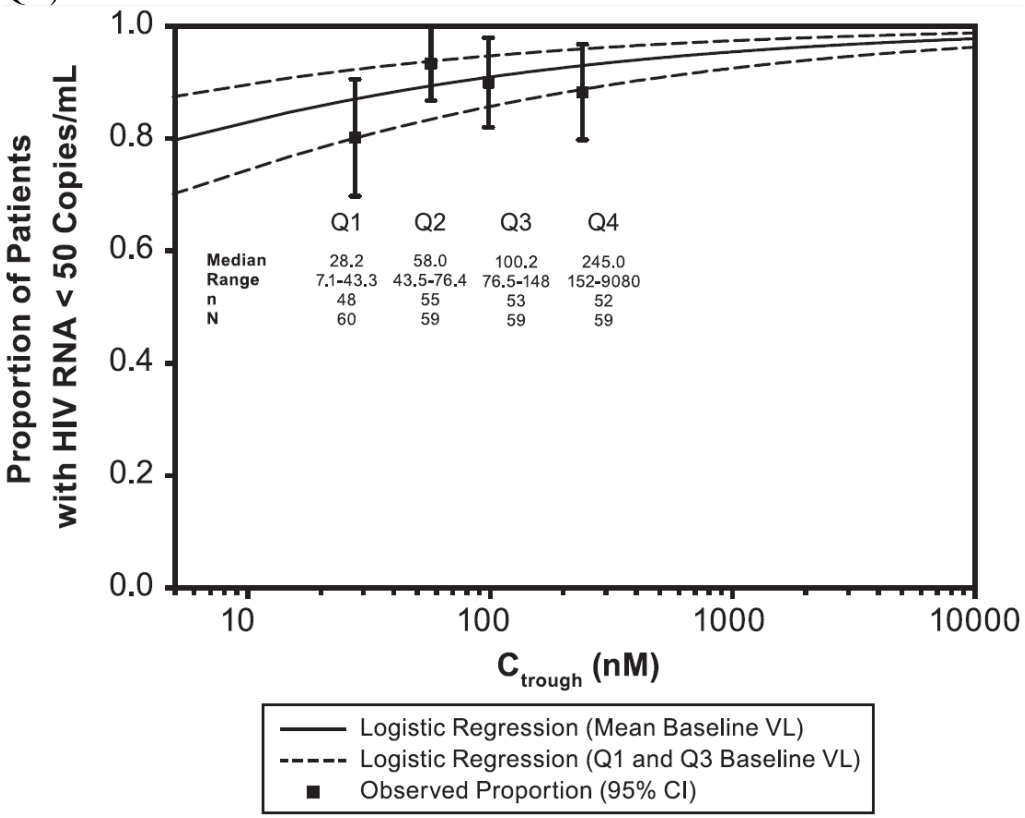


: Distribution of 1200 mg QD Ctrough, where stars show the mean and outliers of the PK boxplot
: Distribution of 800 mg QD Ctrough, where stars show the mean and outliers of the PK boxplot
: Distribution of 400 mg BID Ctrough, where squares show the mean and outliers of the PK boxplot
The observed Ctrough values were divided into 10 bins and the HIV-1 RNA <40 or <50 copies/mL occurrence rate was calculated for the patients in each bin.
The band shows the 95% CI of the predicted probability of achieving HIV-1 RNA <40 or <50 copies/mL.

Source: Link 4, page 13.

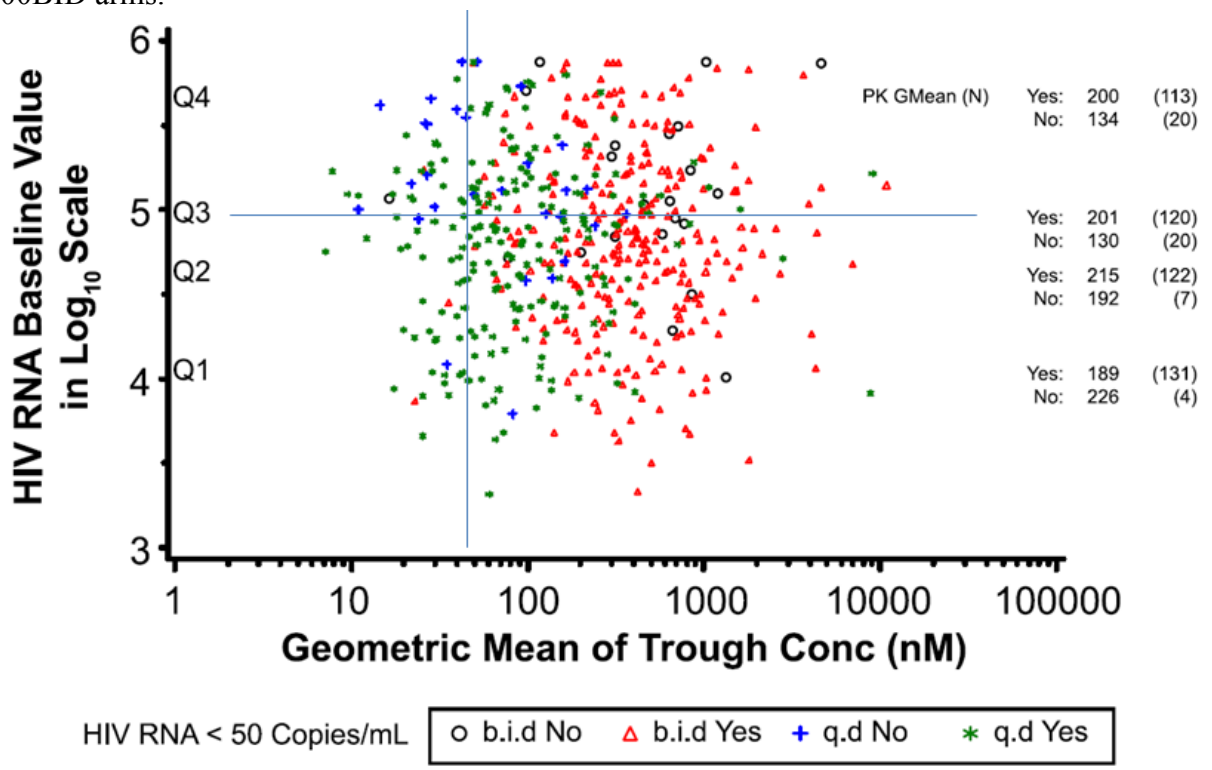
A second objective of the updated E-R analysis was to evaluate food intake as a predictor because food effects differed for 400 mg BID (Ctrough increased 4-fold with a high fat meal relative to fasting) versus 1200 mg QD (Ctrough decreased 12% with a high fat meal). Food intake information in studies PN292 and PN071 was limited to study visits where PK samples were collected and meal type often differed between visits for individual subjects. For this reason, the updated E-R analysis presented above included the most common meal type for evaluation of food effect. Food effect was not found to be a significant predictor of virologic reponse and was not included in the final logistic regression model.

Figure 12. Probability of response versus Ctrough for study PN071 (400 mg BID versus 800 mg QD).



Source: Rizk et al, 2012, AAC.

Figure 13. Ctrough and baseline HIV RNA as predictors of virologic response in the 800QD and 400BID arms.



- A significant number of failures in the QD arm had a trough <45nM
- Very few subjects (=~3) in the BID arm had trough values <45 nM
- Visually, high failure rate among subjects with HIV RNA values above Q3 and Ctrough <45 nM (reference lines on the graph drawn by reviewer)

Source: Figure from Rizk et al, AAC, 2012. Bullet points and reference lines on graph added by reviewer.

6.4 Pediatric Simulation Analysis Report for raltegravir Once Daily (QD) Program

Relevant links

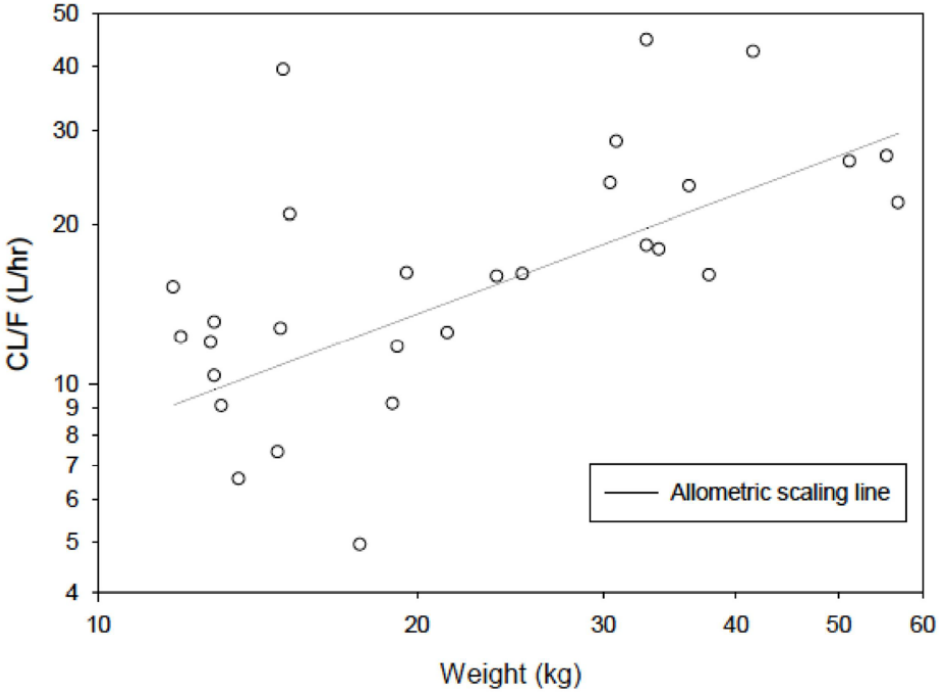
Title	Link
Pediatric 1200 mg QD simulation report [Link 6]	\\cdsesub1\evsprod\nda022145\0325\m5\53-clin-stud-rep\535-rep-effic-safety-stud\qd1200\5353-rep-analys-data-more-one-stud\04c3b7\04c3b7.pdf
Response to Information Request submitted 3/10/2017 [Link 7]	\\cdsesub1\evsprod\nda022145\0343\m1\us\multiple-information-amendment-10mar2017.pdf
Response to Information Request submitted 3/31/2017 [Link 8]	\\cdsesub1\evsprod\nda022145\0345\m1\us\safety-information-amendment-31mar2017.pdf

Twice-daily dosing of raltegravir is currently approved for pediatric patients weighing ≥3 kg. For the film-coated tablet, the adult dose of 400 mg BID is recommended for pediatric patients ≥25 kg. In this application, the applicant proposed dosing of raltegravir 1200 mg QD for pediatric patients weighing ≥40 kg. This proposal was based solely on predicted pediatric exposures upon 1200 mg QD dosing.

The applicant used the adult 1200 mg QD model (see 6.2) to predict pediatric exposures upon 1200 mg QD dosing. Based upon prior pediatric raltegravir PK data from BID dosing where allometric scaling reasonably described the clearance-weight relationship (Figure 14), adult raltegravir clearance from the adult model was allometrically scaled to pediatrics using a power model and exponent of 0.75.

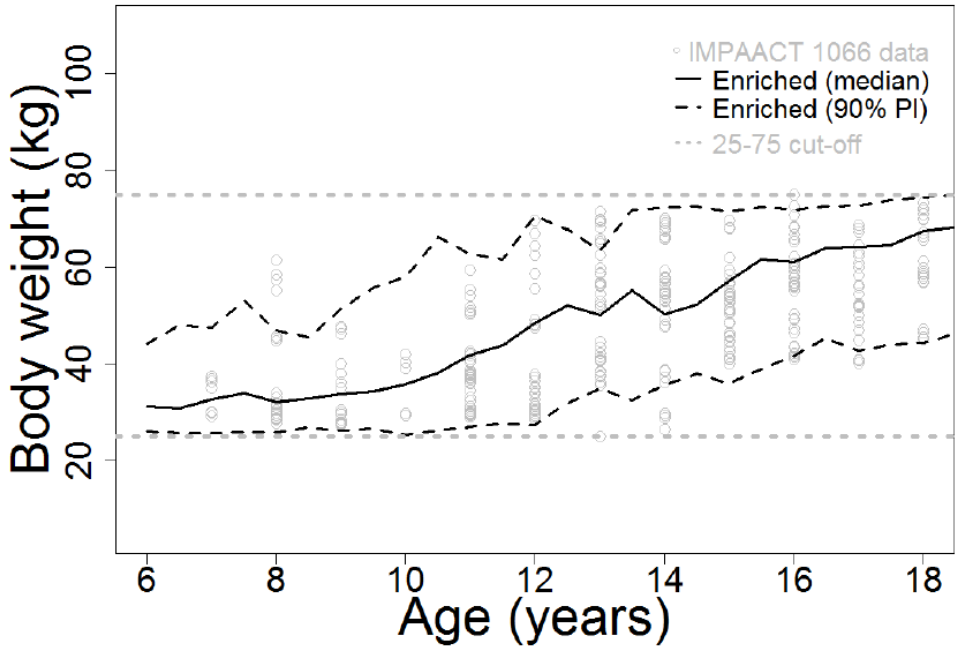
Model-predicted raltegravir exposures depend on race (raltegravir CL decreased 18% for black/other race versus white/Asian) and weight. The age-weight relationship in HIV-infected pediatric subjects administered raltegravir was characterized from IMPACT study P1066. This relationship was used to generate a virtual dataset of 1000 pediatric subjects weighing 25-75 kg for simulation (Figure 15).

Figure 14. Raltegravir clearance-weight relationship from pediatric study PN022 (BID dosing).



Source: Link 7, page 5.

Figure 15. Body weight versus age from study P1066 and enriched dataset.

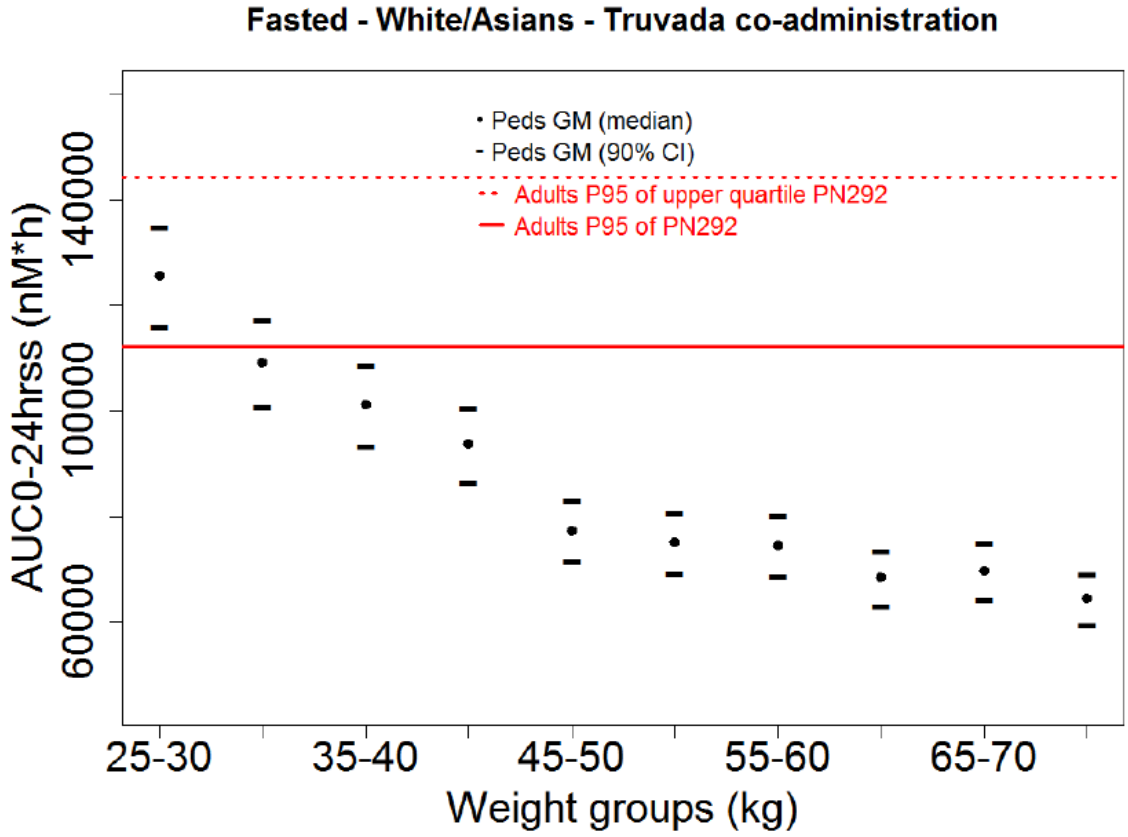


Note: Both observed (N = 103) and enriched data (N = 1000) were bounded within a lower cutoff of 25 kg and an upper cutoff of 75 kg (grey dotted lines). Each symbol represents an individual observation. The black solid line represents the median of the enriched dataset, whereas the black dashed lines represent the 5th and 95th percentiles (90% PI).

Source: Link 6, page 25.

The weight cutoff for use of the adult dose in pediatrics was derived by identifying the lowest pediatric weight group where the geometric mean of the predicted pediatric exposure did not exceed the adult 95th percentile of AUC after 1200 mg QD dosing. AUC was selected (as opposed to Cmax) because it reflects exposure over the entire dosing interval and because no exposure-related safety signals have been associated with raltegravir (Link 3). Eight simulations were conducted to evaluate each combination of race (White/Asian or Black/other), FTC/TDF use (yes or no), and meal type (fasted or high fat meal). The simulation results for fasted, white or Asian pediatric subjects using coadministered Truvada are shown as an example; see Link 1 for all simulation results (Figure 16). In the simulations, weight cutoffs ranged from 30-45 kg; 40 kg was selected by the applicant as the cutoff for the overall pediatric population.

Figure 16. Simulated pediatric raltegravir AUC versus weight for fasted, White/Asian subjects on coadministered Truvada who received raltegravir 1200 mg QD (Table 15).



Source: Link 6, page 30. Note 30-35 kg is the lowest weight group where the geometric mean does not exceed the adult P95 (solid red line). 30 kg would be the weight cutoff for this simulation.

Table 15. Weight cutoffs for use of raltegravir 1200 mg QD in pediatric subjects based on comparison of simulated pediatric AUC and adult 95th percentile of AUC from 1200 mg QD.

Pediatric group	WT cutoff ($AUC_{0\text{-}24hr,ss}$)
Fasted – White/Asian – TRUVADA	30
Fasted – White/Asian – No TRUVADA	30
Fasted – Black/other – TRUVADA	45
Fasted – Black/other – No TRUVADA	35
HFM – White/Asian – TRUVADA	30
HFM – White/Asian – No TRUVADA	30
HFM – Black/other – TRUVADA	45
HFM – Black/other – No TRUVADA	35

Abbreviations: WT = body weight, HFM = high fat meal

Source: Link 6, page 29.

Reviewer's assessment

The applicant used an atypical approach to pursue labeling for use of raltegravir 1200 mg QD in pediatrics. First, for HIV indications a PK, antiviral activity, and safety study is typically conducted to confirm similarity of adult and pediatric exposures at the proposed pediatric dose and to evaluate safety. In this case, approval would instead be based only on simulations of pediatric exposures. Secondly, the central tendency and distribution of adult and pediatric exposures are typically compared; in this case the central tendency of pediatric exposures was compared to the upper limit of adult exposures.

Raltegravir is approved in pediatrics for BID dosing and no exposure-related safety concerns have been identified in adults. For this reason, the review team evaluated the proposal to provide pediatric labeling for 1200 mg QD based on simulated exposures alone. The key limitation of this approach is that safety cannot be extrapolated from adults. We requested that the applicant provide safety data for any pediatric subjects weighing ≥40 kg with observed raltegravir Cmax and AUC within the range of simulated Cmax and AUC following 1200 mg QD in pediatric subjects ≥40 kg. In the response, the sponsor identified six subjects from study P1066 (raltegravir BID dosing) whose observed Cmax and AUC were above the 5th percentile of simulated Cmax and AUC. The weight range was 51-63 kg (Table 16). No safety concerns were reported for these six subjects. The median AUC from the six subjects was lower than the median of simulated exposures in pediatric subjects 40-45 kg and 50-55 kg given 1200 mg QD and comparable to median AUC in adults given 1200 mg QD (Table 17). The AUC range from the six subjects was within the simulated pediatric and observed adult AUC range. Based on the significant overlap of exposures and limited safety data suggesting no safety concerns at exposures associated with 1200 mg QD in pediatric subjects ≥50 kg, the review team (Clinical pharmacology and Clinical) recommended including labeling for dosing of raltegravir 1200 mg QD for pediatric subjects ≥50 kg. The applicant's proposed weight cutoff of 40 kg was not accepted because no safety data are available for this weight group at exposures similar to those expected in pediatric subjects weighing 40 kg and administered 1200 mg QD.

Table 16. Subjects in study P1066 (BID dosing) with observed raltegravir AUC and Cmax above the 5th percentile of pediatric simulated AUC and Cmax from 1200 mg QD.

Patient ID	Cohort	Dose (in mg BID)	Dose (mg/kg)	Age (years)	Gender	Race	Weight (kg)	$AUC_{0\text{-}12hr}$ (uM*hr)	2 x $AUC^{¥}_{0\text{-}12hr}$ (uM*hr)	C_{max} (uM)
670119	I	600	9.9	16	F	White	63.3	78.62	157.24	18.31
670661	I	400	6.814	13	F	Black or African American	58.9	46.08	92.16	15.04
450381	I	400	6.711	16	M	White	58.6	31.55	63.1	10.7
730073	IIB	300	5.3	8	F	Unknown	52.8	30.06	60.12	12.38
300348	I	400	7.1	17	M	American Indian	56.8	28.71	57.42	13.14
504261	IIB	300	5.8	11	F	White	50.6	24.77	49.54	15.71

¥Note that P1066 provided $AUC_{0\text{-}12hr}$ therefore the AUC in this table, taken from P1066, was multiplied by 2 for comparison with $AUC_{0\text{-}24hr}$ from RAL 1200mg QD simulated data.

Source: Link 7, page 11.

Table 17. Comparison of pediatric simulated (1200 mg QD), pediatric observed (300-600 mg BID), and adult raltegravir exposures (1200 mg QD).

Safety Threshold: Adult 95th percentile $AUC_{0\text{-}24,ss}$ exposure of **109 uM*h** in ONCEMRK

Group	Dosing	PK	AUC0-24h[2] (uM*h)	Cmax (uM)	AUC and Cmax Value type
Adults in ONCEMRK	1200 mg QD	Sparse; model-predicted exposures	50 (15, 336) 56 (27)	15 (2, 45) 16 (6)	Median (min, max) Mean (SD)
Healthy adults in relative BA study		Intensive	60 (27, 93) 60 (51, 69)	22 (8, 41) 21 (17, 25)	Median (min, max) Geometric mean (95% CI)
Simulated pediatrics 40-45 kg		Simulated from adult 1200 mg QD model scaled to pediatric	95 (53, 157)	27 (14, 44)	Average of median (5th, 95th) across eight covariate combinations (race, FTC/TDF use, food intake)[3]
Simulated pediatrics 50-55 kg			86 (45, 149)	23 (11, 37)	
6 pediatric subjects (51-63 kg[1]) with observed exposures >5th percentile of simulated exposures for 1200 mg QD	300-600 mg BID	Intensive	62 (50, 157) 80	14 (11, 18) 14	Median (min, max) Mean

[1]Median weight 58 kg
[2]For BID regimens, AUC0-24h = AUC0-12h x 2
[3]The sponsor provided simulated exposures for each of eight covariate combinations by pediatric weight range (for example, combo 1 for 40-45 kg: race = white/Asian; Truvada = yes; Food = fasted). We recorded the median (5th, 95th) for each of the eight scenarios. The average of the eight medians, 5th percentiles, and 95th percentiles was recorded in the table above.

Source: Reviewer's analysis with contribution of the Clinical reviewer (Sarita Boyd, PharmD).

6.5 P290 - A Single Dose Food Effect Study of Raltegravir Formulations

Study #	P290	**Study Period**	July 25, 2013 - August 02, 2013	Study P290
Title	Single Dose Food Effect Study of Raltegravir Regimens			

STUDY SUMMARY (As Reported by the Applicant)

Design

Study Rationale: Determine the impact of food on the PK of raltegravir administered as raltegravir 600 mg x 2 and raltegravir 400 mg x 3

Study Objectives:
PK of raltegravir 600 mg x 2 in fasted, low-fat, and high-fat states
PK of raltegravir 400 mg x 3 in fasted, low-fat, and high-fat states

General Study Design
Open-label, single-dose, randomized, three-period, three-treatment, six-sequence, crossover, food-effect study.

Cohort	Treatment	Drug Product	Fating/Fed Conditions
1	A	Drug Product 1- Reformulated Raltegravir 600 mg Tablet (x2)	Overnight fast of at least 8 hours
1	B	Drug Product 1- Reformulated Raltegravir 600 mg Tablet (x2)	30 minutes after the start of a low-fat breakfast
1	C	Drug Product 1- Reformulated Raltegravir 600 mg Tablet (x2)	30 minutes after the start of a high-fat breakfast
2	D	Drug Product 2- Isentress® 400 mg Tablet (x3)	Overnight fast of at least 8 hours
2	E	Drug Product 2- Isentress® 400 mg Tablet (x3)	30 minutes after the start of a low-fat breakfast
2	F	Drug Product 2- Isentress® 400 mg Tablet (x3)	30 minutes after the start of a high-fat breakfast

- *Dose Selection*: 1200 mg QD is the to-be marketed regimen. raltegravir 400 mg BID is approved for use without regard to food.

-*Meals:* Low fat = 389 kcal, 6.9% fat; High-fat = 997 kcal, 50.6% fat.

- *PK Sampling:* Prior to dosing (0-hour) and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24 and 48 hours post dose.

- *PK Analysis and Parameters*: Non-compartmental. AUCt, AUCinf, Cmax, Ctrough (C24) and Tmax.

- *Statistical Analysis*:
ANOVA (PROC MIXED) was performed on log-transformed AUC0-last, AUC0-inf, C24 and Cmax. Ratios of the geometric means and the corresponding 90% confidence intervals were calculated.

Population: Healthy adults (no clinically significant medical history)

Enrolled	36	Completed	32	Discontinued Due to AE	0	PK Population	36	Safety Population	36

**Subjects 0014, 0018, 0023 and 0033 did not complete all periods of the study but received at least one administration of a study treatment and were, therefore, included in the pharmacokinetic dataset

- *Formulations*:
raltegravir 600 mg tablets: phase 1 formulation
raltegravir 400 mg (commercial tablets)

Bioanalytical Method
Liquid/Liquid Extraction HPLC Tandem Mass Spectrometric Method (HPLC-MS/MS)

Concomitant substances
All medication (prescription or over-the-counter) were prohibited including herbal/natural products, nutritional supplements and vitamins, and grapefruit or products containing grapefruit Exceptions were made for:
• hormonal contraceptives;
• non-systemic and/or topically applied products (prescription or otherwise) and
• the occasional use of common analgesics

Protocol Deviations
The definition of a protocol deviation or their classification as minor versus major was not provided. No major deviations were reported. Minor deviations from the scheduled sampling time were accounted for in the pharmacokinetic calculations since the actual sampling times were used.

Results
- *Pharmacokinetics*

Table 17. Statistical comparison of raltegravir PK parameters for raltegravir 600 mg x 2 administration in the presence and absence of food.

	600x2 mg low-fat vs fasted geometric mean ratio (90% CI)	600x2 mg high-fat vs fasted geometric mean ratio (90% CI)
Ctrough	0.84 (0.63 – 1.1)	0.88 (0.66 – 1.18)
AUCinf	0.6 (0.47 – 0.76)	1.06 (0.87 – 1.28)
Cmax	0.48 (0.37 – 0.62)	0.72 (0.58 – 0.90)

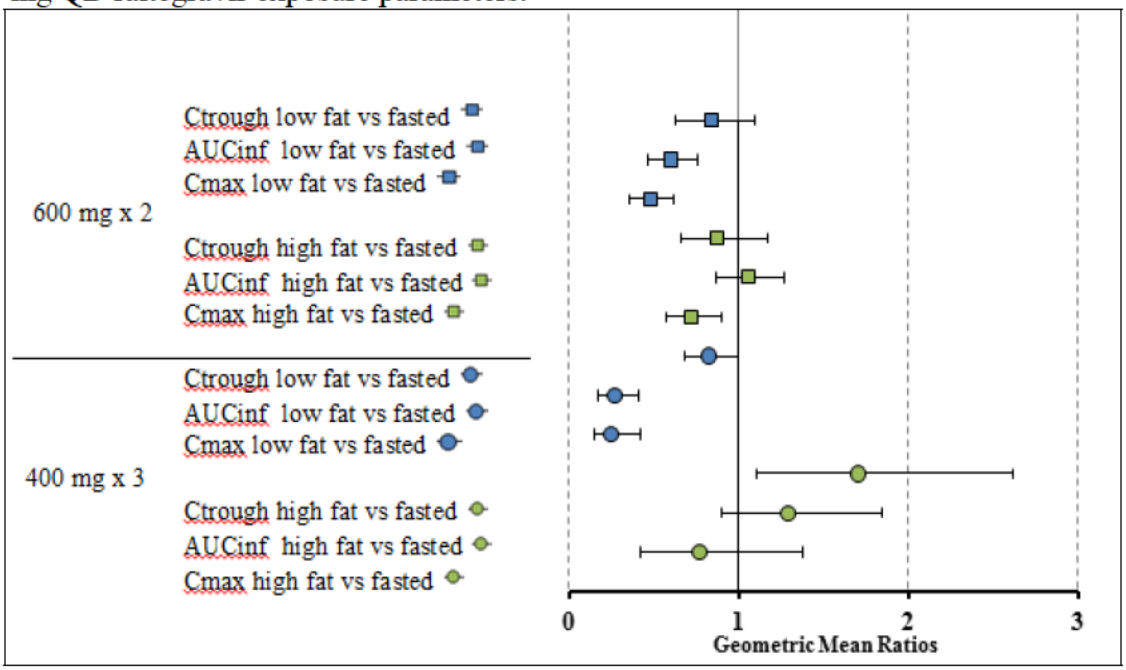
Source: Values taken from CSR.

Table 18. Statistical comparison of raltegravir PK parameters for raltegravir raltegravir 400 mg x 3 administration in the presence and absence of food.

	400x3 mg low-fat vs fasted geometric mean ratio (90% CI)	400x3 mg high-fat vs fasted geometric mean ratio (90% CI)
Ctrough	0.82 (0.68 – 0.99)	1.70 (1.11 – 2.61)
AUC0-inf	0.27 (0.17 – 0.41)	1.29 (0.90 – 1.85)
Cmax	0.25 (0.15 – 0.42)	0.77 (0.42 – 1.38)

Source: Values taken from CSR.

Figure 17. Forest plot of geometric mean ratios comparing low- and high- fat meal effects on 1200 mg QD raltegravir exposure parameters.



Source: prepared by the reviewer. Upper panel = Reformulated raltegravir tablets (2 x 600 mg); lower panel = raltegravir regimen (3 x 400 mg).

- *Concomitant medications:* No use of excluded concomitant medications was reported during the treatment period of the study.

- *Safety*

Was there any death or serious adverse events? ☐ Yes ☑ No

6 subjects experienced a hypertension AE. There was no consistent relationship with the type of treatment

No laboratory abnormalities of clinical importance were reported.

REVIEWER ASSESSMENT

- Discussion

Regarding the design and conduct of the study, there were no issues regarding protocol deviations, adherence, concomitant medications, bioanalysis, or statistical analysis.

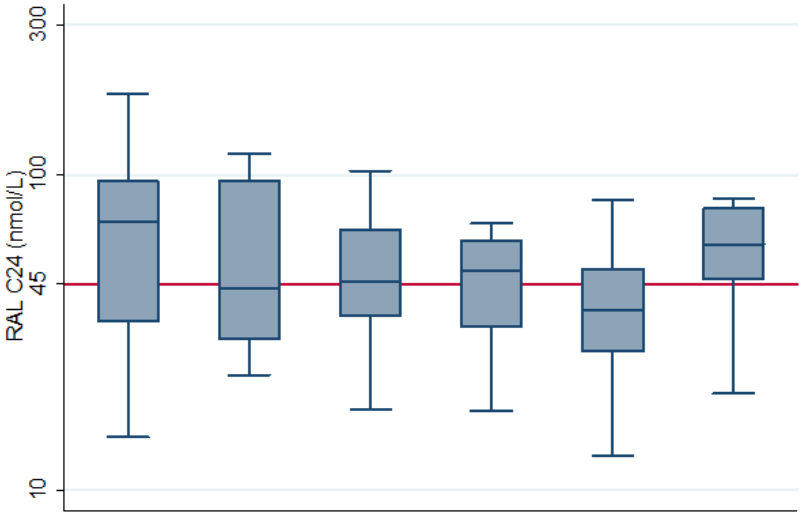
Of note, AUC0-inf values after single doses of raltegravir (3 x 400 mg) with a low fat meal were lower (GMR: 0.27) compared to raltegravir tablets (2 x 600 mg) (GMR: 0.6). However, based on the exposure-efficacy analysis, Ctrough is the exposure parameter of interest. Therefore, the differential effect of food on AUC for the 400 mg x 3 regimen versus 600 mg x 2 regimen is not of concern.

In this study, Ctrough values were comparable across formulations and meal types (Figure 18). Therefore, food status is not expected to compromise efficacy when 1200 mg doses constituted from either formulation are administered.

Figure 18. Ctrough comparison from single dose food effect and formulation study PN290 in healthy subjects.

Treatments (n=16-18 per group)
A = 600 mg x 2 fasting
B = 600 mg x 2 low-fat
C = 600 mg x 2 high-fat
D = 400 mg x 3 fasting
E = 400 mg x 3 low-fat
F = 400 mg x 3 high-fat

Crossover study
-subjects received treatments ABC or DEF



	A	B	C	D	E	F
Median Ctrough (nM)	71	44	46	50	37	60

Source: plotted by reviewer.

A similar impact of food on raltegravir AUC versus Ctrough was observed in a multiple dose food effect study of raltegravir 400 mg BID. In this study, low fat meal intake relative to the fasted state resulted in AUC0-12 and Ctrough ratios of 0.54 and 0.85, respectively (Table 19). raltegravir 400 mg BID regimens are approved without regard to food.

Table 19. Multiple dose raltegravir PK parameters in healthy adults administered raltegravir 400 mg BID in the presence and absence of food.

	Median Tmax (hr)	GM Cmax (uM)	GM C_{12} (nM)	GM AUC_{0-12} (µM·h)
Fasted	3.0	2.71	110	10.0
Low-Fat Meal	3.0	1.31	94	5.38
Moderate-Fat Meal	4.0	2.85	182	11.3
High-Fat Meal	4.0	5.32	453	21.2

Source: [1] Brainard, D. M. et. al, J Clin Pharm, 2011.

- *Labeling Recommendations*

Administration of raltegravir 1200 mg QD with regard to food

In phase 3 study PN292, raltegravir was administered without regard to food. In exposure-response analyses of study PN292, most common meal type was not found to be a predictor of virologic response. There is a significant and variable impact of food on the PK of raltegravir. However, Ctrough is the PK parameter least affected by food, and raltegravir Ctrough (and not AUC or Cmax) has been associated with virologic response. Because raltegravir 1200 mg QD was adminstered without regard to food in study PN292 and because Ctrough was not significantly affected by food, we agree with the applicant's recommendation that raltegravir 1200 mg QD can be administered without regard to food.

Interchangeability of 600 mg x 2 versus 400 mg x 3

Based on the raltegravir Ctrough PK parameter ratios and 90%CIs, (b) (4)

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Instead we propose that the 400 mg and 600 mg strengths can be used interchangeably to constitute a 1200 mg dosing regimen. Also, they can be used interchangeably regardless of meal type.

CLINICAL PHARMACOLOGY REVIEW

P291 - A Multiple Dose Study of Raltegravir Formulations

Study #	P291	**Study Period**	July 30th, 2013 – August 22nd, 2013	Study P291
Title	A Multiple Dose Study of Raltegravir Formulations			

STUDY SUMMARY (As Reported by the Applicant)
Design
Study Rationale: To evaluate the exposure differences between the approved raltegravir 400 mg BID regimen, the proposed dosing regimen of 1200 mg QD utilizing two raltegravir raltegravir tablets (600 mg each), as well as a 1200 mg QD regimen utilizing three tablets of the pre-approved raltegravir formulation tablets (400 mg each).
General Study Design An open-label, multiple-dose, randomized, three-period, three-treatment, six-sequence, crossover, comparative bioavailability study in healthy male and female subjects under fasting conditions P1: Period 1 (treatment A, B, or C) P2: Period 2 (treatment A, B, or C) P3: Period 3 (treatment A, B, or C) Treatment A: 1200 mg QD for 5 days (two 600 mg MK-0518 tablets) Treatment B: 1200 mg QD for 5 days (three Isentress® 400 mg tablets) Treatment C: 400 mg BID on days 1 to 4 and once on day 5 (Isentress® 400 mg tablets) - *Dose Selection*: 1200 mg QD is the to-be marketed regimen. - *PK Sampling:* Treatments A and B: Days 1 & 5: prior to dosing (0-hour) and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours after AM drug administration Days 3 & 4: trough samples collected prior to AM drug administration Treatment C: Days 1 & 5: prior to dosing (0-hour) and 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 12 hours after AM drug administration Days 3 & 4: trough samples collected prior to AM drug administration - *PK Analysis and Parameters*: Non-compartmental AUC24, Cmax, Ctrough (C24) and Tmax for treatments A and B AUC12, Cmax, Ctrough (C12), Tmax and AUC24 (AUC12 x 2) for treatment C - *Statistical Analysis*: **1.** ANOVA (PROC MIXED) was performed on log-transformed AUC24, Ctrough and Cmax estimated on day 5. AUC24 for Treatment C was calculated as 2 x AUC12. Linear mixed effects model containing fixed effects for treatment and period and with an unstructured covariance matrix was used to allow for unequal treatment variances and to model

the correlation between different treatment measurements within the same subject.
The 90% CIs were calculated for the ratios of the geometric least-squares means (GLSMs) for the comparisons between the three regimens (A vs C, A vs B, and B vs C)
2. Accumulation ratios were estimated using two methods:
The individual AUC24 ratios (Day 5/Day 1) were used as a primary method and Ctrough as a secondary method to estimate the number of dosing intervals needed to reach 90% of steady state, T90 for each subject and treatment. These data were analyzed statistically to obtain the geometric/population mean with the 95% confidence intervals for T90 for each treatment. The number of subjects who reached at least 90% of steady-state and their proportion of the total were summarized by treatments
3. The pre-dose concentrations (Ctrough) were analyzed to estimate the inter-occasion variability for each treatment

Population: Healthy adults (no clinically significant medical history)							Administration: fasted		
Enrolled	24	Completed	22	Discontinued Due to AE	2	PK Population	24*	Safety Population	24

*Subjects 0005 and 0007 did not complete all periods of the study but received at least one administration of a study treatment and were, therefore, included in the pharmacokinetic dataset

- *Formulations*:
raltegravir 600 mg tablets: phase 1 formulation
raltegravir 400 mg tablets: commercial tablet

Bioanalytical Method
Liquid/Liquid Extraction HPLC Tandem Mass Spectrometric Method (HPLC-MS/MS)

Concomitant substances
All medication (prescription or over-the-counter) were prohibited including herbal/natural products, nutritional supplements and vitamins, and grapefruit or products containing grapefruit
Exceptions were made for:
• hormonal contraceptives;
• non-systemic and/or topically applied products (prescription or otherwise) and
• the occasional use of common analgesics

Protocol Deviations
The definition of a protocol deviation or their classification as minor versus major was not provided. No major deviations were reported. Two minor protocal deviations (subjects 0005 and 0012) related to ingestion of prune juice and a 1-minute dosing delay on day 1; did not have an effect on the study results.

Results

- *Study Population*
24 subjects were included in the final PK analysis (*Subjects 0005 and 0007 did not complete all periods of the study but received at least one administration and were included in the PK dataset). Mean age (range) was 40 (25 – 55) years, weight 77.8 (60.1 - 96.3) kg, and BMI 26.3 (22.4 - 29.6) kg/m^2 (non-obese). The study population was 33.3% females (n=8), 66.7% males (n=16), with a majority of White race (62.5%, n=15), 20.8% Black (n=5), and 16.7% Asian (n=4)
*Subject 0005 in period 1: had fever and was discontinued
Subject 0007 in period 1: dismissed due to abnormal ALT lab result (refer to "safety" below)

- *Concomitant medications*

Most subjects (84.8%, 28 of 33 subjects) used concomitant non-antiretroviral medications. The most frequently used concomitant medications were in the following drug classes: antibacterials for systemic use (57.6%, 19 of 33 subjects), analgesics and vitamins (each 36.4%, 12 subjects), and antihistamines for systemic use (33.3%, 11 subjects).

- *Pharmacokinetics*

Table 20. Statistical comparison of PK parameters.

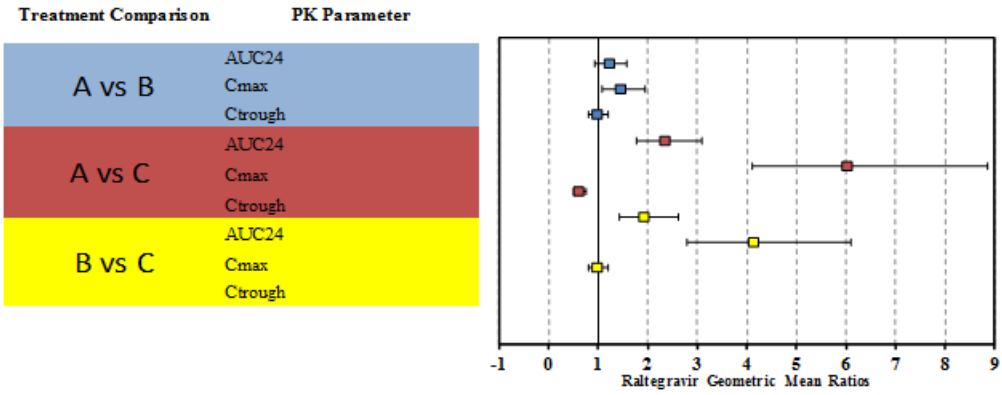
Parameter	*Trt*	*n*	*GM*	*95% CI for GM*	*Contrast*	*GMR (%)*	*90% CI for GMR*	*Pseudo Intra-Sbj CV(%)**
AUC24	**A**	23	59535.4	51375.7 - 68991.0	**A vs C**	234.31	177.17 - 309.87	54.8
(hr·nM)	**B**	22	49013.6	36620.3 - 65601.2	**B vs C**	192.90	141.69 - 262.61	60.1
	C	23	25409.2	17456.7 - 36984.3	**A vs B**	121.47	93.94 - 157.06	49.0
Cmax	**A**	23	20563.5	17002.9 - 24869.9	**A vs C**	602.55	410.25 - 884.97	75.5
(nM)	**B**	22	14110.1	9823.7 - 20266.8	**B vs C**	413.45	280.41 - 609.62	75.4
	C	23	3412.8	2116.7 - 5502.3	**A vs B**	145.74	108.70 - 195.39	55.8
Ctrough	**A**	23	81.1	61.6 - 106.7	**A vs C**	61.96	50.21 - 76.45	40.3
(nM)	**B**	22	83.5	67.7 - 103.0	**B vs C**	63.83	52.39 - 77.78	37.9
	C	23	130.9	103.4 - 165.6	**A vs B**	97.06	79.12 - 119.07	39.4
			Median	***Range***				
Tmax	**A**	23	2.00	0.50- 3.00				
(h)	**B**	22	2.00	0.50- 6.00				
	C	23	1.50	0.50- 4.00				

For Treatment C: AUC24 = AUC12 x 2
** Estimated based on the elements of the variance-covariance matrix as:* $CV(\%) = 100*sqrt[(\sigma_1^2 + \sigma_2^2 - 2*\sigma_{12})/2]$

Treatment A: MK-0518 600 mg tablets (2 x 600 mg q24), Lot No.: WL00053019 (MSD Corp., USA)
Treatment B: Isentress® 400 mg tablets (3 x 400 mg q24), Lot No.: J006167 (MSD Corp., USA)
Treatment C: Isentress® 400 mg tablets (1 x 400 mg q12), Lot No.: J006167 (MSD Corp., USA)

Source: CSR page 6.

Figure 19. Forest plot of geometric mean ratios and their corresponding CIs.



Source: prepared by reviewer.

Time to steady state differed significantly by treatment arm when calculated using AUCratios. However, when calculated using Ctrough, time to steady-state was similar for treatments A and B (Table 21).

Table 21. Time to reach steady-state.

Name of Sponsor: *Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.*
Name of Finished Product: *MK-0518 600 mg Tablets*
Name of Active Ingredient: *Raltegravir*

Inter-occasion Variability of The Pre-Dose Levels

Treatment	*Interoccasion Variance*	*CV(%)*
A	0.0483307	22.3
B	0.060309	24.9
C	0.4093694	71.1

Summary Statistics for Steady-State Parameters by Treatment / Based on AUC24 Ratios

	T90 (days)*		*Subjects (%) at 90% of Steady State*				
Trt	*GM*	*95% CI*	*Day 1*	*Day 2*	*Day 3*	*Day 4*	*Day 5*
A	1.329	-0.024 , 2.683	3 (25.0)	7 (58.3)	12 (100)	12 (100)	12 (100)
B	3.948	1.518 , 6.377	0 (0.0)	2 (22.2)	4 (44.4)	4 (44.4)	6 (66.7)
C	3.461	-2.766 , 9.687	4 (30.8)	8 (61.5)	10 (76.9)	11 (84.6)	11 (84.6)

T90 = The time in days required to attain 90% of theoretical steady-state

Summary Statistics for Steady-State Parameters / Based on Ctrough Analysis

Trt	Parameter	GM	95% CI	CV(%)
A	Ctrough	86.2	68.2 - 108.9	52.9
	T90	2.0	1.5 - 2.8	23.5
	Intra-Sbj CV	25.5	19.4 - 30.5	
B	Ctrough	82.2	66.1- 102.1	42.7
	T90	2.2	1.5 - 3.1	25.5
	Intra-Sbj CV	30.4	23.0 - 36.6	

Source: CSR page 7.

- *Safety*

Was there any death or serious adverse events? ☐ Yes ☑ No

The most commonly reported AEs were hypertension (n=4) and somnolence (n=4). Four subjects experienced increased blood pressure; there was no trend in the AEs between the treatment arms Subject 0007 in period 1was dismissed due to abnormal ALT lab result (43 U/L, against a reference of <33 U/L).

REVIEWER ASSESSMENT

Regarding the design and conduct of the study, there were no issues regarding protocol deviations, adherence, concomitant medications, bioanalysis, or statistical analysis. The washout period was at least 4 days which is acceptable considering the 9-hour terminal half-life.

The study shows relatively similar Ctrough levels for both raltegravir tablets (3 x 400 mg) and raltegravir tablets (2 x 600 mg). Nonetheless, with multiple doses of raltegravir tablets (2 x 600 mg), higher exposure levels in terms of Cmax and AUC0-24 are anticipated in comparison to raltegravir tablets (3 x 400 mg). Considering that Ctrough is the main exposure parameter of interest for raltegravir, the similar Ctrough levels when 1200 mg daily doses utilizing both formulations allows the interchangeability between raltegravir tablets (3 x 400 mg) and raltegravir tablets (2 x 600 mg) to constitute 1200 mg doses.

Labeling Recommendations

Based on the raltegravir Ctrough PK parameter ratios and 90%CIs, (b) (4)

6.6 P812 – Raltegravir-efavirenz drug interaction study

Study #	P812	**Study Period**	6/30/15 – 9/22/15	EDR Link
Title	A Study to Evaluate the Influence of Efavirenz on a Single Dose of raltegravir in Healthy Subjects			

STUDY SUMMARY (As Reported by the Applicant)

Design

Study Rationale: EFV is not known to induce UGT1A1 (major route of raltegravir metabolism). However, EFV and raltegravir are likely to be coadministered as both are antiretrovirals. This study was done to determine the effect of EFV on the PK of raltegravir.

Study Objectives: Measure the multiple dose raltegravir PK profile alone and in the presence of EFV

General Study Design:
Open-label, randomized, 2-period, fixed-sequence study
Period 1: Single dose of 1200 mg raltegravir at bedtime on day 1
Seven day washout between last dose in Period 1 and first dose in Period 2.
Period 2:
-EFV 600 mg QD at bedtime on days 1-14
-Raltegravir single dose of 1200 mg on day 12 coadministered with EFV

Population: Healthy adults (no clinically significant medical history)	Administration: fasted

Enrolled	21	Completed	19	Discontinued Due to AE	1	PK Population	21 (Period 1) 19 (Period 2)	Safety Population	21

Formulations:
Raltegravir 600 mg tablet: to be marketed formulation
EFV: SUSTIVA® 600 mg tablet

Bioanalytical Method

See section 7.2.

Excluded concomitant substances

Caffeine, alcohol, fruit juice, mustard greens, charbroiled meats, and all medications with the exception of acetaminophen (includes herbal, OTC, vitamins).

Protocol Deviations

The definition of a protocol deviation or their classification as minor versus major was not provided. No major deviations were reported. Minor protocol deviations included:
-failure to document when samples were placed in the freezer (one instance)
-actual PK sampling time differed from scheduled sampling time (14 instances, all but two collected within 10 minutes of scheduled time and all collected within 31 minutes of scheduled time)
-Subject not reclined for at least 4 hours after EFV dosing (two subjects on day 1 of period 2)
-EFV actual dosing time differed from scheduled time (one subject, administered one minute early)

Results:

Demographics

Table 22. Demographics.

Characteristic	Value
Male gender	19 (91%)
Age (years)	35 (21-52)
White race	16 (76%)
Hispanic ethnicity	1 (5%)
BMI (kg/m^2)	27 (21-32)

Values are mean (range) or N (%).

Pharmacokinetics

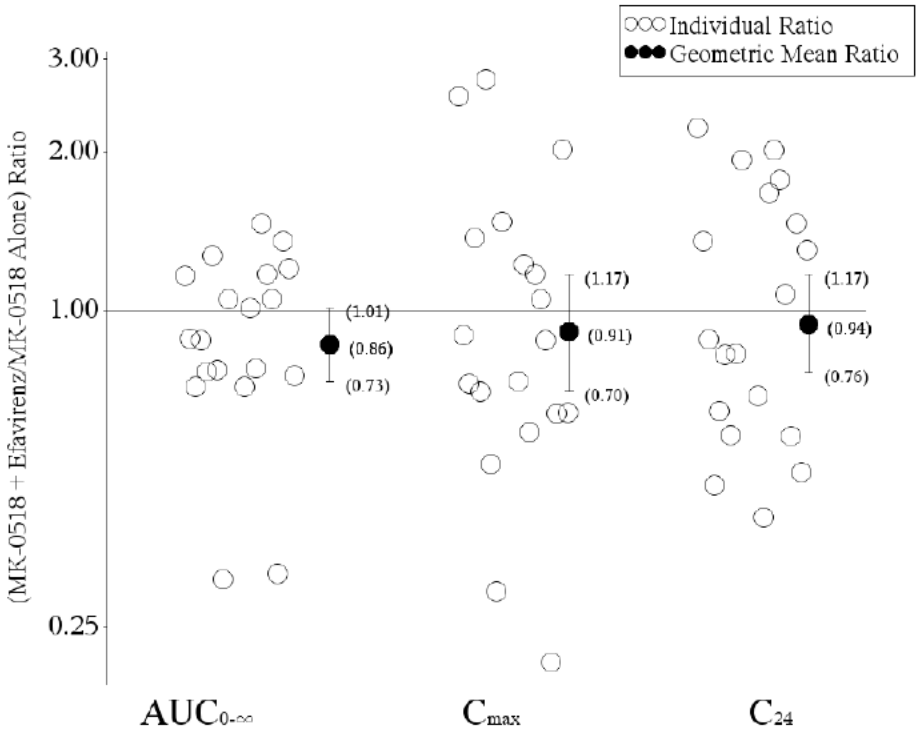
Table 23. Raltegravir PK parameters in the presence and absence of EFV.

MK-0518 Pharmacokinetic Parameters	MK-0518 Alone			MK-0518 + Efavirenz			MK-0518 + Efavirenz/ MK-0518 Alone		Pseudo Within Subject %CV‡
	N	GM	95% CI	N†	GM	95% CI	GMR	90% CI	
$AUC_{0-\infty}$§ (µM•hr)	21	50.1	(42.4, 59.2)	19	43.1	(36.6, 50.9)	0.86	(0.73, 1.01)	29.3
C_{max}§ (µM)	21	15.7	(13.4, 18.5)	19	14.3	(11.4, 17.8)	0.91	(0.70, 1.17)	46.2
C_{24}§ (nM)	21	41.6	(31.8, 54.4)	19	39.2	(29.3, 52.2)	0.94	(0.76, 1.17)	38.9
T_{max}‖ (hr)	21	1.50	(0.50, 4.00)	19	1.50	(0.50, 6.01)			
Apparent terminal $t_{½}$¶ (hr)	21	8.95	95.64	19	8.87	95.23			

MK-0518 Alone: A single oral dose of 1200 mg MK-0518 on Day 1 of Period 1.
MK-0518 + Efavirenz: Multiple oral QD doses of 600 mg efavirenz administered for 14 days, co-administered with a single oral dose of 1200 mg MK-0518 on Day 12 of Period 2.
†Two (2) subjects were discontinued and had no available data for MK-0518 + Efavirenz.
‡Pseudo Within-Subject %CV = 100*sqrt((σ_A^2 + σ_B^2 - 2 σ_{AB})/2), where σ_A^2 and σ_B^2 are the estimated variances on the log scale for the 2 treatment groups, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.
§Back-transformed least-squares mean and confidence interval from the linear mixed-effects model performed on natural log-transformed values.
‖Median (Minimum, Maximum) reported for T_{max}.
¶Geometric mean and geometric coefficient of variation reported for apparent terminal $t_{½}$
GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio

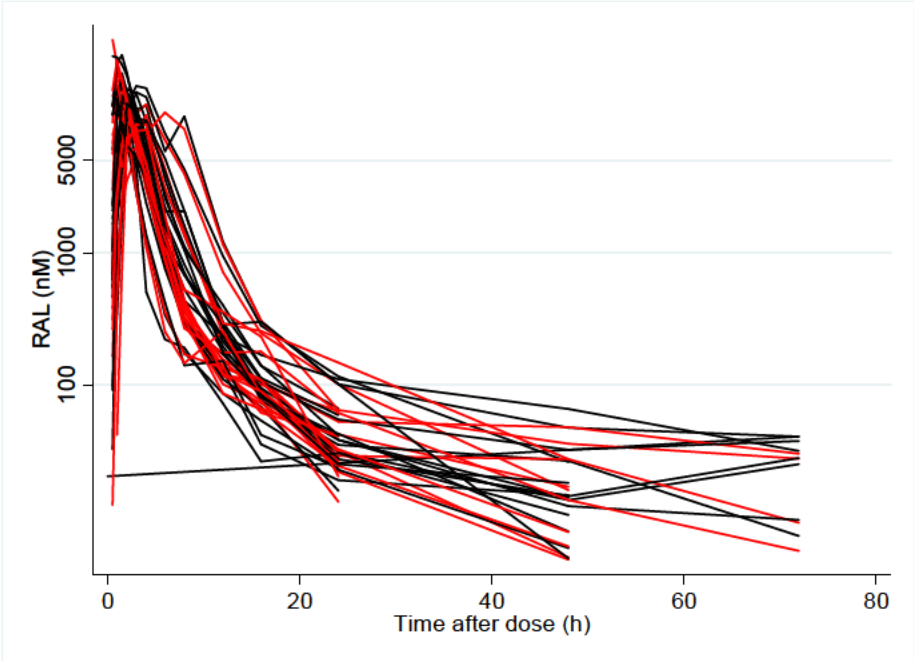
Source: CSR page 46.

Figure 20. Raltegravir PK parameters in the presence and absence of EFV.



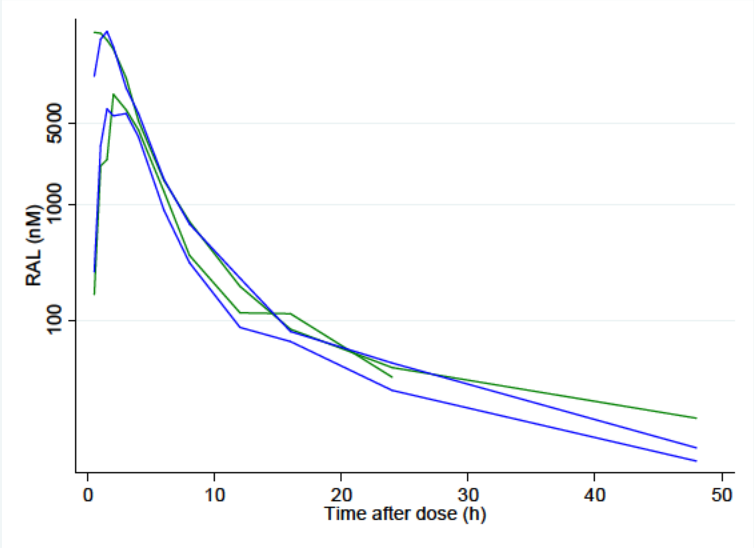
Source: CSR page 48.

Figure 21. Individual subject raltegravir concentration-time profiles in the presence and absence of EFV.



Source: plotted by reviewer. Black = Period 1; Red = Period 2.

Figure 22. Raltegravir concentration-time profiles in the presence and absence of EFV for subjects 0008 and 0018.



Source: plotted by reviewer. Green = Subject 0008; Blue = Subject 0018.

Concomitant medications

No use of excluded concomitant medications was reported during the treatment period of the study.

Safety

One subject discontinued due to an AE of feeling drunk and dizziness and one subject discontinued due to family emergency. There were no reported deaths or serious adverse events. No laboratory abnormalities of clinical importance were reported.

REVIEWER ASSESSMENT

The study design, conduct (bioanalytical methods, protocol deviations), and results were acceptable. Two subjects (0008 and 0018) had significantly reduced raltegravir Cmax and AUC values (ratio <0.32) in the presence of EFV. This reduction appeared to be due to reduced Cmax as the overall shape of the profiles were similar with and without EFV (Figure 22).

Labeling Recommendations

Based on the raltegravir PK parameter ratios and 90%CIs, we agree with the applicant's proposal that there is no clinically significant interaction between raltegravir 1200 mg QD and EFV. This recommendation is consistent with the recommendation of no dose adjustment for coadministration of EFV with raltegravir 400 mg BID. Raltegravir exposures were reduced more by EFV for raltegravir 400 mg versus 1200 mg. When a single dose of raltegravir 400 mg was coadministered with EFV, raltegravir Cmax, AUC, and Cmin ratios were 0.64, 0.64, and 0.79, respectively.

6.7 P823 – Raltegravir-atazanavir drug interaction study

Study #	P823	**Study Period**	7/2/2015 – 9/22/2015	EDR Link
Title	A Study to Evaluate the Influence of Atazanavir on a Single Dose of raltegravir in Healthy Subjects			

STUDY SUMMARY (As Reported by the Applicant)

Design

Study Rationale: ATV is a UGT1A1 inhibitor and UGT1A1 is the major enzyme responsible for raltegravir metabolism. This study was done to determine the effect of ATV on the PK of raltegravir.

Study Objectives: Characterize the plasma PK profile of raltegravir in the presence and absence of ATV

General Study Design:
Open-label, 2-period, fixed-sequence study.
Period 1: Raltegravir single dose of 1200 mg 30 minutes after a moderate-fat breakfast (844 calories, 48% fat) on day 1
Washout: 7 days between dosing in Period 1 and first dosing in Period 2
Period 2:
-ATV 400 mg QD 30 minutes after a moderate-fat breakfast on days 1-9
-Raltegravir 1200 mg coadministered with ATV on day 7

Population: 14 healthy adults | Administration: Fed

Enrolled	14	Completed	12	Discontinued Due to AE	1	PK Population	14	Safety Population	14

Formulations:
Raltegravir 600 mg tablet: to be marketed formulation
REYATAZ® 200 mg capsule

Bioanalytical Method

See section 7.2.

Excluded concomitant substances

Caffeine, alcohol, fruit juice, mustard greens, charbroiled meats, and all medications with the exception of acetaminophen (includes herbal, OTC, vitamins).

Protocol Deviations

The definition of a protocol deviation or their classification as minor versus major was not provided. No major deviations were reported. Minor protocol deviations included:
-"OK to Get Up" form not filled out at the 4.5 hour timepoint on day 1 of periods 1 and 2
-Difference between planned and actual blood collection times (all were within 7 minutes of the scheduled time)
-Difference between planned and actual dose time following meal consumption (<5 minutes late in both instances)
-Use of disallowed medications Benadryl and methylprednisolone by subject 0006 on days 12-16 of Period 2
-Not documented that subject remained seated for 4 hours after dosing for subject 13 on day 7 of period 2
-ECGs done in supine position in error for subject 0014 on day 5 of period 2
-ECGs done less than one minute apart in error for four subjects
-One subject may have consumed excess water within one hour prior to dosing

Results:

Demographics

Table 24. Demographics (n=14).

Characteristic	Value
Male gender	5 (36%)
Age (years)	39 (21-55)
White race	13 (93%)
Hispanic ethnicity	12 (86%)
BMI (kg/m^2)	26 (21-31)

Values are mean (range) or N (%).

Pharmacokinetics

Table 25. Raltegravir PK parameters in the presence and absence of ATV.

	MK-0518 Alone			MK-0518 + Atazanavir			MK-0518 + Atazanavir/ MK-0518 Alone		
MK-0518 Pharmacokinetic Parameters	**N**	**GM**	**95% CI**	**N[¶]**	**GM**	**95% CI**	**GMR**	**90% CI**	**Pseudo Within Subject %CV[†]**
$AUC_{0-\infty}$[‡] (µM•hr)	12	49.6	(40.7, 60.5)	12	83.0	(67.3, 102)	1.67	(1.34, 2.10)	29.7
C_{max}[‡] (µM)	14	18.7	(15.6, 22.4)	12	21.6	(18.0, 26.0)	1.16	(1.01, 1.33)	18.8
C_{24}[‡] (nM)	14	89.6	(67.7, 118)	12	112	(84.4, 150)	1.26	(1.08, 1.46)	20.7
T_{max}[§] (hr)	14	2.00	(0.50, 6.01)	12	3.00	(1.00, 6.06)			
Apparent terminal $t_{½}$[‖] (hr)	12	18.28	46.7	12	12.49	64.2			

MK-0518 Alone: A single oral dose of 1200 mg MK-0518 on Day 1 of Period 1.

MK-0518 + Atazanavir: Multiple oral QD doses of 400 mg atazanavir administered for 9 days, co-administered with a single oral dose of 1200 mg MK-0518 on Day 7 of Period 2.

[†]Pseudo within-subject %CV = 100 x sqrt(($\sigma_A^2 + \sigma_B^2 - 2\sigma_{AB}$)/2), where σ_A^2 and σ_B^2 are the estimated variances on the log scale for the 2 treatment groups, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.

[‡]Back-transformed least-squares mean and confidence interval from the ANOVA linear mixed-effects model performed on natural log-transformed values.

[§]Median and (Minimum, Maximum) reported for T_{max}.

[‖]Geometric mean and percent geometric coefficient of variation reported for apparent terminal $t_{½}$.

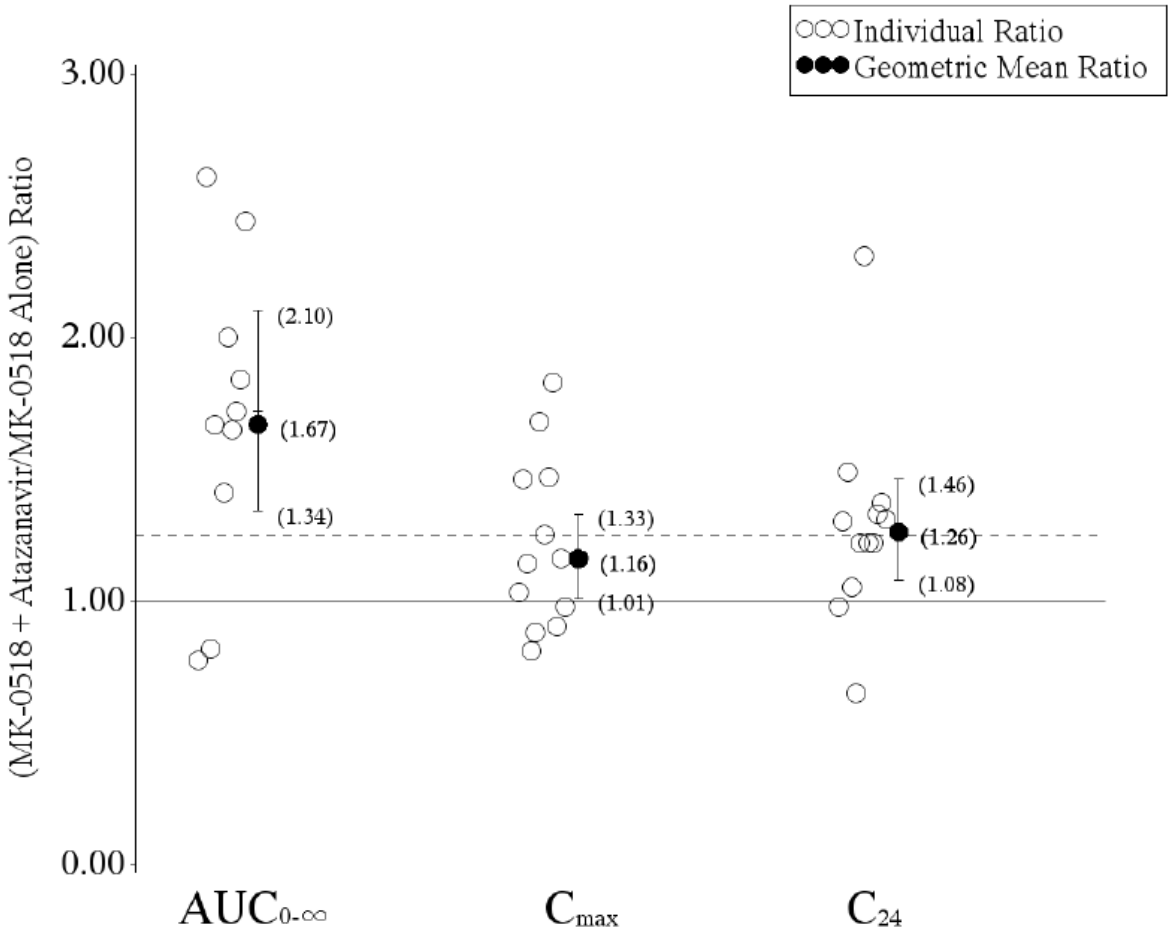
[¶]Two (2) subjects were discontinued and had no available data for MK-0518 + Atazanavir.

GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio

Note: $AUC_{0-\infty}$ and apparent terminal $t_{½}$ were set to missing for 2 subjects receiving MK-0518 alone. Please refer to Section 9.5.4 of the CSR for further details.

Source: CSR page 52.

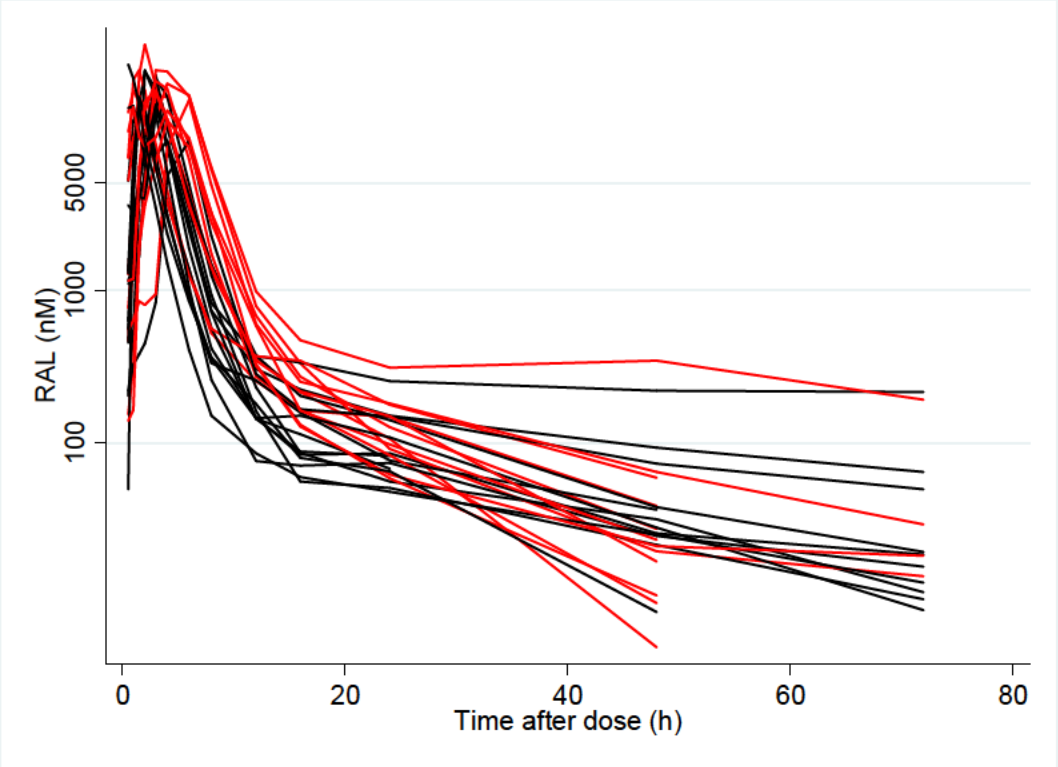
Figure 23. Raltegravir PK parameters in the presence and absence of ATV.



Note: The dotted line represents the reference line at 1.25.

Source: CSR page 54.

Figure 24. Individual subject raltegravir concentration-time profiles in the presence and absence of ATV.



Source: plotted by reviewer. Black = Period 1; Red = Period 2.

Concomitant medications

No use of excluded concomitant medications was reported during the treatment period of the study.

Safety

One subject discontinued due to mild laboratory AE of increased blood bilirubin starting day 2 of period 2 during ATV alone dosing. One subject discontinued after not presenting at check-in for period 2. No SAEs or deaths were reported.

REVIEWER ASSESSMENT

The study design, conduct, and results were acceptable.

Labeling Recommendations

We propose to classify raltegravir 1200 mg QD as having no clinically significant interaction with ATV. See section 3.6.

6.8 P824 – Raltegravir-metal cation-containing antacid drug interaction study

Study #	P824	**Study Period**	10/9/15 – 3/21/16	EDR Link
Title	A Study to Evaluate the Influence of Metal Cation-Containing Antacids on raltegravir Pharmacokinetics in HIV-Infected Subjects on a Stable Raltegravir-Containing Regimen			

STUDY SUMMARY (As Reported by the Applicant)

Design

Study Rationale: Raltegravir contains a divalent metal ion chelating motif. Metal-containing antacids have been found to reduce the exposure of raltegravir 400 mg. This study was conducted to determine the effect of metal-containing antacids TUMS® or MAALOX® on the PK of raltegravir 1200 mg.

Study Objectives: Characterize the plasma PK profile of raltegravir in the presence and absence of TUMS® (administered concomitantly or 12 hours after raltegravir) or MAALOX® (administered 12 hours after raltegravir)

General Study Design:
Non-randomized, single-site, open-label, 4-period, fixed-sequence trial.

- Period 1, Treatment A: 1200 mg QD MK-0518 alone (two tablets of 600 mg)
- Period 2, Treatment B: 3 tablets of TUMS® Ultra Strength (US) 1000 and 1200 mg QD MK-0518 (two tablets of 600 mg) taken concomitantly
- Period 3, Treatment C: 20 mL MAALOX® Maximum Strength (MS) or generic equivalent given 12 hours after administration of 1200 mg QD MK-0518 (two tablets of 600 mg)
- Period 4, Treatment D: 3 tablets of TUMS® Ultra Strength (US) 1000 given 12 hours after administration of 1200 mg QD MK-0518 (two tablets of 600 mg)

Population: HIV-infected adults on a raltegravir-containing antiretroviral (ARV) regimen				Administration: fasted					
Enrolled	20	Completed	18	Discontinued Due to AE	0	PK Population	20	Safety Population	20

Formulations:
Raltegravir: 600 mg tablet: to be marketed formulation
TUMS® (calcium carbonate) Ultra Strength: 1000 mg tablet
Leader Antacid Maximum Strength (generic equivalent to MAALOX®): Each 20 mL dose contained 1600 mg magnesium hydroxide, 1600 mg aluminum hydroxide, and 160 mg simethicone.

Bioanalytical Method

See section 7.2.

Excluded concomitant substances

Excluded medications included ATV, phenobarbital, phenytoin, rifampin, caffeine/xanthine, alcohol, and fruit/fruit juice. All concomitant medications had to be agreed upon by the applicant and investigator.

Protocol Deviations

Major deviations were defined by the applicant as those significantly impacting the completeness, accuracy, and/or reliability of the trial data or that may significantly affect a subject's rights, safety, or well-being. Minor deviations, unlikely to impact the subject's safety/rights or the trial data were not reported. Major deviations included sample taken outside time window (n=6), second sample collected due to hemolyzed sample (n=6), sample drawn after antacid dose (n=1), and serum pregnancy test not performed before dosing (n=1).

Results:

Study population

Two subjects discontinued the study prematurely; one withdrew consent after Period 1, and another was lost to follow-up after completion of Period 4.

Table 26. Demographics (n=20).

Characteristic	Value
Male gender	18 (90%)
Age (years)	50 (29-62)
White race	13 (65%)
Hispanic ethnicity	12 (60%)
BMI (kg/m^2)	26 (20-32)

Values are mean (range) or N (%).

Concomitant medications

There was no reported use of excluded medications or substances. A large number of ARV and non-ARV medications were reported to be used during the treatment period of the study. Most of the non-ARV medications were reported for one subject.

Pharmacokinetics

Table 27. Raltegravir PK parameters in the presence and absence of TUMS® or MAALOX®.

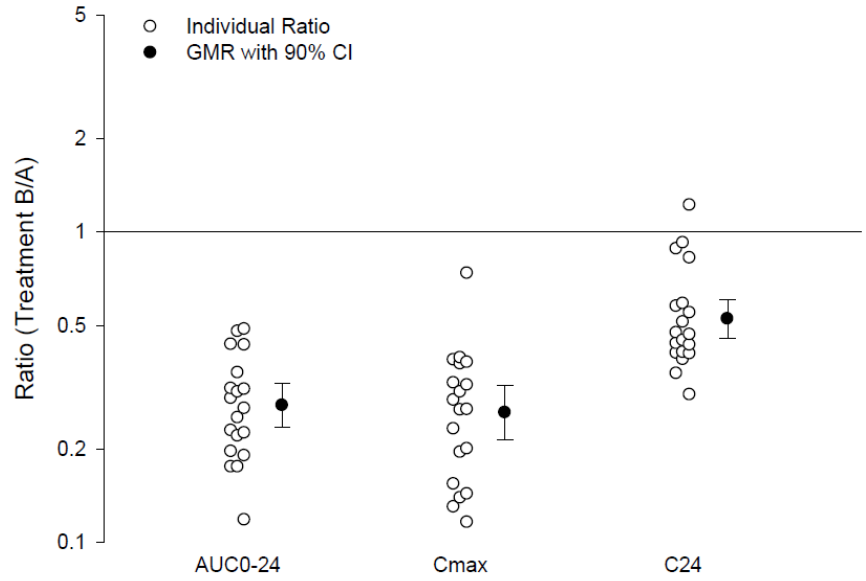
PK Parameter	Treatment	N	$AUC_{0\text{-}24}$‡ (h·µM)	C_{max}‡ (nM)	C_{24}‡ (nM)	T_{max}§ (h)
GM (95% CI)	A	20	53.7 (44.2, 65.2)	20000 (16500, 24300)	75.6 (55.3, 103)	1.50 (0.50, 3.00)
	B	19 [a]	14.8 (12.4, 17.7)	5240 (4230, 6490)	39.6 (29.9, 52.5)	1.50 (1.00, 2.00)
	C	19 [a]	46.3 (36.0, 59.6)	17300 (12800, 23300)	32.0 (23.7, 43.2)	1.50 (0.50, 3.00)
	D	19 [a]	48.5 (39.0, 60.3)	19500 (15900, 24000)	32.4 (24.6, 42.6)	1.50 (0.50, 3.00)
GMR (90% CI)	B/A		0.28 (0.24, 0.32)	0.26 (0.21, 0.32)	0.52 (0.45, 0.61)	
	C/A		0.86 (0.73, 1.03)	0.86 (0.65, 1.15)	0.42 (0.34, 0.52)	
	D/A		0.90 (0.80, 1.03)	0.98 (0.81, 1.17)	0.43 (0.36, 0.51)	
Pseudo Within Subject %CV†	A, B		28.5	35.4	25.9	
	A, C		30.5	50.4	36.8	
	A, D		22.6	32.8	31.0	

† Pseudo Within-Subject %CV = $100 * (\sqrt{(\hat{\sigma}_X^2 + \hat{\sigma}_Y^2 - 2\hat{\sigma}_{XY})/2})$, where $\hat{\sigma}_X^2$ and $\hat{\sigma}_Y^2$ are the estimated variances on the log scale for the two treatment groups, and $\hat{\sigma}_{XY}^2$ is the corresponding estimated covariance, each obtained from the linear mixed effects model.
‡ Back-transformed least squares mean and confidence interval from ANOVA model performed on natural log-transformed values.
§ Median (min, max) reported for T_{max}.
GM=Geometric least-squares mean; GMR=Geometric least-squares mean ratio; CI=Confidence interval; CV= Coefficient of variation.
[a] One (1) subject did not receive treatment B (Period 2), treatment C (Period 3) and treatment D (Period 4) due to consent withdrawal prior to receiving dose in Period 2.

Treatment A: 1200 mg QD MK-0518 alone (two tablets of 600 mg).
Treatment B: 3 tablets of TUMS® Ultra Strength (US) 1000 and 1200 mg QD MK-0518 (two tablets of 600 mg) given concomitantly.
Treatment C: 20 mL MAALOX® Maximum Strength (MS) or a generic substitute given 12 hours after administration of 1200 mg QD MK-0518 (two tablets of 600 mg).
Treatment D: 3 tablets of TUMS® Ultra Strength (US) 1000 given 12 hours after administration of 1200 mg QD MK-0518 (two tablets of 600 mg).

Source: CSR page 55.

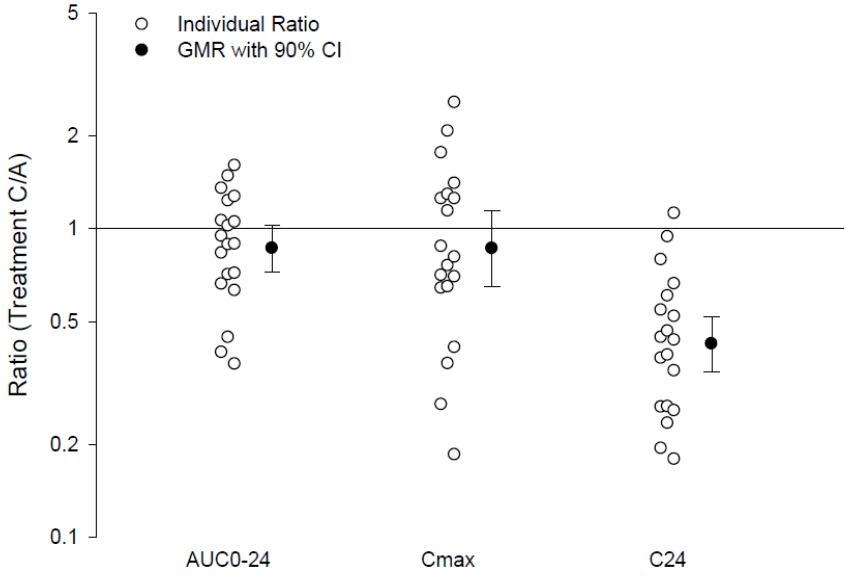
Figure 25. Raltegravir PK parameters in the presence and absence of concomitant TUMS®.



Treatment A: 1200 mg QD MK-0518 alone (two tablets of 600 mg).
Treatment B: 3 tablets of TUMS® Ultra Strength (US) 1000 and 1200 mg QD MK-0518 (two tablets of 600 mg) given concomitantly.

Source: CSR page 59.

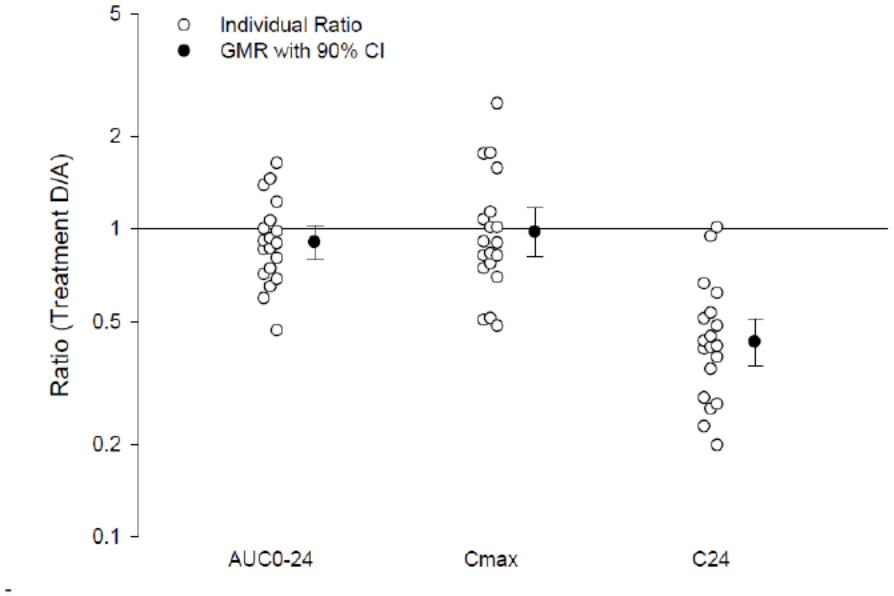
Figure 26. Raltegravir PK parameters in the presence and absence of generic MAALOX® given 12 hours after raltegravir.



Treatment A: 1200 mg QD MK-0518 alone (two tablets of 600 mg).
Treatment C: 20 mL MAALOX® Maximum Strength (MS) or a generic substitute given 12 hours after administration of 1200 mg QD MK-0518 (two tablets of 600 mg).

Source: CSR page 60.

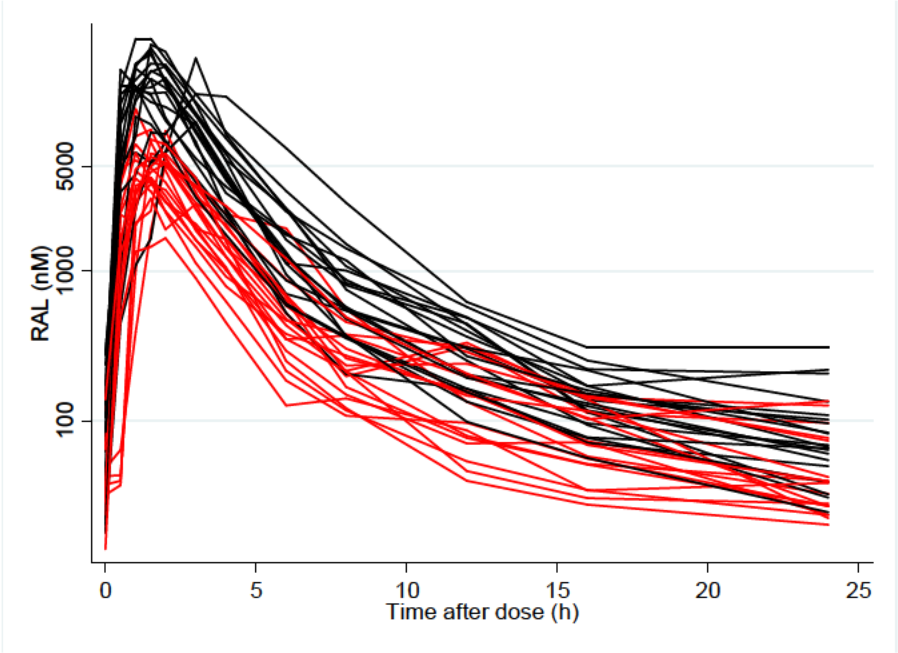
Figure 27. Raltegravir PK parameters in the presence and absence of TUMS® given 12 hours after raltegravir.



Treatment A: 1200 mg QD MK-0518 alone (two tablets of 600 mg).
Treatment D: 3 tablets of TUMS® Ultra Strength (US) 1000 given 12 hours after administration of 1200 mg QD MK-0518 (two tablets of 600 mg).

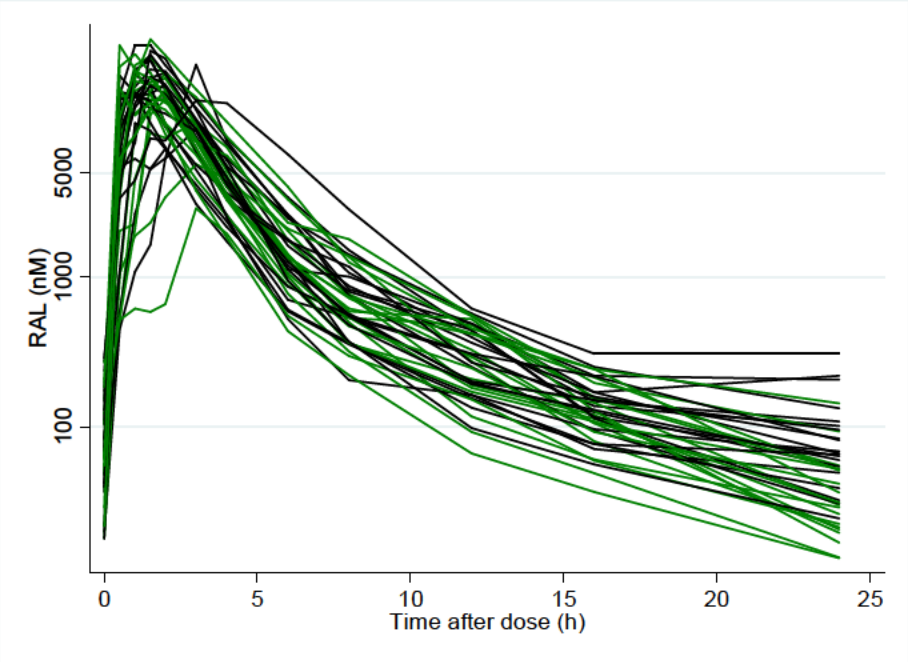
Source: CSR page 61.

Figure 28. Individual subject raltegravir concentration-time profiles in the presence and absence of concomitant TUMS®.



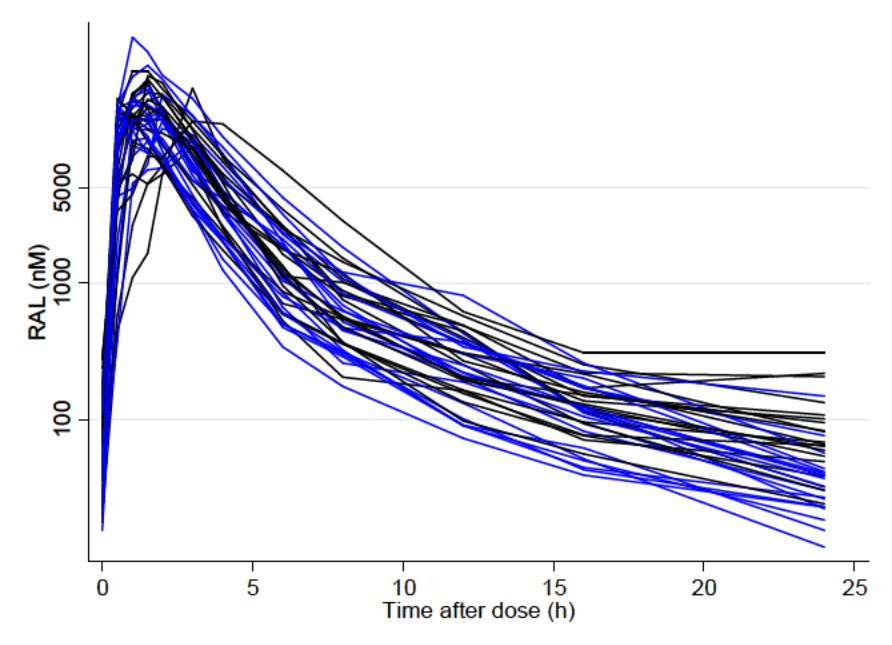
Source: plotted by reviewer. Black = raltegravir alone; Red = raltegravir plus concomitant TUMS®.

Figure 29. Individual subject raltegravir concentration-time profiles in the presence and absence of generic MAALOX® administered 12 hours after raltegravir.



Source: plotted by reviewer. Black = Raltegravir alone; Green = Raltegravir plus generic MAALOX® administered 12 hours after raltegravir.

Figure 30. Individual subject raltegravir concentration-time profiles in the presence and absence of TUMS® administered 12 hours after raltegravir.



Source: plotted by reviewer. Black = Raltegravir alone; Blue = Raltegravir plus TUMS® administered 12 hours after raltegravir.

Safety

No deaths were reported. Four SAEs were reported by one subject (chest pain, dyspnea, orthostatic hypotension, and rash) nine days after period 4 dosing. Rash was considered related to study medication and resolved 21 days after it started. Chest pain, dyspnea, and orthostatic hypotension were considered by the investigator to not be related to study medication. Chest pain and dyspnea resolved after ~2 weeks and orthostatic hypotension after 2 days. This subject was lost to follow up.

REVIEWER ASSESSMENT

The study design, conduct, and results were acceptable.

Labeling Recommendations

In previous studies with raltegravir 400 mg and metal-containing antacids, raltegravir exposures were reduced with Ctrough being the most sensitive PK parameter. In these studies, coadministration with aluminum and magnesium hydroxide antacid resulted in geometric mean Ctrough ratios of 0.37 with simultaneous aluminum and magnesium hydroxide and 0.51 with aluminum and magnesium hydroxide given 6 hours after raltegravir. Coadministration with concomitant calcium carbonate antacid resulted in a Ctrough ratio of 0.68. In current labeling for raltegravir 400 mg BID, coadministration or staggered administration with aluminum and magnesium hydroxide is not recommended and no dose adjustment is recommended for coadministration with calcium carbonate.

Based on the results of the current study with raltegravir 1200 mg, the applicant proposed that coadministration or staggered administration with aluminum and magnesium hydroxide is not recommended and coadministration with calcium carbonate is not recommended. Due to the significantly reduced raltegravir exposures (Ctrough ratios of 0.42 in period C versus A and 0.52 in period B versus A) in the presence of antacid in the current study, we agree with this proposal.

7 Appendix

7.1 Exposure-safety relationships

The applicant stated that no exposure-safety relationships were identified within study PN292. As no AEs were temporally associated with raltegravir administration (i.e. Cmax) and AUC reflects exposure over an entire dosing interval, AUC was selected by the applicant as the most relevant PK parameter for safety assessment.

In our analysis, we evaluated rates of common AEs between the 400 mg BID and 1200 mg QD arms of study PN292. Of note, 1200 mg QD results in a ~6-fold higher Cmax and ~2-fold higher AUC relative to 400 mg BID in healthy adults. Despite the higher Cmax and AUC associated with 1200 mg QD, rates of common AEs by organ class did not appear to be elevated in the QD arm (Table 28). Rates of particular AEs also did not significantly differ between treatment arms (pages 12-15, \\cdsesub1\evsprod\nda022145\0325\m2\27-clin-sum\summary-clin-safety.pdf). Within the 1200 mg QD arm, there was a numerical increase in the proportion of subjects with ≥1 AE with increasing Cmax and AUC quartile (Table 29, Table 30). Taken together, the lack of association with particular AEs across treatment arms in study PN292 is more compelling and we agree that no clear exposure-related AEs were identified in this study.

Table 28. Rates of common AEs by organ class (incidence ≥10%) in study 292.

	Raltegravir 1200 mg QD		Raltegravir 400 mg BID	
	n	(%)	n	(%)
Subjects in population	531		266	
with one or more adverse events	439	(82.7)	231	(86.8)
with no adverse events	92	(17.3)	35	(13.2)
Gastrointestinal disorders	**209**	**(39.4)**	**99**	**(37.2)**
Diarrhoea	58	(10.9)	30	(11.3)
Nausea	60	(11.3)	26	(9.8)
General disorders and administration site conditions	**84**	**(15.8)**	**49**	**(18.4)**
Infections and infestations	**271**	**(51.0)**	**150**	**(56.4)**
Injury, poisoning and procedural complications	**57**	**(10.7)**	**28**	**(10.5)**
Musculoskeletal and connective tissue disorders	**89**	**(16.8)**	**36**	**(13.5)**
Nervous system disorders	**122**	**(23.0)**	**54**	**(20.3)**
Headache	71	(13.4)	29	(10.9)
Psychiatric disorders	**71**	**(13.4)**	**43**	**(16.2)**
Respiratory, thoracic and mediastinal disorders	**76**	**(14.3)**	**40**	**(15.0)**
Skin and subcutaneous tissue disorders	**101**	**(19.0)**	**63**	**(23.7)**

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Note: Raltegravir 1200 mg QD and raltegravir 400 mg BID were administered with TRUVADA™.

Source: page 11, \\cdsesub1\evsprod\nda022145\0325\m2\27-clin-sum\summary-clin-safety.pdf

Table 29. AE summary by raltegravir Cmax quartile in the 1200 mg QD arm of study PN292.

	Raltegravir 1200 mg QD							
	Cmax 1st Quartile		Cmax 2nd Quartile		Cmax 3rd Quartile		Cmax 4th Quartile	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	134		128		132		130	
with one or more adverse events	103	(76.9)	106	(82.8)	111	(84.1)	112	(86.2)
with no adverse event	31	(23.1)	22	(17.2)	21	(15.9)	18	(13.8)
with drug-related† adverse events	30	(22.4)	34	(26.6)	34	(25.8)	28	(21.5)
with serious adverse events	6	(4.5)	5	(3.9)	4	(3.0)	14	(10.8)
with serious drug-related adverse events	0	(0.0)	1	(0.8)	0	(0.0)	0	(0.0)
who died	1	(0.7)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued‡ due to an adverse event	1	(0.7)	0	(0.0)	1	(0.8)	0	(0.0)
discontinued due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued due to a serious adverse event	1	(0.7)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued due to a serious drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

† Determined by the investigator to be related to the drug.
‡ Study medication withdrawn.
Cmax quartiles: Q1= 13100 (nM), median= 16850 (nM), Q3= 20500 (nM).
Cmax= Cmax (nM) at steady state.
Note: Raltegravir 1200 mg QD were administered with TRUVADA™.

Source: page 226, \\cdsesub1\evsprod\nda022145\0325\m2\27-clin-sum\summary-clin-safety.pdf.

Table 30. AE summary by raltegravir AUC quartile in the 1200 mg QD arm of study PN292.

	Raltegravir 1200 mg QD							
	AUC 1st Quartile		AUC 2nd Quartile		AUC 3rd Quartile		AUC 4th Quartile	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	131		133		130		130	
with one or more adverse events	104	(79.4)	109	(82.0)	109	(83.8)	110	(84.6)
with no adverse event	27	(20.6)	24	(18.0)	21	(16.2)	20	(15.4)
with drug-related† adverse events	27	(20.6)	37	(27.8)	34	(26.2)	28	(21.5)
with serious adverse events	6	(4.6)	4	(3.0)	8	(6.2)	11	(8.5)
with serious drug-related adverse events	0	(0.0)	1	(0.8)	0	(0.0)	0	(0.0)
who died	0	(0.0)	0	(0.0)	1	(0.8)	0	(0.0)
discontinued‡ due to an adverse event	0	(0.0)	0	(0.0)	2	(1.5)	0	(0.0)
discontinued due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued due to a serious adverse event	0	(0.0)	0	(0.0)	1	(0.8)	0	(0.0)
discontinued due to a serious drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

† Determined by the investigator to be related to the drug.
‡ Study medication withdrawn.
AUC quartiles: Q1= 42250 (nM*h), median= 54600 (nM*h), Q3= 69000 (nM*h).
AUC= AUC0-24h (nM*h) at steady state.
Note: Raltegravir 1200 mg QD were administered with TRUVADA™.

Source: page 227, \\cdsesub1\evsprod\nda022145\0325\m2\27-clin-sum\summary-clin-safety.pdf.

7.2 Bioanalytical methods

Raltegravir bioanalytical method validation and sample analysis reports were reviewed for the six studies included in the popPK model (PN292, P290, P291, P812, P823, and P824) (Table 31). Because raltegravir is not known to act as a perpetrator drug interactions, the PK of concomitant medications were not evaluated in drug interaction studies P812, P823, or P824. Bioanalytical methods were considered to be acceptable if they met the criteria described in FDA guidance (https://www.fda.gov/downloads/Drugs/Guidances/ucm368107.pdf). All studies measured plasma raltegravir concentrations using method DM-712A (type: LC/MS/MS, calibration range = 2-1000 ng/mL), which we verified was validated per FDA guidance. Sample analysis for all studies was acceptable. The only sample analysis deficiency was in study P291 where an analyte peak was observed in several blank wells, indicating potential carryover. The peak areas of these interfering peaks did not exceed the peak area of the LLOQ. As only five samples out of 532 in study P291 had concentrations within 5-fold of the LLOQ, these interfering peaks are unlikely to impact reported raltegravir concentrations in this study. One observation from sample analysis of study PN292 was that a large number of samples were reassayed due to "suspected or actual sample processing error". However, upon checking a subset of the reassayed values, many values were close to the original value (Link 1, page 91-140).

Table 31. Links to raltegravir bioanalytical method validation and sample analysis reports.

Study	Links 1-6
PN292	\\cdsesub1\evsprod\nda022145\0325\m5\53-clin-stud-rep\535-rep-effic-safety-stud\qd1200\5351-stud-rep-contr\p292v01\publications-based-on-trial.pdf
P290	\\cdsesub1\evsprod\nda022145\0325\m5\53-clin-stud-rep\531-rep-biopharm-stud\5311-ba-stud-rep\p290\publications-based-on-study.pdf
P291	\\cdsesub1\evsprod\nda022145\0325\m5\53-clin-stud-rep\531-rep-biopharm-stud\5311-ba-stud-rep\p291\publications-based-on-study-1.pdf
P812	\\cdsesub1\evsprod\nda022145\0325\m5\53-clin-stud-rep\532-rep-stud-pk-human-biomat\5322-rep-hep-metab-interact-stud\p812\publications-based-on-trial.pdf
P823	\\cdsesub1\evsprod\nda022145\0325\m5\53-clin-stud-rep\532-rep-stud-pk-human-biomat\5322-rep-hep-metab-interact-stud\p823\publications-based-on-study.pdf
P824	\\cdsesub1\evsprod\nda022145\0325\m5\53-clin-stud-rep\532-rep-stud-pk-human-biomat\5322-rep-hep-metab-interact-stud\p824\publications-based-on-trial.pdf

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