Clinical Review
Cross Disciplinary Team Leader Review

Date	April 20, 2017
From	Sarita Boyd, PharmD (Clinical Reviewer) Adam Sherwat, M.D. (Medical Team Leader)
Subject	Clinical and CDTL Review
NDA/BLA # **Supplement#**	NDA 22145 S-36 NDA 205786 S-4 NDA 203045 S-13
Applicant	Merck
Date of Submission	July 27, 2016
PDUFA Goal Date	May 27, 2016
Proprietary Name / **Established (USAN) names**	Isentress HD / raltegravir
Dosage forms / Strength	Film-coated tablet / 600 mg
Proposed Indication(s)	Indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in patients 4 weeks of age and older (unchanged)
Recommended:	Approval

1 Introduction

This review summarizes the main issues for NDAs 22145 S-36, 205786 S-4, and 203045 S-13, which include 48-week efficacy and safety data from ONCEMRK (PN292): *A Phase III Multicenter, Double-Blind, Randomized, Active Comparator-Controlled Clinical Trial to Evaluate the Safety and Efficacy of Reformulated Raltegravir 1200 mg Once Daily Versus Raltegravir 400 mg Twice Daily, Each in Combination with Truvada™, in Treatment-Naïve HIV-1 Infected Subjects.*

2 Background

Isentress (raltegravir) 400 mg film-coated tablet received Accelerated Approval and Traditional Approval on October 12, 2007, and January 29, 2009, respectively, as the first HIV-1 integrase inhibitor. On July 9, 2009, raltegravir received approval for use in treatment-naïve patients based on 48-week efficacy and safety results from the Phase 3 trial STARTMRK (PN021), which showed non-inferiority of raltegravir compared to efavirenz each in combination with tenofovir/emtricitabine (TDF/FTC). The current approved US package insert (USPI) contains 5-year (240-week) efficacy and safety data from STARTMRK. The current USPI also provides dosing recommendations with raltegravir 400 mg tablets for pediatric patients weighing at least 40 kg; with raltegravir chewable tablets for those weighing

at least 25 kg; and with raltegravir for oral suspension for those at least 4 weeks of age and weighing less than 25 kg. Dosing frequency with approved formulations to date is twice daily.

The Applicant previously conducted a Phase 3 trial (PN071, QDMRK) comparing once daily raltegravir at a dosage of 800 mg (2 x 400 mg tablets) to twice daily raltegravir, each in combination with FTC/TDF, in treatment-naïve adults. Failure to meet the primary endpoint of non-inferiority at Week 48 resulted in termination of the trial in 2010. Non-inferiority was predefined as a lower bound of the 95% confidence interval (CI) for the treatment difference (once daily minus twice daily) not less than -10%. The proportion of participants achieving HIV RNA <50 copies/mL with once daily 800 mg raltegravir and twice daily raltegravir was 83% and 89%, respectively, with a treatment difference of -5.7% [95% CI (-10.7%, -0.83%)]. Thus, the lower bound of the 95% CI was less than -10%.

After failure of the once daily 800 mg raltegravir dosage in QDMRK, the Applicant continued pursuit of once daily dosing by evaluating a higher dosage of 1200 mg in several Phase 1 trials and one Phase 3 trial ONCEMRK, which are the basis for this submission.

Since the initial approval of raltegravir, two additional HIV integrase inhibitors, elvitegravir (EVG), and dolutegravir, have been approved. Notably, products containing dolutegravir or elvitegravir as part of a fixed-dose single-tablet regimen dosed once daily are available for HIV treatment-naïve patients.

3 CMC/Biopharmaceutics

Please refer to the CMC and Biopharmaceutics reviews by Drs. Allan Fenselau and Yang Zhao, respectively, for complete details. Both reviewers found no deficiencies and recommend approval.

3.1 Drug Substance

The manufacturing process for the drug substance raltegravir used in the 600 mg tablet is the same as that used in the currently approved 400 mg tablet except the drug substance is (b) (4).

3.2 Drug Product

The drug product (600 mg tablet) is a faster eroding and higher drug load formulation than the 400 mg tablet. The composition of the product is raltegravir and the following excipients: hypromellose 2910, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate. The tablets are coated with (b) (4) for color differentiation.

3.3 Impurities/Degradants

Two impurities ((b) (4)) were observed above the reporting threshold from initial release in variable conditions in stability studies. Both impurities remained stable

through 12 months of long term conditions and 6 months of accelerated conditions, and both impurities remained below the proposed acceptance criteria.

3.4 Stability and Shelf Life

Based on stability and long-term storage data, CMC recommends approval of a 24 month shelf life when stored under the specified conditions.

3.5 Facilities Inspection

Two approved facilities currently manufacture the raltegravir drug substance. Because (b) (4) was added to the manufacturing process, the additional site for (b) (4) was inspected. Dr. Fenselau states in his review that the Overall Manufacturing Inspection Recommendations by the Office of Process and Facilities recommended Approval based on the inspection profile of the (b) (4) facility.

4 Nonclinical Pharmacology/Toxicology

The submission contains no new nonclinical data. The application for once daily raltegravir (1200 mg) is fully supported by nonclinical studies previously conducted and reviewed for twice daily raltegravir. The Applicant, however, proposed changes to the pregnancy and lactation sections in compliance with the Pregnancy and Lactation Labeling Rule (PLLR). Please refer to the Pharmacology/Toxicology review by Dr. Ita Yuen for additional details.

5 Clinical Pharmacology/Biopharmaceutics

Please refer to the Clinical Pharmacology review by Dr. Mario Sampson for complete details.

5.1 General Pharmacology/Pharmacokinetic Properties

Once daily raltegravir 1200 mg has a median time to maximum concentration (Tmax) of 1.5 to 2 hours when fasting compared to 3 hours with twice daily raltegravir. Metabolism and elimination of once daily raltegravir and twice daily raltegravir is similar. The major elimination pathway is via UGT 1A1-mediated glucuronidation. The apparent terminal half-life is 9 to 12 hours. Steady state is reached in 2 days with little or no accumulation after multiple dose administration. Because a high fat meal effects once daily raltegravir to a lesser extent compared to twice daily raltegravir, the once daily formulation of raltegravir may also be administered without regard to food.

Once daily raltegravir 1200 mg results in a lower mean minimum plasma concentration (Cmin) but a higher area under the concentration-time curve (AUC_{24}) and a higher maximum plasma concentration (Cmax) compared to twice daily raltegravir 400 mg. For the purpose of this review, Cmin and Ctrough (trough plasma concentration) are used interchangeably.

5.2 Population Pharmacokinetic Model

The Applicant developed a pharmacokinetics (PK) model using data from participants who received once daily raltegravir 1200 mg in five Phase 1 trials and the Phase 3 trial ONCEMRK. Dr. Sampson, Clinical Pharmacology Reviewer, assessed the model and concluded it was sufficient to provide individual subject exposures for use in exposure-response analyses as well as for scaling to a pediatric population to provide predictions of pediatric exposures upon once daily raltegravir 1200 mg dosing. Please refer to Section 10 of this review for evaluation of once daily raltegravir for use in the pediatric population, including modeling and simulation assessments.

5.3 Exposure-Efficacy Analyses

The following two tables illustrate exposure-efficacy assessments based on AUC and Cmax followed by Ctrough).

Table 1. Response Rates for Once Daily Raltegravir 1200 mg 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: Clinical Pharmacology Review Dr. Sampson

Table 2. Response Rates for Once Daily Raltegravir 1200 mg as a Function of Trough Concentrations (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: Clinical Pharmacology Review Dr. Sampson

Reviewer Comment: Based on Dr. Sampson's exposure-response analyses, none of the PK parameters Cmax, AUC, or Cmin impacted virologic response rates in ONCEMRK suggesting an absence of any clinically meaningful exposure-response relationship.

5.4 Exposure-Safety Analyses

The Applicant provided exposure-safety assessments based on ONCEMRK. Clinical Pharmacology Reviewer Dr. Sampson concluded that despite an approximate 6-fold higher Cmax and 2-fold higher AUC with once daily raltegravir compared to twice daily raltegravir in healthy adults, the rates of AEs between groups in ONCEMRK were similar. Furthermore, AUC was selected as the most relevant PK parameter for safety assessment because no AEs were temporally associated with acute raltegravir administration (i.e. Cmax) and AUC reflects exposure over an entire dosing interval.

Reviewer Comment: Based on a review of the Applicant's report of various categories of AEs for each quartile of AUC and Cmax in ONCEMRK, I agree with Dr. Sampson's assessment that no clear exposure-related AEs were identified.

5.5 Drug-Drug Interactions

The Applicant conducted drug-drug interaction (DDI) studies to evaluate the individual effect of aluminum/magnesium hydroxide antacids, calcium carbonate antacids, atazanavir 400 mg, and efavirenz on the PK of once daily raltegravir 1200 mg. Based on the study results or extrapolation from DDI studies with raltegravir 400 mg, the Clinical Pharmacology review team conclude that coadministration of once daily raltegravir 1200 mg with calcium carbonate antacids, rifampin, tipranavir/ritonavir, or etravirine is not recommended. These recommendations are contrary to the current recommendations for raltegravir 400 mg twice daily which may be coadministered with each of these medications with or without dosage adjustment. The rationale for differing recommendations is not that the magnitude of interaction is greater with once daily 1200 mg compared to twice daily 400 mg raltegravir (observed or expected) but that the clinical impact is greater on the once daily dosage. Cmin with once daily compared to twice daily raltegravir is lower in the absence of DDIs and an additional reduction in Cmin due to these DDIs may result in subtherapeutic raltegravir concentrations and an increased risk of virologic failure.

Based on DDI study results, the Clinical Pharmacology review team concluded the following recommendations for once daily raltegravir, which are the same as for twice daily raltegravir.

- Coadministration of aluminum/magnesium hydroxide antacids and raltegravir 1200 mg once daily is not recommended.
- No dosage adjustment is recommended when atazanavir or atazanavir/ritonavir is coadministered with raltegravir 1200 mg once daily because the increase in raltegravir AUC is not expected to alter the safety profile of raltegravir.
- No dosage adjustment is recommended when efavirenz is coadministered with efavirenz.

Reviewer Comment: We agree with the clinical comments proposed by the Clinical Pharmacology team for DDIs in Section 7.

5.6 Interchangeability of 400 mg and 600 mg Tablets to Create a 1200 mg Once Daily Dose

The Applicant proposes (b) (4) . Clinical Pharmacology Reviewer Dr. Sampson concluded that Ctrough values were similar and above 45 nM and that AUC and Cmax values were similar for the majority of participants receiving 3 x 400 mg compared to 2 x 600 mg (healthy participants in Phase 1 trial PN291 and HIV-infected participants in ONCEMRK). Therefore, constructing the 1200 mg dose from three 400 mg tablets or from two 600 mg tablets would not impact efficacy or safety of once daily raltegravir.

Reviewer Comment: We agree with Dr. Sampson that the Applicant's proposed labeling is not supported (b) (4) .

6 Clinical Microbiology

Raltegravir inhibits HIV-1 integrase, an HIV-1 encoded enzyme required for viral replication, thereby inhibiting integration of HIV-1 DNA into the host cell genome.

HIV-1 integrase coding sequence mutations contributing to raltegravir resistance generally include amino acid substitutions Y143C/H/R, Q148H/K/R, or N155H plus one or more additional substitutions (i.e., L74M, E92Q, Q95K/R, T97A, E138A/K, G140A/S, V151I, G163R, H183P, Y226C/D/F/H, S230R, and D232N). Substitutions E92Q and F121C occasionally occur in the absence of substitutions at Y143, Q148, or N155 in raltegravir-treated failures.

No participants in ONCEMRK at baseline had primary raltegravir resistance-associated substitutions, including E92 and F121, or primary FTC or TDF resistance substitutions. Ten subjects, four in the once daily group and six in the twice daily group, had EVG resistance-associated substitutions, all of whom achieved HIV RNA <40 copies/mL by Week 48.

Through Week 48, the rate of virologic failure was 8% in each group: 42/527 and 22/264 participants with once daily raltegravir and twice daily raltegravir, respectively. Resistance results were available in 14/42 and 3/22 virologic failures in each group, respectively. Raltegravir resistance-associated substitutions were observed in 4/14 and 0/3 virologic failures in the once daily raltegravir and twice daily raltegravir groups, respectively. Primary substitution N155H (with or without additional integrase substitutions) was observed in three failures; and E92Q and L74M were observed in the fourth failure in the once daily raltegravir group. FTC resistance-associated substitution M184V appeared in 5/14 and 0/3 participants in the once daily raltegravir and twice daily raltegravir groups, respectively. TDF resistance-associated substitutions (e.g., K65R) were not observed in any of the virologic failures. Please refer to Dr. Sung Rhee's virology review for additional details.

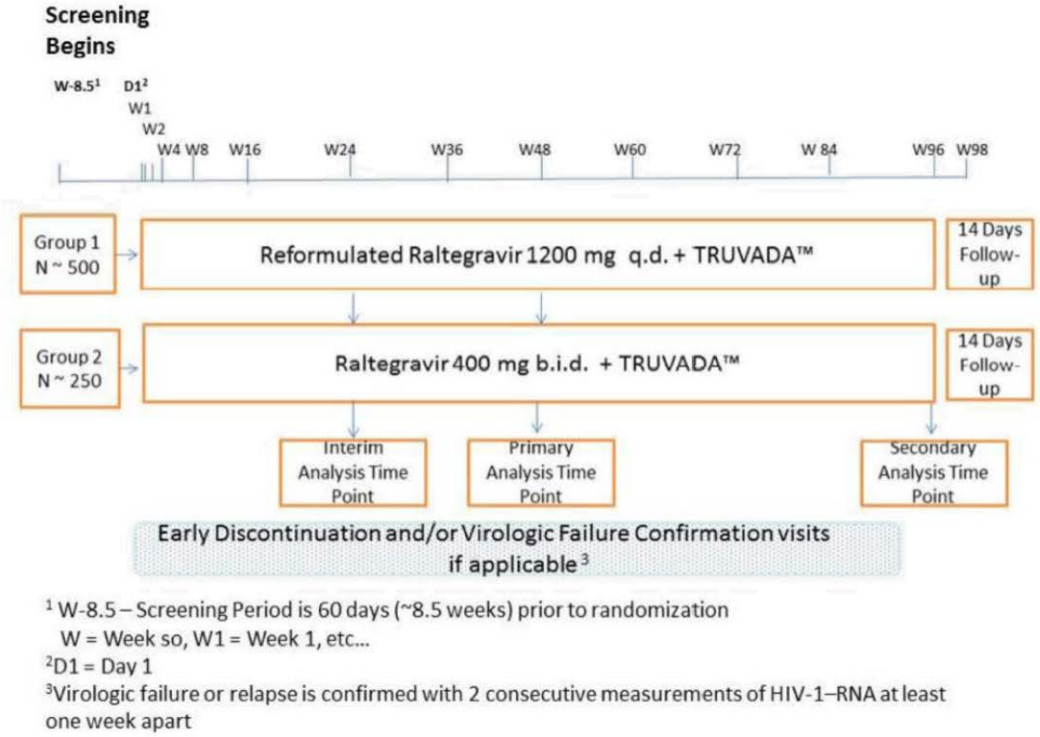
Reviewer Comment: The rate of virologic failure was similar in both treatment groups. The number of virologic failures with available resistance test results is too few to conclude that failure with once daily raltegravir increases development of resistance-associated substitutions compared to failure with twice daily raltegravir. The available results do not raise significant concerns about virologic failure or development of resistance-associated substitutions for once daily raltegravir compared to twice daily raltegravir. However, we will reassess the data at the scheduled completion of ONCEMRK (i.e., Week 96) to confirm the durability of the virologic response in the once daily treatment group and assess for any differences in the development of resistance-associated substitutions between treatment groups.

7 Clinical/Statistical- Efficacy

7.1 Overview

ONCEMRK is an ongoing multicenter, double-blind, randomized (2:1), active-controlled trial evaluating raltegravir 1200 mg once daily compared with raltegravir 400 mg twice daily, each in combination with FTC/TDF, in treatment-naïve HIV-infected adults. Randomization was stratified according to screening HIV RNA (≤ or >100,000 copies/mL) and chronic hepatitis B and/or C virus (HBV and/or HCV) infection, resulting in four possible randomization strata. The primary endpoint is the proportion of participants achieving HIV RNA <40 copies/mL at Week 48.

Figure 1. ONCEMRK Trial Design



[1] W-8.5 – Screening Period is 60 days (~8.5 weeks) prior to randomization
W = Week so, W1 = Week 1, etc...
[2]D1 = Day 1
[3]Virologic failure or relapse is confirmed with 2 consecutive measurements of HIV-1–RNA at least one week apart

Source: MK-0518 Clinical Study Report P292V01

The trial began on May 26, 2014, and is ongoing in the extension phase to Week 96. The sNDA contains Week 48 analysis with a data cutoff date of December 21, 2015. The trial is being conducted at 139 centers across Argentina (3), Australia (5), Belgium (4), Canada (7), Chile (4), Colombia (5), France (9), Germany (10), Guatemala (4), Ireland (1), Israel (5), Italy (9), Malaysia (4), Peru (3), the Philippines (1), Portugal (5), Puerto Rico (3), Russia (8), South Africa (5), South Korea (1), Spain (8), Switzerland (4), Taiwan (3), Thailand (4), the United Kingdom (5), and the United States (31). The Applicant states the trial was conducted in conformance with Good Clinical Practice (GCP) and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

7.2 Subject Disposition

Of the 913 subjects screened, 802 were randomized (2:1) of which five subjects did not receive any study drug. The remaining 797 subjects received at least one dose of therapy (531 once daily, 266 twice daily) and comprise the full analysis set (FAS) population used in the efficacy analyses. Most subjects in the FAS completed 48 weeks of treatment: 92% in the once daily raltegravir group and 91% in the twice daily raltegravir group.

7.3 Protocol Deviations

For this trial the Applicant defines a major protocol deviation as any protocol deviation which may significantly/adversely impact the completeness, accuracy, and/or reliability of the trial data or that may significantly/adversely affect a participant's rights, safety, or well-being. The Applicant reports and summarizes 349 major protocol deviations none of which they consider to meaningfully impact the completeness, accuracy, and/or reliability of the trial results. No treated participants are excluded from any analysis. The number and type of protocol deviations were factors in selecting study sites for clinical inspection (see Section 11).

The Applicant reports deviations with GCP and Good Documentation Practice (GDP) at Site 157, which enrolled 11 participants (one of these participants transferred to another site approximately four months after randomization). Notably, there was a delay in reporting of AEs which resulted in exclusion of these AEs from the data included in the Week 48 database lock. These AEs were included in the Safety Update Report later submitted to the sNDA. This site was selected for a clinical inspection (see Section 11).

Reviewer Comment: The number and categories of the major protocol deviations in totality are concerning. However, the reported summaries of all 349 major protocol deviations support the Applicant's conclusion that the deviations do not meaningfully impact the trial results or participant safety.

7.4 Demographics

The table below describes the baseline demographics and characteristics for participants in the FAS. HIV RNA and HBV/HCV designations varied in each group from the time of screening

to baseline, and the table includes baseline designations only. Please see Dr. LaRee Tracy's statistical review for additional details.

Table 3. ONCEMRK: Baseline Demographics and Characteristics (FAS)

Characteristic	Raltegravir 1200 mg QD + TRUVADA (n=531)	Raltegravir 400 mg BID + TRUVADA (n=266)
	%	%
Sex		
Male	82.9	88.0
Female	17.1	12.0
Age		
Mean (SD)	35 (10)	37 (11)
18-64	99.2	98.9
≥65	0.8	1.1
Race		
White	56.7	64.7
Black	18.5	13.5
Asian	15.6	15.0
Multiple	8.7	5.3
American Indian/Alaska Native	0.6	1.1
Native Hawaiian or Other Islander	0	0.4
CD4 cell count/mm^3		
Mean CD4 (SD)	407 (213)	429 (217)
Median CD4	380	416
CD4 ≤50	1.7	2.3
CD4 >50 and ≤200	11.3	11.7
CD4 >200	87.0	86.0
HIV-1 RNA copies/mL		
Mean (SD)	132757 (316174)	120976 (218852)
HIV RNA (log10 c/mL) (SD)	4.61 (0.69)	4.61 (0.68)
HIV RNA ≤100,000	71.9	71.1
HIV RNA >100,000	28.1	29.0
Hepatitis B and/or C Virus		
HBV Positive	2.1	1.5
HCV Positive	0.8	1.9
HBV or HCV Positive*	2.8	3.0
Region		
Europe	37.7	42.1
North America	23.5	25.9
Asia/Pacific	16.2	17.3
Latin America	14.5	9.8
Africa	8.1	4.9

*One subject positive for HCV and HBV infection
Source: FDA Statistical Reviewer Dr. LaRee Tracy

Reviewer Comment: Baseline demographics and characteristics were generally similar between groups. A difference of at least 5% between groups was present for sex and race: the once daily raltegravir group had fewer male participants, fewer White participants, and more

Black participants. Efficacy and safety between groups based on sex and race are discussed in the Sections 7.5 and 8.8.1, respectively.

7.5 Efficacy Results

The following two tables display Week 48 results overall and by subgroup, respectively, using the FDA snapshot approach. Due to small numbers of participants with HBV and/or HCV co-infection at baseline, subgroup analysis in this population was not performed. Subgroup analysis was performed for baseline HIV RNA rather than screening HIV RNA, the latter of which was used for stratification at the time of randomization. Statistical reviewer Dr. Tracy assessed concordance between screening and baseline HIV RNA and found discordance in 13% and 11% of participants in the once daily raltegravir and twice daily raltegravir groups, respectively.

Table 4. ONCEMRK W48: Primary Analysis of HIV-1 RNA

Based on FDA Snapshot analysis approach	**Raltegravir 1200 mg once daily + FTC/TDF (n=531)**		**Raltegravir 400 mg twice daily + FTC/TDF (n=266)**		**Diff (once daily-twice daily)* 95% CI**
	n	**%**	**n**	**%**	
HIV-1 RNA <40 c/mL at W48	472	88.9	235	88.3	0.51 (-4.2, 5.2)
HIV-1 RNA ≥40 c/mL at W48	29	5.5	16	6.0	
No HIV-1 RNA measured at W48	30	5.6	15	5.6	
Discontinued due to AE/death	6	1.1	6	2.3	
On trial but missing assessment	4	0.7	2	0.8	
Discontinued due other reasons#	20	3.8	7	2.6	

#Other includes: lost to follow-up (n=6 QD; n=2 BID), non-compliance with study drug (n=3 QD, n=1 BID); physician decision to withdrawal participant (n=2 QD); pregnancy (n=1 QD); participant withdrawal (n=8 QD, n=4 BID)
*stratum-adjusted MH difference in proportion with harmonic mean of sample size per group for each stratum (screening HIV-1 RNA ≤100000 c/mL or HIV-RNA >100000 c/mL)
Source: FDA Statistical Reviewer Dr. LaRee Tracy

Reviewer Comment: *The Week 48 virologic outcome analysis based on the FDA snapshot method show once daily raltegravir is non-inferior to twice daily raltegravir. The point estimate and the 95% confidence interval for the difference between groups are convincing, with a lower bound well above -10%. The percentage of participants with confirmed virologic failure (HIV RNA ≥40 copies/mL) was also similar in both groups. The results demonstrate that the lower Cmin levels observed with once daily raltegravir (1200 mg) compared to twice daily raltegravir adequately achieve and maintain viral suppression through 48 weeks of treatment. Participants who discontinued study due to physician decision or participant withdrawal (as noted in Table 4 above), did so for primarily administrative reasons and not for AEs deemed related to the use of raltegravir.*

Table 5. ONCEMRK W48: HIV-RNA <40 c/mL by Subgroup (NC=F)

	Raltegravir 1200 mg once daily + FTC/TDF (n=531)		Raltegravir 400 mg twice daily + FTC/TDF (n=266)		Diff (95% CI)
	n	%	n	%	
Sex					
Males	440	393 (89.3)	234	206 (88.0)	1.3 (-3.7, 6.5)
Females	91	79 (86.8)	32	29 (90.6)	-3.8 (-15.1, 10.7)
Baseline Age (median of 35 years)					
Age < 35	251	230 (91.6)	139	127 (91.4)	0.3 (-5.4, 6.4)
Age ≥ 35	280	242 (86.4)	127	108 (85.0)	1.4 (-5.7, 9.1)
Race					
Asian	83	76 (91.6)	40	36 (90.0)	1.6 (-9.1, 14.1)
Black/AA	98	83 (84.7)	36	29 (80.6)	4.1 (-9.8, 19.9)
Other	49	43 (87.8)	18	17 (94.4)	-6.7 (-19.9, 12.5)
White/Caucasian	301	270 (89.7)	172	153 (89.0)	0.7 (-4.9, 6.8)
Baseline HIV RNA					
≤ 100,000 c/mL	382	348 (91.1)	189	173 (91.5)	-0.4 (-5.2, 4.7)
>100,000 c/mL	149	124 (83.2)	77	62 (80.5)	2.7 (-7.7, 13.7)

Reviewer Comment: Efficacy results by sex, age, and race were similar between groups, and clinically meaningful trends were not apparent for any demographic receiving once daily raltegravir compared to twice daily raltegravir. The trial included an insufficient number of participants 65 years of age and older (6 participants across both groups) to perform analysis in this subpopulation. Efficacy results by baseline HIV RNA were also similar.

Participants in both groups of the FAS experienced similar increases in CD4 cell count from baseline through Week 48. The mean increases from baseline CD4 cell count in participants receiving once daily raltegravir compared to twice daily raltegravir were 218 and 221 cells/mm^3, respectively.

8 Safety

8.1 Overview and Methods

The source of data for the safety review is ONCEMRK (Protocol 292). The Applicant's data cutoff date for the original sNDA submission was February 10, 2016. Using the Applicant's SDTM and ADaM datasets and applying a specific Week 48 cutoff (Day 1 through 378), the primary reviewer conducted all safety analyses presented in this section in JReview 11.0

and/or JMP Clinical 5.1, unless otherwise specified. The Applicant used MedDRA version 18.1 for coding.

Four months after sNDA submission, the Applicant submitted a Safety Update Report (SUR) which contains additional safety data through July 8, 2016. The SUR also includes Week 48 safety information for Site 157 some of which was excluded in the original sNDA submission (see Section 7.3); these data are incorporated in Week 48 analyses below unless otherwise indicated. Deaths, SAEs, and discontinuations due to AE that occurred during the SUR period (Day >378) at all sites are summarized in each respective section.

Presentation and discussion of deaths, serious adverse events (SAEs), and discontinuations due to AE include clinical and laboratory AEs combined. As a result, the findings presented in this review may differ slightly from the Applicant's report which separates clinical AEs and laboratory AEs (i.e., reported PTs contained in the Investigations SOC). Other safety results in this review separate clinical and laboratory AEs, consistent with the Applicant's approach. Overall, the findings are generally consistent with those of the Applicant.

The following table summarizes the major safety results from ONCEMRK through Week 48 irrespective of causality.

Table 6. ONCEMRK W48: Safety Overview

N (%)	RAL 1200 mg once daily + FTC/TDF (n=531)	RAL 400 mg twice daily + FTC/TDF (n=266)
Deaths	2 (<1)	1 (<1)
SAEs	33 (6)	25 (9)
D/C d/t AE	6 (1)	6 (2)

The Week 48 data from ONCEMRK submitted in this sNDA are adequate to characterize the safety profile of raltegravir when administered as 1200 mg once daily. Safety results are available for all participants who received at least one treatment dose: 531 in the once daily group and 266 in the twice daily group. There are no new safety concerns for once daily raltegravir that were not previously assessed during the NDA and sNDA reviews for twice daily raltegravir. The safety profile of once daily raltegravir over 48 weeks is comparable to that of twice daily raltegravir.

8.2 Deaths

Three deaths occurred in ONCEMRK through Week 48: two in the once daily raltegravir group and one in the twice daily raltegravir group. Each death is summarized in the table below, and additional details for deaths in the once daily raltegravir group are provided in the subsequent narrative. None of the deaths were deemed related to study drug. There were no additional deaths in either group during the SUR period.

Table 7. ONCEMRK W48: Deaths

Event (PT)	Event Onset	D/C Study Drug	Death	Causality	Baseline CD4 (mm^3) VL (c/mL)	Country
RAL 1200 mg once daily + FTC/TDF						
Miliary TB	Day 7	Day 9	Day 36	Not Related	CD4 70 VL >2 million	South Africa
Immunoblastic lymphoma	Day 36	Day 36	Day 81	Not Related	CD4 277 VL 156K	Columbia
RAL 400 mg twice daily + FTC/TDF						
AIDS, worsening (multiple OIs)	Day 17	Day 32	Day 50	Not Related	CD4 19 VL 231K	U.S.

Subject Number 0046-100269 (raltegravir 1200 mg once daily): Immunoblastic lymphoma

A 31-year-old multiracial Hispanic male with medical history significant for arterial hypertension, bilateral lumbar pain, and hyperuricemia was randomized to the once daily raltegravir group. On Day 36 after experiencing exacerbation of low back pain, the participant received an abdominal and testicular ultrasound, which showed bilateral ectases, an enlarged kidney, and bilateral epididymitis. Blood urea nitrogen and serum creatinine were 29 mg/dL and 1.6 mg/dL, respectively. Lymphatic system neoplasm (renal large cell lymphoma) and renal failure were reported as SAEs. HIV RNA was 124 copies/mL. The participant discontinued study drug and began hemodialysis. On Day 58 the participant was hospitalized to continue hemodialysis and chemotherapy. The participant underwent multiple diagnostic tests from Day 58 until his death on Day 81. The cause of death was reported as lymphatic system neoplasm.

Reviewer Comment: Immunoblastic lymphoma was unlikely related to once daily raltegravir treatment. Lymphoma occurred within the first few weeks of treatment, and HIV is a known risk factor for malignancy including lymphoma. Additionally, bilateral lumbar pain was present at baseline suggesting the condition was pre-existing.

Subject Number 0035-101970 (raltegravir 1200 mg once daily): Tuberculosis

A 44-year-old black female with medical history significant for AIDS and pulmonary TB was randomized to the once daily raltegravir group. On Day -3 (three days before randomization), the participant had a dry, non-productive cough, malaise, and soreness, with no dyspnea, and the Investigator attributed the symptoms to influenza. A chest x-ray on Day -2 was clear. On Day 7 the participant was hospitalized with acute dyspnea. A chest x-ray on Day 8 showed suspected military tuberculosis (TB). The participant discontinued study drug and began "other ART" and TB treatment. The participant experienced neurologic deterioration and on

Day 26 discontinued other ART. CT scan on Day 31 showed more lesions of TB. The cause of death was military TB. An autopsy was not performed.

Reviewer Comment: The participant exhibited respiratory symptoms at baseline, had a history of pulmonary TB, had advanced HIV/AIDS, and was in a region where TB is common. TB was not related to once daily raltegravir treatment though immune reconstitution syndrome as a result of ART initiation may have contributed to the participant's clinical response. Immune reconstitution syndrome is listed as a Warning and Precaution for raltegravir and has been associated with ART irrespective of the regimen.

8.3 Serious Adverse Events (SAEs)

SAEs of any grade occurred at a slightly lower rate with once daily raltegravir (33/531 [6%]) compared twice daily raltegravir (25/266 [9%]). SAEs by System Organ Class (SOC) occurred most frequently in "Infections and infestations" for each group: 13/531 (2%) and 11/266 (4%) with once daily versus twice daily raltegravir, respectively. SAEs by SOC and Preferred Term (PT) were similar between groups, and no trends emerged.

The following table lists SAEs that occurred in more than one participant across both groups through Week 48; all were deemed not related to study drug by the investigator.

Table 8. ONCEMRK W48: Serious Adverse Events (SAEs) Occurring in >1 Participant

Dictionary Derived Term (PT)	RAL 1200 mg once daily + FTC/TDF (n=531)	RAL 400 mg twice daily + FTC/TDF (n=266)
Depression	3 (0.6%)	1 (0.4%)
Gastroenteritis	2 (0.4%)	1 (0.4%)
Alcoholism	1 (0.2%)	1 (0.4%)
Tuberculosis	1 (0.2%)	1 (0.4%)
Gastritis	0	2 (0.8%)
Proctitis	2 (0.4%)	0
Calculus urinary	1 (0.2%)	1 (0.4%)

Depression was the most common SAE reported (Subject Number 0157-100128, 0160-101816, 0151-101891, and 0079-100095). Psychiatric conditions were pre-existing in all four participants, and two of these participants also reported suicide attempt or suicidal thoughts. Section 6.1 of the current raltegravir label contains the following language pertaining to depression.

> Less Common Adverse Reactions Observed in Treatment-Naïve and Treatment-Experienced Studies

The following ADRs occurred in <2% of treatment-naïve or treatment-experienced subjects receiving ISENTRESS in a combination regimen. These events have been included because of their seriousness, increased frequency on ISENTRESS compared with efavirenz or placebo, or investigator's assessment of potential causal relationship.

Psychiatric Disorders: depression (particularly in subjects with a pre-existing history of psychiatric illness), including suicidal ideation and behaviors

Gastrointestinal events were the most common cluster of potentially similar SAEs reported across SOCs (Gastrointestinal disorders, Hepatobiliary disorders, and Infections and infestations). PTs included gastritis, gastroenteritis, and gastrointestinal perforation. Events were relatively balanced between treatment groups, and all were deemed not related to study drug. Gastritis is currently listed in the raltegravir label as a less common adverse reaction in Section 6.1.

Three SAEs overall were deemed related to study drug by the investigator, two of which were serious because of overdose. In the once daily raltegravir group, one participant inadvertently took a double-dose of FTC/TDF for one day and experienced a mild headache. In the twice daily raltegravir group, one participant inadvertently took two extra tablets (later determined to be placebo) for one day and experienced nausea, headache, and vomiting. Also in the twice daily raltegravir group, there was one report of drug ineffective, where HIV RNA increased from <40 copies/mL to 770 copies/mL but subsequently resuppressed to <40 copies/mL.

Five SAEs led to discontinuation of study drug, two of which were fatal and occurred in the once daily raltegravir group (see Section 8.2). The remaining three SAEs leading to discontinuation were non-fatal and not related to study drug: gastroenterovirus norovirus in the once daily raltegravir group; and TB and Burkitt’s lymphoma in the twice daily raltegravir group.

In the SUR period, 27 additional participants experienced a SAE: 15 in the once daily raltegravir group and 12 in the twice daily raltegravir group. All were deemed not related to study drug. One participant, in the twice daily raltegravir group, experienced serious fractures leading to treatment discontinuation; events were related to a motor vehicle accident. One participant, also in the twice daily raltegravir group, experienced serious depression; though in this case the participant had no prior history of psychiatric illness.

Reviewer Comment: Overall, the SAEs reported in ONCEMRK do not raise new safety concerns particularly because the majority of SAEs appear unrelated to raltegravir. Participants generally either had an alternate explanation for the SAE or experienced resolution of the SAE with continued study treatment. Based on a review of narratives, we agree with the investigator assessments of unrelated or unlikely related causality. Trends emerged for depression and gastrointestinal-related events (compared to other serious events), but the events were balanced between groups and consistent with current language in the USPI.

8.4 Dropouts and/or Discontinuations Due to Adverse Events (AEs)

A similar, low percentage of participants discontinued study drug due to an AE in the once daily raltegravir group (6/531 [1%]) compared to the twice daily raltegravir group (6/266 [2%]) through Week 48. The following table lists all AEs that led to discontinuation of study drug. TB was the only AE leading to treatment discontinuation in more than one participant.

Table 9. ONCEMRK W48: Adverse Events Leading to Treatment Discontinuation

Dictionary Derived Term (PT)	RAL 1200 mg once daily + FTC/TDF (n=531)	RAL 400 mg twice daily + FTC/TDF (n=266)
ALT/AST increased	1 (0.2%)	0
Blood CK increased	1 (0.2%)	0
Thrombocytopenia	0	1 (0.4%)
Immunoblastic lymphoma	1 (0.2%)	0 (0.0%)
Burkitt's lymphoma	0	1 (0.4%)
Gastroenteritis norovirus	1 (0.2%)	0
Hepatitis B	1 (0.2%)	0
Tuberculosis	1 (0.2%)	2 (0.8%)
Syncope	0	1 (0.4%)
Drug eruption	0	1 (0.4%)

Two participants in each group discontinued study drug due to raltegravir-related events. In the once daily raltegravir group, both related discontinuations were due to laboratory abnormalities, while the related discontinuations in the twice daily raltegravir group were due to drug eruption and thrombocytopenia.

Subject Number 0133-100058 (raltegravir 1200 mg once daily): ALT and AST increased
The participant was a 31-year-old male with asymptomatic Grade 2 ALT (152 IU/L) and Grade 1 AST (59 IU/L) elevations at baseline. Per screening serologies, the participant was not co-infected with hepatitis B or C virus. Starting on Day 169 and continuing through Day 222 when study drug was interrupted/discontinued, ALT increased to Grade 3 (ranging 261-398 IU/L), and AST increased but remained Grade 1 (86-100 IU/L). There were no associated elevations in serum bilirubin or alkaline phosphatase. On Day 197, the participant was diagnosed with hepatic steatosis by abdominal MRI, which was deemed unrelated to study drug. ALT and AST remained elevated until study discontinuation on Day 281. ALT and AST decreased to baseline values at the 14-day follow-up visit after study discontinuation.

Reviewer Comment: ALT and AST elevations from baseline appear possibly related to raltegravir particularly because of positive dechallenge. Though the participant was found to

have hepatic steatosis, which may explain the event, any contribution of raltegravir is difficult to exclude. See Section 8.6.1 for thorough hepatobiliary laboratory and safety analysis.

Subject Number 0036-100324 (raltegravir 1200 mg once daily): Blood creatine phosphokinase (CK) increased
The participant was a 20-year-old male with Grade 1 CK elevation (758 IU/L) at baseline. On two separate occasions (Day 29 and Day 142), CK increased to Grade 4 (5440 IU/L and 6600 IU/L, respectively) with no report of associated clinical symptoms. CK values returned to Grade 1 (baseline) the same day (Day 29) and within a week of Day 149, respectively; the participant discontinued study drug on Day 144. Information on prior physical exertion was not provided. On Day 38, an abnormal ECG was reported though details were not provided. Cardiac enzyme results were not provided.

Reviewer Comment: CK elevations from baseline appear possibly related to raltegravir in the absence of information to rule out other causes (e.g., physical exertion). Due to the absence of clinical symptoms, the event appears to reflect a laboratory abnormality with little known clinical significance. See Section 8.6.4 for CK laboratory analysis.

Subject Number 0129-100473 (raltegravir 400 mg twice daily): Thrombocytopenia
A 57-year-old male with a normal platelet count at baseline had a significant decline in platelet count (24,000/mm^3) at Day 253 (Week 36) for which he received concentrated platelets on Days 263, 274, 278, and 300. Due to persistent thrombocytopenia, the participant discontinued raltegravir on Day 331 and subsequently began darunavir/cobicistat (and continued FTC/TDF). Conjunctival hemorrhage (mild) and ecchymosis (mild), clinical symptoms associated with severe thrombocytopenia, were reported on Day 332. Platelet count on Days 333 and 352, following raltegravir discontinuation, was 10,000/mm^3 and 6,000/mm^3, respectively. Thrombocytopenia was unresolved at the time of study discontinuation. The investigator and Sponsor assessed the events as related to raltegravir.

Reviewer Comment: Attributing the events to raltegravir is reasonable. The severity and persistence of thrombocytopenia along with development of associated clinical events are concerning. The current raltegravir USPI states that no treatment-naïve participants treated with either raltegravir or efavirenz (each with FTC/TDF) in STARTMRK developed Grade 4 platelet decrease through Week 240, while 1% of treatment-experienced participants treated with raltegravir (and optimized background drugs) in BENCKMRK 1 and 2 developed Grade 4 platelet decrease through Week 96. HIV is also associated with thrombocytopenia, but the participant's HIV RNA was suppressed during the entirety of the reported event. For the purpose of the submitted sNDA, this event occurred only in the twice daily raltegravir group, suggesting that once daily raltegravir does not increase any potential risk compared to twice daily raltegravir. See Section 8.6.3 for complete hematologic laboratory findings in ONCEMRK.

Subject Number 0152-100445 (raltegravir 400 mg twice daily): Drug eruption
A 26-year-old male experienced "moderate drug eruption" on Day 15 leading to discontinuation of raltegravir on Day 30. Eosinophil count remained within normal range, and

the event resolved as of Day 65. A more detailed description of the event was not provided. The Investigator and Sponsor assessed the event as related.

Reviewer Comment: The event appears related to raltegravir based on the information provided, but details are lacking to fully assess the clinical significance of the event. Severe skin and hypersensitivity reactions are listed as a Warning and Precaution in the current raltegravir USPI.

Overall, discontinuations due to AE in ONCEMRK were infrequent and relatively balanced between groups and either reasonably unrelated to once or twice daily raltegravir or consistent with current language in the USPI.

8.5 Treatment Emergent Adverse Events and Adverse Drug Reactions

In this section, the term adverse event (AE) indicates the event occurred irrespective of causality. The term adverse drug reaction (ADR) indicates the AE was deemed at least possibly related to study drug by the investigator. Treatment-emergent indicates the AE or ADR occurred while receiving study drug or within 14 days of discontinuation.

The following table provides an overview of treatment-emergent clinical AEs and ADRs in each group by severity and relatedness through Week 48. Clinical ADRs Grade 3-4 (severe) with once daily raltegravir were abdominal pain and erectile dysfunction, neither of which were serious or led to discontinuation. Clinical ADRs Grade 3-4 with twice daily raltegravir were drug ineffective (see Section 8.3.2), thrombocytopenia (see Section 8.3.3), back pain, and erectile dysfunction.

Table 10. ONCEMRK W48: Adverse Events (AE) and Adverse Drug Reactions (ADR)

	RAL 1200 mg once daily + FTC/TDF (n=531)	RAL 400 mg twice daily + FTC/TDF (n=266)
Clinical AE	439 (83%)	231 (87%)
Clinical AE Grade 2-4	199 (38%)	138 (52%)
Clinical AE Grade 3-4	46 (9%)	29 (11%)
Clinical ADR	130 (25%)	68 (26%)
Clinical ADR Grade 2-4	31 (6%)	13 (5%)
Clinical ADR Grade 3-4	2 (<1%)	4 (2%)

AE = adverse event (irrespective of causality)
ADR = adverse drug reaction (AE deemed related to study drug)

The current raltegravir USPI lists ADRs of moderate to severe intensity (similar to Grade 2 or higher) that occurred in >2% of treatment-naïve adults who received raltegravir 400 mg twice

daily in STARTMRK through Week 240: nausea, fatigue, headache, dizziness, and insomnia. In ONCEMRK through Week 48, no PTs or cluster of PTs met these criteria.

The following table shows ADRs that occurred in at least 2% of participants in either group irrespective of severity through Week 48. For abdominal pain, fatigue, rash, and insomnia, similar PTs were combined to minimize dilution of a potential signal. Abdominal pain was the only ADR that occurred in ≥2% more participants receiving once daily raltegravir compared to twice daily raltegravir. However, related abdominal pain was mild in the majority of participants, and the percentage of moderate or severe related abdominal pain was similar between groups. Overall, no new or major safety concerns emerged.

Table 11. ONCEMRK W48: Adverse Drug Reactions (ADRs), All Severity, Reported in ≥2% of Participants

Dictionary Derived Term (PT)	RAL 1200 mg once daily + FTC/TDF (n=531)	RAL 400 mg twice daily + FTC/TDF (n=266)
Nausea	39 (7%)	18 (7%)
Abdominal pain[1]	22 (4%)	5 (2%)
Headache	16 (3%)	12 (5%)
Vomiting	13 (2%)	3 (1%)
Dizziness	12 (2%)	8 (3%)
Diarrhea	12 (2%)	7 (3%)
Decreased appetite	11 (2%)	0 (0%)
Fatigue[2]	11 (2%)	5 (2%)
Rash[3]	10 (2%)	4 (2%)
Abnormal dreams	9 (2%)	4 (2%)
Insomnia[4]	8 (2%)	4 (2%)

[1]Abdominal discomfort, Abdominal pain, Abdominal pain lower, Abdominal pain upper, Abdominal tenderness
[2]Asthenia, Fatigue, Sluggishness
[3]Dermatitis allergic, Drug eruption, Rash, Rash generalized, Rash papular
[4]Insomnia, Middle insomnia

8.6 Laboratory Findings and Associated Safety Analyses

8.6.1 Hepatobiliary Laboratory Findings and Safety Analysis

The following table displays the worst change from baseline through Week 48 for major hepatic laboratory parameters. The main comparison is raltegravir once daily compared to raltegravir twice daily in ONCEMRK, but also included in the table are results (percentages only) for raltegravir twice daily in STARTMRK through Week 48. The source of the STARTMRK results is the ISENTRESS USPI from July 8, 2009.

Table 12. ONCEMRK (W48) and STARTMRK (W48): Hepatic Laboratory Results, Worst Change from Baseline

Laboratory Parameter Grade N (%)	ONCEMRK W48		STARTMRK W48
	RAL 1200 mg once daily + FTC/TDF (n=531)	RAL 400 mg twice daily + FTC/TDF (n=266)	RAL 400 mg twice daily + FTC/TDF (n=281)
Total Bilirubin			
Grade 1: 1.1-1.5 x ULN	27 (5)	14 (5)	NA
Grade 2: 1.6-2.5 x ULN	7 (1)	2 (1)	(4)
Grade 3: 2.6-5.0 x ULN	3 (1)	0 (0)	(<1)
Grade 4: >5.0 x ULN	1 (<1)	0 (0)	(0)
ALT			
Grade 1: 1.25-2.5 x ULN	49 (9)	33 (12)	NA
Grade 2: 2.6-5.0 x ULN	13 (2)	2 (1)	(4)
Grade 3: 5.1-10.0 x ULN	5 (1)	1 (<1)	(<1)
Grade 4: >10.0 x ULN	2 (<1)	0 (0)	(<1)
AST			
Grade 1: 1.25-2.5 x ULN	39 (7)	29 (11)	NA
Grade 2: 2.6-5.0 x ULN	16 (3)	5 (2)	(4)
Grade 3: 5.1-10.0 x ULN	6 (1)	1 (<1)	(1)
Grade 4: >10.0 x ULN	2 (<1)	0 (0)	(<1)
ALP			
Grade 1: 1.25-2.5 x ULN	12 (2)	3 (1)	NA
Grade 2: 2.6-5.0 x ULN	6 (1)	0 (0)	<1
Grade 3: 5.1-10.0 x ULN	0 (0)	0 (0)	0
Grade 4: >10.0 x ULN	0 (0)	0 (0)	0

NA = not available in the ISENTRESS USPI approved July 8, 2009

Reviewer Comment: ALT, AST, ALP, and total bilirubin elevations were relatively low and similar between groups in ONCEMRK, though there were slightly more elevations in the once daily raltegravir group compared to the twice daily raltegravir group. From a historical perspective, similar elevations occurred with twice daily raltegravir in STARTMRK, though cross-study comparison is less compelling than within study comparison.

One participant met drug-induced liver injury (DILI) criteria of ≥3x ULN AST or ALT value and ≥2x ULN bilirubin value with ALP value <2x ULN. Subject 0001-101225, a 31-year-old male in the once daily raltegravir group, had Grade 4 ALT and Grade 4 total bilirubin elevations with ALP <2x ULN on Day 15. The participant had active hepatitis B virus (HBV) infection based on screening serologies but normal AST, ALT, and total bilirubin at screening. On Day 1, the participant had Grade 3 ALT and AST elevations with normal bilirubin levels, assessed as related to worsening HBV. By Day 15 when DILI criteria were met, ALT and AST

increased to 998 IU/L and 565 IU/L, while total bilirubin increased to 2.8 mg/dL. The participant discontinued study drug on Day 17. ALT, AST, and total bilirubin remained Grade 4 on Day 28 before decreasing to normal or Grade 1 on Day 43. The participant was asymptomatic. The Investigator and Sponsor assessed the event as not related to study drug but rather to pre-existing HBV flare beginning on Day 1 and not a true DILI case. The external Data Monitoring Committee also reviewed the case.

Reviewer Comment: The Investigator and Applicant's assessment is reasonable that the case is not true DILI due to pre-existing HBV that flared at baseline. However, it is difficult to exclude any contribution of raltegravir to worsening liver-related laboratory tests, and the HBV flare subsided after discontinuation of study drug. See Section 8.8.2 for discussion of participants with HBV and/or hepatitis C virus (HCV) co-infection.

Six participants receiving once daily raltegravir experienced Grade 3 or 4 ALT elevations without an associated bilirubin elevation (compared to one participant receiving twice daily raltegravir). However, alternate explanations or confounding factors were reported for most participants: acute HCV (2), nonspecific hepatitis (with baseline HCV) (1), hepatic steatosis (see Section 8.4) (1), and concomitant isoniazid treatment (1). In one participant, no concurrent AEs were reported, and the elevations resolved on treatment.

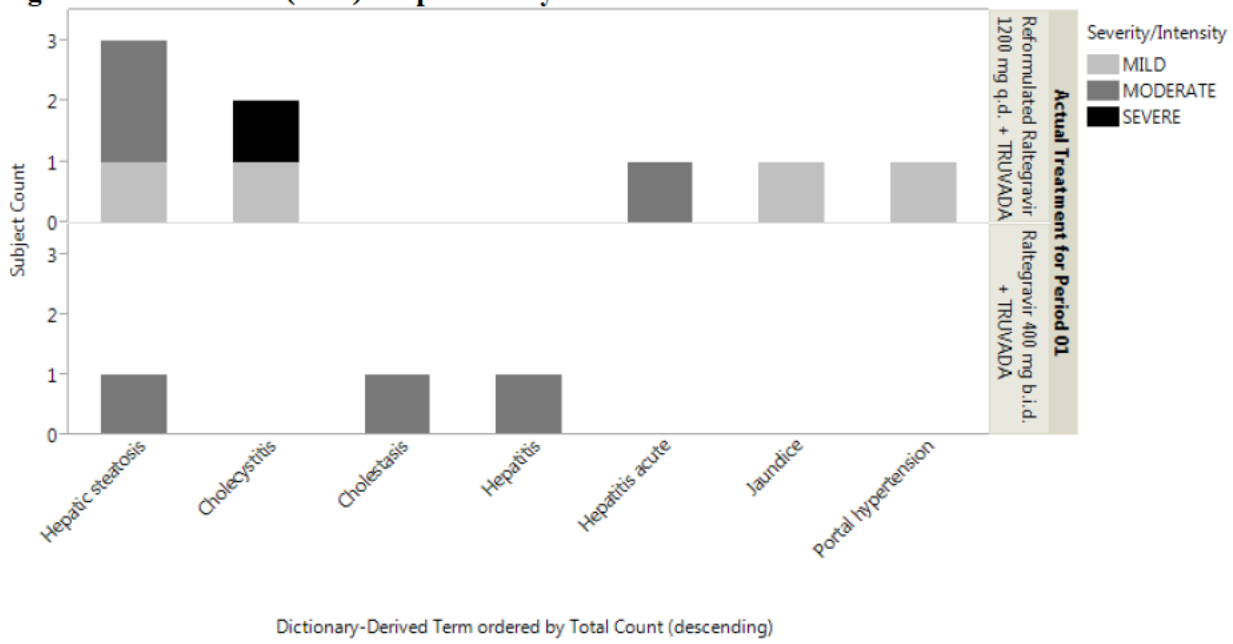
Three participants receiving once daily raltegravir experienced Grade 3 total bilirubin elevation (compared to zero participants receiving twice daily raltegravir). None of the three participants met Hy's Law criteria, experienced an SAE, or discontinued raltegravir due to an AE.

> Subject 0152-100329 had a medical history of sickle cell anemia and vaso-occlusive crisis and a baseline total bilirubin elevation of 3.1 mg/dL (Grade 2). The participant's bilirubin remained elevated between 2.0-2.8 mg/dL (Grade 2) during study treatment until Day 142 when it increased to 3.4 mg/dL (Grade 3). Throughout study treatment AST was slightly elevated (Grade 1), and ALT remained within normal limits. The participant had no reported AEs but discontinued study drug on Day 169 due to physician decision.
>
> Subject 0105-100259 had an elevated total bilirubin level of 1.6 mg/dL at screening, which normalized by the baseline visit. Medical history was unremarkable for conditions associated with elevated total bilirubin. At the first visit on study treatment, total bilirubin (largely indirect bilirubin) was again elevated and remained elevated (peak level 4.2 mg/dL, Grade 3) through Week 48. ALT and AST remained within normal limits. Mild ocular icterus was reported on Day 337 at which visit total bilirubin was 2.6 mg/dL. Despite elevation in bilirubin, there was no evidence of impairment in hepatic synthetic function based on reported AEs or laboratory abnormalities such as albumin.
>
> Subject 0147-101853 had an elevated total bilirubin level of 2.3 mg/dL (Grade 3) temporally associated with initiation of dapsone and reported AE G6PD deficiency.

ALT and AST also increased to Grade 1 levels. Laboratory values normalized following discontinuation of dapsone.

AEs under the Hepatobiliary Disorders SOC occurred in 6/531 (1%) and 3/266 (1%) participants receiving once daily raltegravir and twice daily raltegravir, respectively. The following graph illustrates the absolute number of PTs reported within the SOC Hepatobiliary disorders. The shading depicts the severity of each event. One participant receiving once daily raltegravir experienced two events (jaundice and cholecystitis). Given a 2:1 randomization for once daily raltegravir versus twice daily, both groups appeared similar for all hepatobiliary PTs and for moderate-to-severe hepatobiliary PTs. None of the events were related to study drug or led to treatment discontinuation. None of the participants had HBV or HCV co-infection at baseline.

Figure 2. ONCEMRK (W48): Hepatobiliary Disorders



Reviewer Comment: Overall, hepatobiliary safety with once daily raltegravir compared to twice daily raltegravir was comparable and consistent with current labeling. No major issues of concern arose in ONCEMRK.

8.6.2 Kidney-Related Laboratory Findings and Safety Analysis

The following table displays the worst change from baseline through Week 48 for serum creatinine. Increases in serum creatinine for participants receiving once daily raltegravir were infrequent, mild, and similar to participants receiving twice daily raltegravir.

Table 13. ONCEMRK (W48): Serum Creatinine, Worst Change from Baseline

Laboratory Parameter Grade N (%)	RAL 1200 mg once daily + FTC/TDF (n=531)	RAL 400 mg twice daily + FTC/TDF (n=266)

Laboratory Parameter Grade N (%)	RAL 1200 mg once daily + FTC/TDF (n=531)	RAL 400 mg twice daily + FTC/TDF (n=266)
Serum Creatinine		
Grade 1: 1.1-1.3 x ULN	4 (1)	3(1)
Grade 2: 1.4-1.8 x ULN	0 (0)	1 (<1)
Grade 3: 1.9-3.4 x ULN	0 (0)	0 (0)
Grade 4: ≥3.5 x ULN	0 (0)	0 (0)

AEs under the Renal and Urinary Disorders SOC occurred in 13/531 (2%) and 6/266 (1%) participants receiving once daily raltegravir and twice daily raltegravir, respectively. Two participants in each group experienced renal failure; in the once daily raltegravir group, one participant also had immunoblastic lymphoma (see Section 8.2) and one participant experienced transient increase in serum creatinine (1.45 mg/dL) which immediately normalized with continued treatment. One participant in each group experienced serious but unrelated urinary calculus. The current raltegravir USPI lists nephrolithiasis and renal failure under less common adverse reactions.

Reviewer Comment: Overall, kidney-related safety with once daily raltegravir versus twice daily raltegravir was comparable and consistent with current labeling. No new major issues of concern arose in ONCEMRK.

8.6.3 Hematologic Laboratory Findings and Safety Analysis

Table 14. ONCEMRK (W48): Hematologic Laboratory Results, Worst Change from Baseline

Laboratory Parameter Grade N (%)	RAL 1200 mg once daily + FTC/TDF (n=531)	RAL 400 mg twice daily + FTC/TDF (n=266)
Hemoglobin (mg/dL)		
Grade 1: 8.5-10.0	5 (1)	1 (<1)
Grade 2: 7.5-8.4	0 (0)	0 (0)
Grade 3: 6.5-7.4	0 (0)	0 (0)
Grade 4: <6.5	0 (0)	0 (0)
Neutrophils (10^3/uL)		
Grade 1: 1.00-1.30	21 (4)	10 (4)
Grade 2: 0.75-0.999	7 (1)	2 (1)
Grade 3: 0.5-0.749	5 (1)	3 (1)
Grade 4: <0.50	0 (0)	0 (0)
Platelets (10^3/uL)		
Grade 1: 100-124.999	7 (1)	5 (2)
Grade 2: 50-99.999	4 (1)	1 (<1)
Grade 3: 25-49.999	0 (0)	0 (0)
Grade 4: <25	0 (0)	1 (<1)

AEs under the Blood and Lymphatic Disorders SOC occurred in 25/531 (5%) and 8/266 (3%) participants receiving once daily raltegravir and twice daily raltegravir, respectively. The difference between groups was largely driven by lymphadenopathy/lymphadenitis, which occurred more frequently in participants receiving once daily raltegravir. None of the events under this SOC were serious or severe, and only one AE (anemia) in the once daily raltegravir group was related to study drug. In general, hemoglobin decrease was uncommon and at worst mild in severity.

Reviewer Comment: Overall, hematologic-related events that occurred with once daily raltegravir versus twice daily raltegravir were comparable. No new major issues of concern arose in ONCEMRK.

8.6.4 Miscellaneous Laboratory Findings and Safety Analyses

The following table displays the worst change from baseline through Week 48 for creatine kinase and lipase.

Table 15. ONCEMRK (W48): Laboratory Results, Worst Change from Baseline

Laboratory Parameter Grade N (%)	RAL 1200 mg once daily + FTC/TDF (n=531)	RAL 400 mg twice daily + FTC/TDF (n=266)
Creatine Kinase		
Grade 1: 3.0-5.9 x ULN	31 (6)	20 (8)
Grade 2: 6.0-9.9 x ULN	17 (3)	6 (2)
Grade 3: 10.0-19.9 x ULN	6 (1)	7 (3)
Grade 4: ≥20.0 x ULN	10 (2)	4 (2)
Lipase		
Grade 1: 1.1-1.5 x ULN	35 (7)	25 (9)
Grade 2: 1.6-3.0 x ULN	27 (5)	12 (5)
Grade 3: 3.1- 5.0 x ULN	8 (2)	1 (<1)
Grade 4: >5.0 x ULN	5 (1)	0 (0)

AEs under the Musculoskeletal and Connective Tissue Disorders SOC occurred in 89/531 (17%) and 36/266 (14%) participants receiving once daily raltegravir and twice daily raltegravir, respectively. One event (back pain in a participant receiving once daily raltegravir) was serious but deemed unrelated to study drug. Myalgia related to study drug occurred in three participants and one participant receiving once daily raltegravir and twice daily raltegravir, respectively; outcome of AE was recovered or recovering for all participants. There were no reports of myopathy or rhabdomyolysis.

The current raltegravir USPI contains the following language under Less Common ADRs in Section 6.1.

> Grade 2-4 creatine kinase laboratory abnormalities were observed in subjects treated with ISENTRESS. Myopathy and rhabdomyolysis have been reported.

Pancreatitis occurred in two participants receiving once daily raltegravir; neither event was serious, severe, or related. The current raltegravir USPI does not include pancreatitis in any section.

Analyses of cardiac, endocrine, gastrointestinal, psychiatric, and skin and subcutaneous tissue events by SOC showed no major imbalances between groups or concerns not already discussed in this review.

Reviewer Comment: Overall safety with once daily raltegravir compared to twice daily raltegravir is comparable and consistent with current labeling. No new major issues of concern arose in ONCEMRK.

8.7 QT

A thorough QTc study (PN024) was previously conducted as part of the raltegravir twice daily development program. The dose evaluated in PN024 was 1600 mg of raltegravir (4 x 400 mg tablets). The Cmax from a single supratherapeutic dose of raltegravir 1600 mg was 19.6 uM, which did not prolong the QTc interval. The Applicant did not observe any meaningful trends at the 1800 mg dose in PN293 in which enhanced ECG monitoring occurred. At a Type C meeting in 2013, FDA concurred with the Applicant that an additional QTc study would not be required to support raltegravir once daily dosing.

8.8 Special Populations

8.8.1 Demographic Factors

Sex

The majority of participants in both groups were male (83-88%). There were 440 male and 91 female participants in the once daily raltegravir group and 234 male and 32 female participants in the twice daily raltegravir group. The following table lists clinical AEs that occurred at a difference of at least 5% in males versus females treated with once daily raltegravir irrespective of causality. When considering causality, no drug-related clinical AEs occurred in at least 5% more of one sex compared to the other with once daily raltegravir. The biggest difference was for drug-related nausea, which occurred in 4% more females (11%) compared to males (7%) receiving once daily raltegravir.

Table 16. ONCEMRK (W48): Clinical AEs, Regardless of Causality, by Sex in the Once Daily Raltegravir Group

Dictionary Derived Term (PT)	Male (%) n=440	Female (%) n=91
Nausea	10	18
URI	6	13
Vomiting	5	12

Dictionary Derived Term (PT)	Male (%) n=440	Female (%) n=91
Insomnia	5	0

In males receiving once daily raltegravir compared to twice daily raltegravir, drug-related clinical AEs occurred at a similar frequency (<5% difference)group. In females, drug-related nausea occurred more frequently with once daily raltegravir (11%) compared to twice daily raltegravir (6%), while drug-related headache occurred less frequently with once daily raltegravir (1%) compared to twice daily raltegravir (6%).

Reviewer Comment: Differences by sex do not appear clinically significant or warrant labeling changes, although interpretation is difficult due to the small sample size of females and infrequency of related AEs.

Race

The following races and ethnicities were represented in the once daily raltegravir group: White (57%), Black (18%), Asian (16%), Multiple (9%), and American Indian/Alaska Native (<1%). The following table shows clinical AEs by race that occurred in at least 4% of participants receiving once daily raltegravir irrespective of causality. The racial group that reported the highest percentage of each AE is highlighted in the table, with the exception of the American Indian/Alaska Native group which included only three total participants. Black participants receiving once daily raltegravir reported the highest rate of many of the listed AEs. When considering causality, drug-related AEs occurred at a similar rate (difference of <5%) in Black, Asian, and Multiple races each compared to White participants receiving once daily raltegravir.

Table 17. ONCEMRK (W48): Clinical AEs by Race in the Once Daily Raltegravir Group

Dictionary Derived Term (PT)	White N=301	Black/African American N=98	Asian N=83	Multiple N=46	American Indian/ Alaska Native N=3
Headache	40 (13%)	14 (14%)	7 (8%)	10 (22%)	1 (33%)
Nausea	37 (12%)	15 (15%)	4 (5%)	3 (7%)	1 (33%)
Abdominal pain[1]	35 (12%)	15 (15%)	3 (4%)	6 (13%)	0
Diarrhea	29 (10%)	9 (9%)	7 (8%)	12 (26%)	1 (33%)
Nasopharyngitis	34 (11%)	3 (3%)	5 (6%)	2 (4%)	0
Fatigue[2]	25 (8%)	9 (9%)	4 (5%)	2 (4%)	0
Rash[3]	17 (6%)	13 (13%)	2 (2%)	3 (7%)	1 (33%)
URI	19 (6%)	13 (13%)	7 (8%)	1 (2%)	0
Vomiting	16 (5%)	12 (12%)	4 (5%)	3 (7%)	0
Cough	16 (5%)	8 (8%)	3 (4%)	2 (4%)	0
Dizziness	13 (4%)	5 (5%)	5 (6%)	1 (2%)	1 (33%)
Back pain	16 (5%)	4 (4%)	2 (2%)	2 (4%)	0

[1]Abdominal discomfort, Abdominal pain, Abdominal pain lower, Abdominal pain upper, Abdominal tenderness
[2]Asthenia, Fatigue, Sluggishness
[3]Dermatitis allergic, Drug eruption, Rash, Rash generalized, Rash papular

The following races and ethnicities were represented in the twice daily raltegravir group: White (65%), Black (14%), Asian (15%), Multiple (5%), and American Indian/Alaska Native (1%). In the twice daily raltegravir group, Black participants reported higher rates (by at least 5%) of diarrhea, headache, and fatigue compared to White participants irrespective of causality. Asian participants reported higher rates (by at least 5%) of pruritus, dizziness, pyrexia, accidental overdose, abdominal distension compared to White participants irrespective of causality.

Reviewer Comment: Differences by race do not appear clinically significant or warrant labeling changes, although interpretation is difficult due to sample sizes and infrequency of related AEs.

Age

There were seven participants across both groups aged 65 years and older. As such, it was not feasible to conduct safety analysis by age, particularly for older adults in whom the safety profile may differ.

8.8.2 HBV and/or HCV Coinfection

The following table displays the worst change from baseline through Week 48 for major hepatic laboratory parameters for participants with baseline HBV and/or HCV coinfection compared to HIV monoinfection for each group. The main comparison is raltegravir once daily compared to raltegravir twice daily in ONCEMRK, but also included in the table are results for raltegravir twice daily in STARTMRK through Week 48. The source of the STARTMRK results is the ISENTRESS USPI from July 8, 2009.

Table 18. ONCEMRK (W48) and STARTMRK (W48): Hepatic Laboratory Abnormalities, Worst Change from Baseline, in Participants with HBV and/or HCV Coinfection

Protocol and Treatment Group	N (%) Co-infected	Subjects with ≥ G2 and Worse Grade from Baseline: ALT, AST, Tbili at Week 48 (%)
ONCEMRK: RAL 1200 mg once daily + FTC/TDF (n=531)	15 (3)	Coinfected: 33, 13, 13 Monoinfected: 3, 4, 2
ONCEMRK: RAL 400 mg twice daily + FTC/TDF (n=266)	8 (3)	Coinfected: 13, 0, 0 Monoinfected: 1, 2, 1
STARTMRK RAL 400 mg twice daily + FTC/TDF (n=281)	18 (6)	Coinfected: 22, 17, 11 Monoinfected: 4, 4, 3

Of the coinfected participants in the once daily raltegravir group, one experienced drug-related clinical AEs (abnormal dreams and decreased appetite); one discontinued treatment due to unrelated hepatitis B; and none experienced a SAE. Coinfected participants in the twice daily raltegravir group in ONCEMRK experienced a similar or higher rate of each type of event.

Reviewer Comment: Grade 2-4 ALT, AST, and total bilirubin elevations occurred more frequently in coinfected participants receiving once daily raltegravir compared to twice daily raltegravir in ONCEMRK. Because of the low number of coinfected participants, it is difficult to draw specific conclusions from these data. From a historical perspective, similar elevations occurred in coinfected participants receiving twice daily raltegravir in STARTMRK, though cross-study comparison has its limitations. Trends of greater frequency of hepatic laboratory abnormalities in coinfected versus monoinfected participants were observed for participants receiving once daily raltegravir. However, rare occurrences of clinical AEs in coinfected participants diminish the clinical significance of these laboratory abnormalities. Since the Sponsor's proposed labeling already clearly describes the laboratory abnormalities of interest, no additional labeling changes are recommended based on this analysis.

8.8.3 Drug Interaction: Proton Pump Inhibitors and/or H2 Antagonists

A pharmacokinetic (PK) interaction with proton pump inhibitors (PPIs) results in increased concentrations of the twice daily raltegravir formulation: 3-fold and 4-fold higher AUC and Cmax, respectively. The following table displays the PK data in the current raltegravir USPI.

Table 19. Current USPI: Effect of Omeprazole on the Pharmacokinetics of Raltegravir in Adults

Coadministered Drug	Coadministered Drug Dose/Schedule	Raltegravir Dose/Schedule	Ratio (90% Confidence Interval) of Raltegravir Pharmacokinetic Parameters with/without Coadministered Drug; No Effect = 1.00			
			n	C_{max}	AUC	C_{min}
omeprazole	20 mg daily	400 mg single dose	14 (10 for AUC)	4.15 (2.82, 6.10)	3.12 (2.13, 4.56)	1.46 (1.10, 1.93)

Like PPIs, H2 antagonists increase gastric pH thereby possibly affecting solubility of raltegravir. As such, analyses of potential negative effect of PPIs and H2 antagonists on raltegravir safety were combined. The effect of PPIs or H2 antagonists on the PK of the once daily raltegravir formulation (600 mg tablet) is unknown because no PK data were submitted with this supplement. The rationale for combining analyses of PPIs and H2 antagonists is that H2 antagonists, like PPIs, increase gastric pH thereby possibly affecting solubility of raltegravir. Safety analysis was conducted to explore the effect of potentially higher raltegravir concentrations when combined with a systemically acting acid-reducing agent such as a PPI or an H2 antagonist. The following table shows a high-level safety overview of any potential interaction with these agents in both treatment groups. Participants were not stratified for use of PPI or H2 antagonist, and concomitant use was defined as at least one dose of a PPI or H2 antagonist in combination with raltegravir.

Table 20. ONCEMRK (W48): Safety of Raltegravir with and without Concomitant Use of a PPI or H2 Antagonist

	Raltegravir 1200 mg once daily + FTC/TDF (n=531)		RAL 400 mg twice daily + FTC/TDF (n=266)	
	With PPI/H2A N=61	No PPI/H2A N=470	With PPI/H2A N=42	No PPI/H2A N=224
Related AE	23%	25%	29%	25%
SAE	8%[1]	6%	24%	7%
D/C due to AE	0%	1%	2%	2%
Severe AE	15%	9%	24%	8%
Severe Related AE	2%	1%	2%	1%

[1]PPI initiated after SAE and lasted 2-7 days during hospitalization in 3/5 participants in the once daily raltegravir group (see next Table)

There were no related SAEs with concomitant use of a PPI or H2 antagonist in either group. There were also no apparent differences in laboratory abnormalities with and without PPI or H2 antagonist use in either group.

Table 21. SAEs with Concomitant Use of PPI or H2 Antagonist and Once Daily Raltegravir

PT	Comment/Assessment
Acute coronary syndrome	PPI taken for 3 days during hospitalization
Alcoholism	Unrelated to concomitant use
Back pain	PPI taken for 8 days during hospitalization
Cholecystitis	Unrelated to concomitant use
Hepatitis acute	PPI taken for 2 days during hospitalization

The following SAEs occurred with concomitant use of a PPI or H2 antagonist in the twice daily raltegravir group: AIDS, breast cancer, cerebral toxoplasmosis, gastritis (2), osteomyelitis, otitis externa, queyrat erythroplasia (squamous cell carcinoma), subcutaneous abscess, and tuberculosis.

Reviewer Comment: Given the available data, concomitant use of a PPI or H2 antagonist and once daily raltegravir does not present any safety concerns (similar to twice daily raltegravir in ONCEMRK and STARTMRK).

8.8.4 Pregnancy

This section summarizes pregnancy reports as presented by the Applicant in the Clinical Overview. Three participants, all in the once daily raltegravir group, reported a pregnancy

through Week 48. One additional participant, also in the once daily raltegravir group, reported a pregnancy in the SUR but had discontinued study drug 100 days prior to pregnancy. The summaries below describe the three pregnancies that occurred while participants were receiving study drug and contain available information through the SUR period.

Subject 0053-101840 became pregnant with last menstrual period on Day 242 and had the last dose of study therapy on Day 306. The participant had active anemia. During the pregnancy she was hospitalized once for premature rupture of membranes, which was ruled out. On Day 505, at 37 weeks of gestation, she delivered a normal female baby by C-section.

Subject 0113-100282 became pregnant with last menstrual period on Day 58 and had the last dose of study therapy on Day 107. The participant discontinued from study and delivered a normal female baby by C-section on Day 329 without complications.

Subject 0146-100289 became pregnant with last menstrual period on Day 374 and had the last dose of study therapy on Day 410. The participant delivered a healthy female baby, without congenital anomalies or other abnormalities, by vaginal delivery at 38 weeks gestation.

9 Advisory Committee Meeting

Not applicable

10 Pediatrics

Raltegravir is currently approved for patients 4 weeks of age and older and is dosed twice daily regardless of age or formulation. The current tablet formulation (dosed 400 mg twice daily) is labeled for use in pediatric patients who weigh at least 25 kg and can swallow the tablet.

In the agreed initial pediatric study plan (iPSP) for once daily raltegravir dated October 1, 2014, the Applicant proposed (b) (4) In the agreed iPSP the Applicant also indicated a plan to use population PK modeling to predict raltegravir exposures of once daily raltegravir 1200 mg in pediatric patients at least 6 years of age weighing at least 25 kg. The goal was to identify a weight range such that raltegravir exposures were within the exposure range determined to be safe in adults in ONCEMRK. The agreed iPSP further stated, "unless modeling and simulation data definitively exclude a significant portion of the pediatric population, the Applicant plans to conduct one small open-label, non-comparative, PK and safety study evaluating a 1200 mg QD dose of reformulated raltegravir with an appropriate background regimen in HIV-1 infected pediatric patients above the defined weight threshold."

In the sNDA submission, the Applicant proposes dosage and administration of once daily raltegravir 1200 mg for pediatric patients weighing at least 40 kg without conducting an open-label, non-comparative, PK and safety study in this population. Additionally, the Applicant proposes waiver requests for once daily raltegravir in pediatric patients weighing less than 40 kg.

As planned, the Applicant submitted modeling and simulation of once daily raltegravir 1200 mg in pediatric patients using a population PK model based on adult data from five Phase 1 studies and one Phase 3 study (ONCEMRK). The Applicant generated a virtual population of 1000 pediatric patients (10 weight groups in increments of 5 kg, 100 patients per weight group) based on data from HIV-infected pediatric participants in IMPAACT P1066.

The Applicant asserts that AUC is the most appropriate PK parameter to characterize the clinical significance of elevations in raltegravir plasma concentrations on safety because it is a better reflection of total exposure over a dosing interval rather than a transient peak concentration. Additionally, no acute safety findings in collective trials with once and twice daily raltegravir were associated with peak concentrations. In ONCEMRK specifically, no new safety concerns emerged in adults with once daily raltegravir 1200 mg dosing. Dr. Mario Sampson, Clinical Pharmacology Reviewer, agrees that AUC is acceptable to use for the exposure-safety assessment of raltegravir.

The adult 95th percentile $AUC_{0\text{-}24,ss}$ exposure value from ONCEMRK was 109 uM*h, which the Applicant uses as a safety threshold. The Applicant's simulated results show once daily raltegravir 1200mg exposure (upper bound of the 90% CI for $AUC_{0\text{-}24,ss}$) is not expected to exceed 109 uM*h for the following pediatric groups weighing 40-45 kg: White/Asian with/ without FTC/TDF and with fasting or a high-fat meal; Black without FTC/TDF and with fasting or a high-fat meal. However, the simulated upper bound of the 90% CI for $AUC_{0\text{-}24,ss}$ is expected to exceed 109 uM*h for Black patients weighing 40-45 kg who take raltegravir 1200 mg once daily with FTC/TDF, irrespective of fasting or high-fat meal; in this population, the upper bound remains lower than 109 uM*h starting with the 45-50 kg weight band.

Nonetheless, the Applicant proposes a weight cutoff of 40 kg because all pediatric simulated exposures using a minimum weight of 40 kg were within the adult exposure range observed in adults in ONCEMRK; the Applicant applies an exposure limit of the upper quartile of adults in the 95th percentile rather than the actual 95th percentile value of 109 uM*h. For each combination of race, food intake, and FTC/TDF coadministration, as well as the exposure in the upper quartile of adults in the 95th percentile range, the Applicant concludes the following weight cutoffs are appropriate:

Table 22. Weight Cutoffs for the Different Pediatric Groups based on $AUC_{0\text{-}24,ss}$ Comparisons of Raltegravir 1200 mg Once Daily

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: based on visual comparison from Figures 6 to 9 of this report
Source: Applicant's Pediatric Modeling & Simulation Report

Because the Applicant's proposals are based on modeling and simulation results rather than actual PK and safety results in pediatric patients, we asked the Applicant to provide a summary of safety experience with twice daily raltegravir in pediatric patients weighing at least 40 kg who had observed raltegravir AUC and Cmax within the range of simulated AUC and Cmax for the proposed population. The Applicant identified six pediatric participants in the IMPAACT P1066 trial who had raltegravir exposures within the range of simulated exposures for the proposed population. The following table describes the six participants. Of note the lowest weight was approximately 50 kg rather than 40 kg. There were no safety concerns in these pediatric participants.

Table 23. IMPAACT P1066 Participants with 2 x $AUC_{0\text{-}12}$ > 44.4 uM*hr and/or Cmax > 18.0 uM and Weight ≥ 40 kg

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: Applicant's Response to FDA Information Request Dated 06-Mar-2017

The following table shows combined data available for assessing whether there is a minimum weight limit for pediatric patients where simulated exposures are within the range of exposures previously observed in the pediatric population. Furthermore, it includes a summary of the six subjects for whom the Applicant provided actual PK and safety data.

Table 24. FDA Clinical Pharmacology Analyses of Adult and Pediatric Exposures

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 (5^{th}, 95^{th}) 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 >50 kg[1] with observed exposures > 5^{th} percentile of simulated exposures for 1200 mg QD	400 mg BID	Intensive	62 (50, 157) 80	14 (11, 18) 14	Median (min, max) Mean

[1]Median weight 58 kg (range 51-63 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 (5^{th}, 95^{th}) for each of the eight scenarios. The average of the eight medians, 5^{th} percentiles, and 95^{th} percentiles was recorded in the table above.
Source: FDA Clinical Reviewer and Clinical Pharmacology Reviewer Dr. Mario Sampson using Applicant's Data

Reviewer Comment (with Clinical Pharmacology Reviewer Dr. Mario Sampson): Although once daily raltegravir 1200 mg has not been studied in pediatric patients, we believe the following justification adequately supports labeling of 1200 mg (2 x 600 mg) once daily raltegravir for use in pediatric patients at least 12 years of age and weighing at least 50 kg.

Modeling and simulation (M&S) analyses predict once daily raltegravir 1200 mg in pediatric patients at least 50 kg will result in comparable exposures to adults who received once daily raltegravir 1200 mg. In addition, safety data from six pediatric participants weighing approximately 50-63 kg who received approved doses of twice daily raltegravir had exposures (AUC) within the range of 1) predicted pediatric exposures with once daily raltegravir 1200 mg and 2) observed exposures in adults who received raltegravir 1200 mg once daily. A PREA PMR(s) will be issued for pediatric patients weighing less 50 kg resulting in additional PK and safety information in the pediatric population with once daily raltegravir.

The Division agrees M&S analyses predict 1200 mg once daily raltegravir in pediatric patients weighing 40-49 kg will result in exposures that do not exceed the range of exposures (AUC) in adults who received 1200 mg raltegravir in ONCEMRK. However, confirmation of safety for this level of exposure in this population is necessary prior to labeling considerations.

The Applicant is requesting a waiver for the once daily raltegravir formulation for the following age groups:

(b) (4)

The Applicant's rationale for a waiver in these pediatric populations is that this product (1) is not likely to be used by a substantial number of pediatric patients in these age groups, and (2) does not represent a meaningful therapeutic benefit over existing therapies of raltegravir twice daily regimens utilizing pediatric-appropriate formulations.

Reviewer: The Division believes that once daily dosing for raltegravir, a drug which has been extensively studied in pediatric patients ranging from neonates to adolescents, would represent a meaningful therapeutic benefit over existing twice daily raltegravir. Because chewable tablet and oral suspension dosage forms are available for twice daily raltegravir, new formulations may not be necessary. The Division plans to (b) (4), (b) (5) *. The Division maintains agreement with granting a waiver for ages less than 6 years.*

Though the Division has discussed the preliminary plan with members of the Pediatric Review Committee (PeRC), the Division has not formally met with the PeRC at the time of this review. The meeting is scheduled for April 26, 2017.

11 Other Relevant Regulatory Issues

Financial Disclosures

Financial disclosures do not affect approvability of this application. See Appendix 1 for additional details.

Clinical Site Inspections

The Office of Scientific Investigations inspected the clinical sites of Drs. Berger, Hagins, Kaplan, Avihingsanon, and Perri in support of this NDA. The final classification of three sites (Drs. Berger, Kaplan, and Avihingsanon) was No Action Indicated (NAI). The final classification of two sites (Drs. Hagins and Perri) was Voluntary Action Indicated (VAI). OSI found minor regulatory deviations at one domestic and one foreign site, which do not appear to have significant effect on safety or efficacy. The final OSI inspection report specifically for

Dr. Hagins (Site 157; see Section 7.3) stated there were no data integrity issues or safety concerns with this site and that data from this site are reliable and may be used in support of the application. Overall, OSI concluded that inspection of the five clinical sites support validity of the data as reported by the Applicant for this sNDA.

12 Labeling

The Division of Medication Error Prevention and Analysis (DMEPA) approved the Applicant's proposed proprietary name ISENTRESS HD. The raltegravir USPI was updated throughout to specify (1) ISENTRESS and ISENTRESS HD when referring to 400 mg twice daily and 1200 mg once daily formulations, respectively, and (2) the appropriate form of tenofovir (i.e., tenofovir disoproxil fumarate) used in clinical trials with any formulation of raltegravir.

Discussions regarding our labeling recommendations are ongoing at this time and have not been finalized with the Applicant. The final agreed upon USPI and USPPI will be available at the time of approval. Our proposed agreements and edits to the USPI and USPPI are summarized as follows. Dr. Stacey Min, Associate Director of Labeling, made substantial contributions to formatting and editing the USPI which are included below.

INDICATIONS and USAGE (1)

- Added: [redacted] (b) (4)
- Deleted: The use of other active agents with ISENTRESS is associated with a greater likelihood of treatment response [see Clinical Studies (14)]. Rationale: This statement is obvious and no longer warranted.

DOSAGE AND ADMINISTRATION (2)

- General Dosing Recommendations and Method of Administration subsections were combined as they both contain important administration information.
- Deleted: [redacted] (b) (4) Rationale: See Section 5.6 of this review.
- The Applicant recommended a dose of 1200 mg once daily for patients who are virologically suppressed on an initial regimen of ISENTRESS 400 mg twice daily in the absence of a specific switch study. Response: The addition is reasonable based on extrapolation of ONCEMRK results which showed similar efficacy and safety with both regimens, particularly since the comparison was done in a randomized, double-blind, direct-comparator trial. The results indicate the regimens are interchangeable in treatment-naïve patients who are virologically suppressed on either initial regimen. PK data also support this recommendation.
- Dosing tables for adult and pediatric patients were reformatted for improved readability.

- [redacted] (b) (4) . Rationale: See Section 10 of this review.

ADVERSE REACTIONS (6)

- Included commonly reported adverse reactions (instead of adverse events) occurring in at least 2% (instead of (b) (4)%) of participants in either treatment group in ONCEMRK in a table (instead of text) and with similar terms combined. Rationale: The proposed revision is more relevant and helpful because it includes causality assessment and captures a reasonable number of common adverse drug reactions even if most were mild.
- Merged laboratory tables for the STARTMRK and ONCEMRK trials similar to the formatting in the TIVICAY label.
- Added ISENTRESS HD to the subsection Less Common Adverse Reactions Observed in Treatment-Naïve and Treatment-Experienced Studies even though once daily raltegravir 1200 mg did not meet criteria for terms in this subsection except for dyspepsia. Rationale: Exclusion implies once daily raltegravir may be safer than twice daily, but ONCEMRK showed once daily and twice daily raltegravir have a similar safety profile.

DRUG INTERACTIONS (7), CLINICAL PHARMACOLOGY (12)

- Edited to reflect conclusions described in Section 5.5 of this review.
- Tables reformatted or added for improved readability

PREGNANCY (8.1), LACTATION (8.2)

- Updated in accordance with PLLR formatting. Consultants from the Division of Pediatric and Maternal Health (DPMH) assisted with revising these sections.

CLINICAL STUDIES (14)

- Added a table (instead of text) with description of clinical studies displaying relevant information including trial name, type of study, patient population, dose, and formulation of drug.
- Merged demographic and efficacy tables for the STARTMRK and ONCEMRK trials similar to the formatting in the TIVICAY label.

PATIENT COUNSELING (17)

- Revised in accordance with the Guidance for Industry on Patient Counseling Information Section of Labeling.

13 Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

We recommend approval of raltegravir (Isentress HD) 600 mg tablet (dosed 1200 mg once daily) for adults and for pediatric patients at least 12 years of age and weighing at least 50 kg.

- Risk Benefit Assessment

The indication for the raltegravir 600 mg tablet administered as two tablets (1200 mg) once daily in combination with other antiretroviral agents in adults is directly supported by the primary efficacy results from the pivotal Phase 3 trial ONCEMRK. The indication of the same dosage and administration in pediatric patients at least 12 years of age and weighing at least 50 kg is supported by modeling and simulation analyses in addition to safety data in six pediatric participants from the IMPAACT P1066 trial. The efficacy and safety profile of once daily raltegravir is comparable to that of twice daily raltegravir. Therefore, the benefit-risk profile of once daily raltegravir is favorable and is comparable to that of twice daily raltegravir, with the added convenience of once daily dosing.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

There are no recommended postmarket REMS for this supplement.

- Recommendation for other Postmarketing Requirements and Commitments

The following PREA PMRs are recommended for once daily raltegravir pending discussion with the PeRC. Completion of these evaluations post rather than preapproval is appropriate because adult studies are complete and ready for approval.

- Recommended Comments to Applicant

We have no comments to add to the labeling comments sent to the Applicant on April 11, 2017, as of the time of finalization of the review.

14 Appendix 1

Covered Clinical Study: ONCEMRK PN292

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 689 Clinical Investigators/Subinvestigators		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 2. Neither of the two investigators are Merck employees, but both have a spouse who is a Merck employee.		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Significant payments of other sorts: Proprietary interest in the product tested held by investigator: Significant equity interest held by investigator in sponsor of covered study:		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 1		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from applicant)

One investigator did not return the form with requested information. The Applicant performed an internal search for this investigator for proprietary or financial interests and significant payments of other sorts; no financial interests or arrangements were identified. Financial disclosures do not affect approvability of this application.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SARITA D BOYD
04/20/2017

ADAM I SHERWAT
04/20/2017

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ADAM I SHERWAT
04/20/2017