アイセントレス錠600mg
に関する資料

MSD 株式会社

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1.1 Background

1.1.1 Therapeutic Class

Raltegravir (also known as ISENTRESS®, MK-0518 and L-000900612) is a human immunodeficiency virus (HIV) integrase strand transfer inhibitor active against HIV type 1 (HIV-1) [Sec. 2.4].

1.1.2 Approved Indications and Purpose of this Application

Raltegravir (ISENTRESS®, MK-0518, L-000900612) in combination with other antiretroviral agents (ART) is licensed worldwide for the treatment of HIV-1 infection in patients 4 weeks of age or older. It is dosed twice daily (BID) in all current formulations. Raltegravir is available and marketed as a 400 mg film-coated tablet formulation for patients weighing at least 25 kg, as a chewable tablet formulation in 100 mg (scored) and 25 mg strengths for patients weighing at least 10 kg, and as granules for suspension in patients weighing at least 3 kg. (References to the raltegravir 400 mg tablet in this document and throughout this submission refer to the marketed ISENTRESS® 400 mg film-coated tablet currently registered for twice daily use)

Licensure is now being sought for the use of a 600 mg film-coated tablet formulation (hereafter referred to as the 600 mg tablet), which has been developed for use as two tablets (1200 mg) taken once daily (QD). Raltegravir QD (2 x 600 mg tablets) will simplify dosing of raltegravir, providing a once daily dosing of a product with proven efficacy and safety in the treatment of HIV-1 infection. No revision is being sought to the current indication.

This application provides 1) the chemistry, manufacturing and control data; 2) pharmacokinetic (PK) data with modeling and simulation results; and 3) safety and efficacy data to support the use of raltegravir 1200 mg QD (2 x 600 mg tablets) in HIV-1 infected treatment-naïve patients and patients who are virologically suppressed on an initial regimen of ISENTRESS® 400 mg BID including adult and pediatric patients weighing at least 40 kg. The clinical development program included a single Phase 3 study (Protocol 292 [PN292]) and six Phase 1 studies (PN290, PN291, PN293, PN812, PN823, PN824).

1.1.3 Scientific Background

Over 25 individual agents are licensed to treat HIV-1 infection. These agents are members of 6 distinct mechanistic classes: nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), fusion/entry inhibitors (EIs), integrase strand transfer inhibitors (InSTI; also commonly referred to as integrase inhibitors), and pharmacokinetic enhancers [Ref. 5.4: 04DK0G, 04DK20]. Current guidelines for the management of treatment-naïve HIV-1 infected patients in various regions including the United States (US), United Kingdom (UK), and Europe (EACS) and elsewhere recommend 2 NRTIs and a third agent, generally of the InSTI or PI class [Ref. 5.4: 03QZJS, 04DK0G, 04DK20].

HIV infection requires life-long therapy, and patients must be highly adherent to avoid virologic failure and the development of resistance. HIV-infected patients often have concomitant medical conditions, necessitating the use of multiple medications for non-HIV related conditions. Thus, any measure to simplify HIV treatment increases the potential for improved adherence and overall therapeutic success. Raltegravir, with a well-established safety and efficacy profile, is currently administered twice daily. Once daily administration of raltegravir, as a regimen of two 600 mg tablets, will simplify therapy and thus has the potential to increase effectiveness by enhancing adherence.

For HIV therapy, it is estimated that HIV patients must be at least 95% adherent to maintain long-term efficacy [Ref. 5.4: 04DBN6, 04DCQR]. A meta-analysis of 207 studies across multiple socioeconomic cohorts found that although adherence is strongly related to psychological factors and beliefs about the necessity of treatment, simpler treatment regimens were also significantly related to adherence [Ref. 5.4: 04DBN4]. Among factors affecting the complexity of a dose regimen, pill count, dosing frequency, and adverse experiences are among the most significant in affecting adherence [Ref. 5.4: 04DCLH]. Cohen found an association between daily antiretroviral pill burden and treatment adherence, hospitalization risk, and other healthcare utilization and costs in a US Medicaid population with HIV [Ref. 5.4: 04DCQZ]. In a meta-analysis of randomized controlled studies from 4 electronic databases through 31 March 2013, lower pill burden was associated with both better adherence and virological suppression; adherence, but not virological suppression, was slightly better with once- vs twice-daily regimens [Ref. 5.4: 04DBNH]. In a meta-analysis of 11 randomized, controlled studies (n = 3029), once daily dosing improved adherence, particularly at treatment initiation and if all of the medications were administered once per day; these effects were compatible with better virologic outcome in selected subgroups [Ref. 5.4: 04DBP4]. On the basis of these findings, international guidelines now recommend the simplification of antiretroviral therapy where possible [Ref. 5.4: 04DCLS, 04DCQH, 04DCQ9].

Raltegravir was the first approved InSTI ART. Raltegravir inhibits the HIV integrase enzyme from inserting viral DNA into the host genome, an essential step in HIV replication. Raltegravir 400 mg BID has demonstrated characteristics which make it a useful option as first-line therapy for HIV-infected patients. These characteristics include potent antiviral activity, a favorable tolerability and safety profile, and few and manageable drug-drug interactions (DDIs). A once daily raltegravir dosing option would provide a more convenient treatment option for HIV-1 infected treatment-naïve patients and for continued treatment in patients who are virologically suppressed on an initial regimen of ISENTRESS® 400 mg BID, in adults and also in pediatric patients weighing at least 40 kg. It would facilitate adherence and improve the probability of achieving and maintaining optimal efficacy while retaining many of the favorable attributes of the ISENTRESS® 400 mg BID regimen.

1.1.4 Chemical and Pharmaceutical Properties

Raltegravir is currently available for twice daily dosing in the strengths and formulations mentioned above; a description of each formulation is available in the raltegravir product labels.

A 600 mg film-coated tablet formulation has been developed for use in a once daily regimen of two tablets as raltegravir 1200 mg QD (2 x 600 mg tablets) [Sec. 2.7.1]. This formulation is the subject of this Application.

The 400 mg tablet contains 434.4 mg of raltegravir (as potassium salt), equivalent to 400 mg of raltegravir and the following inactive ingredients: microcrystalline cellulose, dibasic calcium phosphate, lactose monohydrate, hypromellose, poloxamer 407, magnesium stearate, sodium stearyl fumarate and an OPADRY® II film coat, which contains the following inactive ingredients: polyvinyl alcohol, polyethylene glycol, talc, titanium dioxide, red iron oxide, and yellow iron oxide.

The 600 mg tablet contains 651.6 mg of raltegravir (as potassium salt), equivalent to 600 mg of raltegravir. Each 600 mg tablet contains the following inactive ingredients: hypromellose, croscarmellose sodium, microcrystalline cellulose, and magnesium stearate. The OPADRY® II film coat contains hypromellose, lactose monohydrate, triacetin, yellow iron oxide, ferrosoferric oxide, and titanium dioxide. The tablet may also contain trace amount of carnauba wax.

1.1.5 Overview of the Clinical Development Program

The development program in support of the raltegravir 1200 mg QD (2 x 600 mg tablets) dosing regimen included 6 Phase 1 studies (PN290, PN291, PN293, PN812, PN823, PN824) and one Phase 3 study (PN292). Results of these studies, along with modeling and simulation as described within this Application, support the addition of a 1200 mg QD (2 x 600 mg tablets) dosing regimen to the raltegravir product labeling.

A once daily regimen of raltegravir, using 800 mg QD (2 x 400 mg tablets) was previously evaluated in a Phase 3 study (PN071, QDMRK) [Ref. 5.4: 03RFJG, 03RJMH, 03RJMK]. PN071 evaluated the safety and efficacy of an investigational raltegravir dose, 800 mg QD [2 x 400 mg tablets], versus raltegravir 400 mg BID, each given in combination with a once-daily fixed-dose combination (FDC) of emtricitabine and tenofovir disoproxil fumarate (TRUVADA™), in adult treatment-naïve HIV-1-infected subjects. This study was terminated in 2010 after the primary efficacy analysis at Week 48 demonstrated that raltegravir 800 mg QD failed to meet the predefined statistical criterion for non-inferiority (lower bound of 95% CI for the treatment difference [QD-BID] not less than -10%), despite the response rates (proportion of subjects achieving HIV RNA < 50 copies/mL) exceeding 80% in both groups: 83% for 800 mg QD versus 89% for 400 mg BID. The treatment difference between the 800 mg QD group and 400 mg BID group was -5.7%, with an associated 95% CI of (-10.7%, -0.83%). The safety and tolerability profiles of the two study regimens were similar and consistent with raltegravir product labeling. Pharmacokinetic (PK) and efficacy data from PN071 were used to better understand the raltegravir PK/pharmacodynamic (PD) relationship. These analyses showed that a higher C_{trough} value increases the probability of achieving an HIV RNA level of <50 copies/ml, and a drop-off in efficacy was observed for subjects in the lowest quartile of C_{trough} (<25th percentile). Additionally, viral suppression of approximately 80% (<50 copies/mL) was achieved even in the lowest quartile of C_{trough} values [Ref. 5.4: 03RP3X].

Subsequent to PN071, the Sponsor conducted several Phase 1 studies to further characterize the PK profile of the 600 mg tablet at doses up to 1800 mg once daily, as well as to define exposure margins for safety and tolerability for the two formulations of raltegravir (400 mg and 600 mg tablets). The Phase 1 studies include: (1) a single-dose food effect study (PN290) evaluating raltegravir 1200 mg QD (as 3 x 400 mg tablets) and raltegravir 1200 mg QD (as 2 x 600 mg tablets) each administered in the fasted state, with a low-fat meal, and with a high-fat meal; (2) a multiple-dose (MD) study (PN291) evaluating raltegravir 1200 mg QD (as 3 x 400 mg tablets), raltegravir 1200 mg QD (as 2 x 600 mg tablets), and raltegravir 400 mg BID each administered for 5 days; and (3) a MD study (PN293) evaluating raltegravir 1800 mg QD (as 3 x 600 mg tablets) and matching placebo QD administered for 28 days ([Ref. 5.3.1.1: P290], [Ref. 5.3.1.1: P291], [Ref. 5.3.3.1: P293]).

To support selection of the QD dose and formulation for the Phase 3 study, full raltegravir PK profiles from PN035 (a food effect study previously conducted for ISENTRESS® 400 mg BID in healthy subjects), PN290 and PN291 were used in the PK/PD viral dynamic model to simulate the anticipated long-term efficacy for a combination regimen of raltegravir + NRTIs in treatment naïve HIV-infected patients [Ref. 5.3.5.3: 04CNKQ]. A dose of 1200 mg QD was predicted to have efficacy similar to raltegravir 400 mg BID, and a high probability of demonstrating non-inferiority in a Phase 3 trial. The 1200 mg QD dose was also expected to adequately increase raltegravir exposures (particularly C_{trough}) compared to the 800 mg QD dose, thus bringing the QD regimen closer to the BID regimen on the raltegravir exposure-efficacy curve. Therefore, raltegravir 1200 mg QD was the dose selected for further evaluation. Further analyses suggested that the 600 mg tablet formulation with better bioavailability and higher drug loading had less sensitivity to food intake and therefore this formulation was chosen to study the 1200 mg daily dose (administered as 2 x 600 mg tablets) in the current Phase 3 study (PN292).

PN292 is a double-blind study to evaluate the safety and efficacy of raltegravir 1200 mg QD (2 x 600 mg tablets) versus raltegravir 400 mg BID, each in combination with TRUVADA™, in treatment-naïve HIV-1 infected adult subjects. In total, 802 subjects were randomized in a 2:1 ratio: 533 to receive raltegravir 1200 mg QD (2 x 600 mg tablets) and 269 to receive raltegravir 400 mg BID. The primary Week 48 safety and efficacy analysis results are described within this Application ([Ref. 5.3.5.1: P292V01]). The 96-week study is currently ongoing and a secondary, final analysis will be performed at study completion.

In addition, three Phase 1 clinical pharmacokinetic DDI studies were conducted with efavirenz (PN812), atazanavir (PN823), and metal-cation antacids (PN824), to evaluate the effect of such coadministered drugs on raltegravir PK when raltegravir is administered as 1200 mg QD (2 x 600 mg tablets). These three studies were designed to corroborate the results observed for these DDIs when raltegravir is administered as 400 mg BID. Additionally, the impact of concomitant medications such as UGT modulators (inhibitor or inducer), TRUVADA™, proton-pump inhibitors (PPIs), and H_2 blockers were also evaluated using combined Phase 1 and Phase 3 data and population PK analysis [Sec. 2.7.2.3.3].

Population PK modeling with covariate analyses were conducted to understand the PK of raltegravir once daily and identify clinically meaningful intrinsic and extrinsic factors, using data from subjects receiving raltegravir 1200 mg QD (2 x 600 mg tablet) in five Phase 1

studies (PN290, PN291, PN812, PN823, PN824) with dense PK sampling and a double-blinded Phase 3 study (PN292) with sparse PK sampling [Sec. 2.7.2.2.2.1], [Sec. 2.7.2.3]. Additionally, exposure-response analyses of efficacy endpoints of interest (HIV RNA <40 copies/mL, change from baseline in cluster of differentiation 4 [CD4] cell count) with PN292 data were performed to characterize the potential relationship between PK and response endpoints in support of the recommended raltegravir 1200 mg once daily dosing regimen [Sec. 2.7.2.2.2.2]. Additionally, exploratory safety analyses based on PK exposure quartiles were conducted to confirm the lack of PK-safety relationship [Sec. 2.7.2.2.2.3].

Data from the Phase 3 study PN292 as well as modeling and simulation, support the intended use of raltegravir 1200 mg QD in HIV-1 infected treatment-naïve patients and for continued treatment in patients who are virologically suppressed on an initial regimen of ISENTRESS® 400 mg BID. Additionally, recently released Regulatory guidance regarding clinical trial designs for antiretroviral drugs confirms that the PN292 study design is adequate to support approval in the intended treatment population [Ref. 5.4: 04DT6Q].

Population modeling and simulation approaches were used to support the use of raltegravir 1200 mg QD (2 x 600 mg) dosing regimen in pediatric patients, where clinical experience of the same QD regimen is not available [Sec. 2.7.2.2.2.4]. The goal was to predict pediatric exposures as a function of weight, and to find a weight range such that raltegravir exposures were contained within the exposure range determined to be safe in adults from PN292. Because the PK exposure in children is expected to be similar to or higher than adults following the administration of the same dosing regimen, efficacy in children is expected to be maintained, and safety is the primary focus of the pediatric exposure simulations. Based on these analyses, the minimum body weight recommended for raltegravir 1200 mg QD used in pediatric patients is 40 kg [Sec. 2.7.2.3.2.2.1].

No new nonclinical studies have been performed to support the raltegravir 1200 mg QD Development Program [Sec. 2.4]. The nonclinical studies that supported administration of raltegravir BID also support raltegravir QD. Differences in the expected plasma exposures in humans administered 1200 mg (2 x 600 mg tablets) raltegravir QD and raltegravir 400 mg BID doses have been determined in clinical evaluation, necessitating presentation of the systemic exposure multiples achieved in pivotal toxicity and reproductive toxicity studies to the 1200 mg QD dose. Maximum oral and/or intravenous doses based on tolerability, formulation feasibility and/or systemic exposure were used in toxicity studies in rats, mice, and dogs to define the toxicity profile of raltegravir. Nonclinical evaluations did not demonstrate any direct potential toxicity relevant to human risk. Safety margins have been determined for each of the toxicities identified. Raltegravir was not shown to be a direct carcinogen when administered to rats and mice for 2 years. In developmental and reproductive toxicity studies, raltegravir has been shown not to pose a significant hazard to reproduction or to the developing fetus based on studies in rats and rabbits. Therefore, the results of these nonclinical toxicity studies support raltegravir use in clinical treatment of HIV-1 infection. All excipients used in the marketed approved 400 mg BID dose and raltegravir 600 mg film-coated tablet are commonly used in pharmaceutical manufacturing, therefore the nonclinical safety assessment studies conducted with nonclinical raltegravir formulations support 400 mg raltegravir BID and 1200 raltegravir QD clinical use.

[Table 2.5: 1] provides an overview of each clinical study included in the raltegravir Once Daily Development Program.

Table 2.5: 1 Overview of the Clinical Studies Included in the Once Daily Application

Protocol	Study Treatment	Number of Subjects Receiving Raltegravir†	Key Purpose	Major PK, Efficacy, and Safety Findings Regarding Raltegravir
Phase 1 Studies				
290 [Ref. 5.3.1.1: P290]	Raltegravir 1200 mg (2 x 600 mg tablets) Raltegravir 1200 mg (3 x 400 mg tablets)	36 Healthy male and female subjects ≥ 18 and ≤ 55 years of age	Food Effect	• All study treatments were generally well tolerated and there were no discontinuations due to adverse events (AEs) and no serious AEs (SAEs) reported during the treatment period. • Food had varied effects on the pharmacokinetics of raltegravir for both formulations. The impact of the food effect on the pharmacokinetics was assessed using simulations; simulations revealed that the 600 mg tablet had a smaller food effect profile as compared to the 400 mg tablet.
291 [Ref. 5.3.1.1: P291]	Raltegravir 1200 mg QD (2 x 600 mg tablets) for 5 days Raltegravir 1200 mg QD (3 x 400 mg tablets) for 5 days Raltegravir 400 mg BID (1 x 400 mg tablet) for 5 days	24 Healthy male and female subjects ≥ 18 and ≤ 55 years of age	PK	• All study treatments were generally well tolerated and there were no discontinuations due to AEs and no SAEs reported during the treatment period. • The population mean values for the C_{trough} were very similar between the raltegravir 600 mg tablet and 400 mg tablet when administered as 1200 mg once a day: 86.2 nM and 82.2 nM respectively. Likewise, the number of days required to reach at least 90% of steady-state was also very similar between the raltegravir 600 mg tablet and 400 mg tablet: 2.0 and 2.2, respectively. • The raltegravir 600 mg tablet and 400 mg tablet administered as 1200 mg QD showed higher bioavailability when compared to treatment with the 400 mg tablet dosed as 400 mg BID. The AUC_{24} geometric mean (GM) was 2.3 and 1.9 times larger, respectively.
293 [Ref. 5.3.3.1: P293]	Raltegravir 1800 mg QD (3 x 600 mg tablets) for 28 days	24 Healthy male and female subjects ≥ 18 and ≤ 55 years of age	PK and safety	• Administration of raltegravir 1800 mg QD (3 x 600 mg tablets) was generally well tolerated in healthy subjects. No SAEs were reported, and no subject discontinued the study due to adverse events. • The mean values of C_{max}, C_{24hr}, $AUC_{0\text{-}24hr}$ were 25300 nM, 110 nM, 60300 h·nM and 29000 nM, 88.5 nM, 74500 h·nM after multiple-dose administration of raltegravir on Days 14 and 28 in healthy subjects, respectively. • The median value of T_{max} was 1.5 hours after multiple-dose administration of raltegravir on Days 14 and 28 in healthy subjects. • The percentage of subjects with trough concentrations of raltegravir >45 nM after multiple-dose administration of raltegravir on Days 7, 10, 14, 21 and 28 ranged from 56 to 78%.

812 [Ref. 5.3.2.2: P812]	Raltegravir 1200 mg QD (2 x 600 mg tablets); Efavirenz 600 mg QD (1 x 600 mg tablet) + raltegravir 1200 mg QD (2 x 600 mg tablets) on Day 12	21 Healthy male and female subjects ≥ 19 and ≤ 55 years of age	Drug-Drug Inter-action	• Administration of single 1200 mg oral doses of raltegravir alone and coadministered with multiple oral doses of efavirenz was generally well tolerated. No SAEs were reported. One subject was discontinued from the study by the Investigator prior to the second dose of efavirenz alone due to the AEs of dizziness and feeling drunk which the investigator attributed to efavirenz. • Raltegravir was rapidly absorbed with an observed median T_{max} of 1.5 hours following both treatments. • The geometric mean apparent terminal t½ values were similar following dosing with raltegravir alone and raltegravir + efavirenz (8.95 hours and 8.87 hours, respectively). • Co-administration with efavirenz yielded GMRs (raltegravir + efavirenz/ raltegravir alone) (90% CIs) for raltegravir $AUC_{0-\infty}$, C_{max}, and C_{24} of 0.86 (0.73, 1.01), 0.91 (0.70, 1.17), and 0.94 (0.76, 1.17), respectively. • While the co-administration of efavirenz and raltegravir modestly reduces plasma levels of raltegravir, these changes are not considered clinically meaningful (lower bound of 90% CI of C_{24} geometric mean ratio (GMR) is greater than lower clinical bound); thus, coadministration of raltegarvir 1200 mg QD and efavirenz is permitted (refer to [Sec. 2.7.2] for bounds discussion).
823 [Ref. 5.3.2.2: P823]	Raltegravir 1200 mg QD (2 x 600 mg tablets); Atazanavir 400 mg QD (2 x 200 mg tablets) + raltegravir 1200 mg QD (2 x 600 mg tablets) on Day 7	14 Healthy male and female subjects ≥ 19 and ≤ 55 years of age	Drug-Drug Inter-action	• Multiple oral doses of atazanavir and single oral doses of raltegravir were generally well tolerated when co-administered in healthy adult subjects in this study. No SAEs were reported. The Investigator discontinued 1 subject on Day 5 of Period 2 due to the mild laboratory AEs of increased blood bilirubin and increased unconjugated blood bilirubin, which the Investigator considered related to atazanavir alone. • Co-administration with atazanavir yielded GMRs (90% CIs) for raltegravir $AUC_{0-\infty}$, C_{max}, and C_{24} of 1.67 (1.34, 2.10), 1.16 (1.01, 1.33), and 1.26 (1.08, 1.46), respectively. • The impact of the atazanavir on raltegravir 1200 mg QD PK is significant, with an upper bound of 90% CI of AUC GMR greater than the upper clinical bound of 2.0; thus, coadministration of raltegravir 1200 mg QD and atazanavir is not recommended (refer to [Sec. 2.7.2] for bounds discussion).

824 [Ref. 5.3.2.2: P824]	Raltegravir 1200 mg QD (2 x 600 mg tablets) 5 days prior to Period 1; Raltegravir 1200 mg QD (2 x 600 mg tablets) Raltegravir 1200 mg QD (2 x 600 mg tablets) + 3 tablets of TUMS® Ultra Strength (US) 1000 mg given concomitantly Raltegravir 1200 mg QD (2 x 600 mg tablets) + 20 mL MAALOX® Maximum Strength (MS) given 12 hours after administration Raltegravir 1200 mg QD (2 x 600 mg tablets) + 3 tablets of TUMS® Ultra Strength (US) 1000 mg given 12 hours after administration	22 HIV-infected volunteers Male and female subjects ≥ 19 and ≤ 55 years of age	Drug-Drug Inter-action	• Raltegravir, administered alone or with TUMS® Ultra Strength (US) and MAALOX® MS (or generic equivalent), was generally well-tolerated in HIV-infected subjects. No deaths were reported. Four (4) SAEs were reported by 1 subject. This subject was briefly hospitalized for chest pain, dyspnoea, orthostatic hypotension and rash 9 days following dosing with raltegravir and TUMS® Ultra Strength (US), staggered by 12 hours later. Each of the SAEs were of moderate intensity. The rash was considered reasonably related to the study medication and the chest pain, dyspnoea and orthostatic hypotension were considered not related. The orthostatic hypotension resolved after 2 days and the other three SAEs resolved within 21 days. • Three (3) tablets of TUMS® Ultra Strength 1000 mg given concomitantly with 1200 mg raltegravir yielded GMRs (90% confidence intervals [CIs]) for raltegravir AUC_{0-24}, C_{max}, and C_{24} of 0.28 (0.24, 0.32), 0.26 (0.21, 0.32), and 0.52 (0.45, 0.61) respectively, compared to 1200 mg raltegravir alone. Median T_{max} remained unchanged. • Twenty (20) mL MAALOX® MS (or generic equivalent) given 12 hours after administration of 1200 mg raltegravir yielded GMRs (90% CIs) for raltegravir AUC_{0-24}, C_{max}, and C_{24} of 0.86 (0.73, 1.03), 0.86 (0.65, 1.15), and 0.42 (0.34, 0.52) respectively, compared to 1200 mg raltegravir alone. Median T_{max} remained unchanged. • Three (3) tablets of TUMS® Ultra Strength 1000 given 12 hours after administration of 1200 mg raltegravir yielded GMRs (90% CIs) for raltegravir AUC_{0-24}, C_{max}, and C_{24} of 0.90 (0.80, 1.03), 0.98 (0.81, 1.17), and 0.43 (0.36, 0.51) respectively, compared to 1200 mg raltegravir alone. Median T_{max} remained unchanged. • The impact of the metal-cation antacids generated clinically meaningful reduction in the plasma trough levels of raltegravir (lower bound of 90% CI of C_{24} GMR is lower than lower clinical bound of 0.75); thus, coadministration of aluminum/magnesium and calcium carbonate containing antacids (concomitantly or staggered by 12 hours) with raltegravir 1200 mg QD is not recommended (refer to [Sec. 2.7.2] for bounds discussion).
Phase 3 Study				
292 [Ref. 5.3.5.1: P292V01]	Raltegravir 1200 mg QD (2 x 600 mg tablets) + TRUVADA™ QD; Raltegravir 400 mg BID (1 x 400 mg	802 Male and female HIV-1 infected, treatment-naive subjects ≥ 18 years of age	Inter-vention al	• Compared to raltegravir 400 mg BID at Week 48, raltegravir 1200 mg QD demonstrated potent and statistically non-inferior antiretroviral activity (HIV RNA <40 copies/mL), and similar robust immunologic efficacy (as measured by change from baseline in CD4 cell counts), when each is given in combination with TRUVADA™. Efficacy of both groups was consistent regardless of baseline demographic and prognostic factors, including high baseline viral load.

	tablet) + TRUVADA™ QD			• Raltegravir 1200 mg QD was generally well tolerated with a similar overall safety profile to raltegravir 400 mg BID. Both treatments were generally well tolerated regardless of baseline demographic and prognostic factors. • Based on the observed sparse concentration of raltegravir (collected up to treatment week 24), the geometric mean and corresponding 95% CI of C_{all}, C_{trough} and C_{min} after administration of multiple doses of 1200 mg QD were 963.52 nM (887.85, 1045.64) 122.08 nM (109.97, 135.53), and 79 nM (71.28, 87.54), respectively. The values of PK exposure endpoints, particularly C_{trough} and C_{min}, of raltegravir 400 mg BID observed in this study were generally consistent with those previously observed in the raltegravir BID development program. • No clinically significant association was found between PK exposures and the primary and secondary efficacy endpoints (HIV RNA <40 copies/mL and change in baseline CD4 cell counts) for raltegravir data from PN292. Maximum response was likely achieved across the PK exposure range for both raltegravir 1200 mg QD and ISENRESS 400 mg BID treatment regimens. These conclusions are consistent with previous PK/PD findings from ISENTRESS® 400 mg BID. • No clinically meaningful adverse events that were related to raltegravir administration were observed in PN292. Exploratory safety analysis based on PK exposure quartiles (AUC_{0-24h} and C_{max}) confirmed the lack of any potential increased risks associated with the highest exposures from the raltegravir 1200 mg QD regimen.

Data Source: [Ref. 5.3.1.1: P290], [Ref. 5.3.1.1: P291], [Ref. 5.3.3.1: P293], [Ref. 5.3.2.2: P812], [Ref. 5.3.2.2: P823], [Ref. 5.3.2.2: P824], [Ref. 5.3.5.1: P292V01]

1.1.6 Regulatory Guidance and Advice

Advice from the United States Food and Drug Administration (FDA)

Agency advice was sought during the raltegravir Once Daily Development Program. Formal guidance was obtained from the US FDA on [redacted] in 20[redacted]. FDA concurrence was obtained on the following key points [redacted]:

1. [redacted].
2. The following points regarding [redacted] were confirmed: [redacted].
3. [redacted]
4. [redacted].

Per Agency request, [redacted] was submitted for Agency review and approval [redacted]. The proposal included, [redacted]. The approved [redacted] also included agreement to [redacted].

Scientific Advice from the Committee for Medicinal Products for Human Use

[redacted] However in 20[redacted], the Applicant received CHMP scientific advice for [redacted]. The CHMP indicated in its advice regarding [redacted] and was previously agreed to by the CHMP (EMEA/CHMP/[redacted]) and FDA.

[redacted]

1.2 Implications to Product Label

The proposed raltegravir product labeling in the US and EU and worldwide has been updated to appropriately reflect the information regarding the new dosing regimen of 1200 mg QD (2 x 600 mg tablets). There is no proposed revision to the current raltegravir indication. The dosage and administration section has been revised to include the intended patient population (HIV-1 infected treatment-naïve patients and patients who are virologically suppressed on an initial regimen of ISENTRESS® 400 mg BID including adult and pediatric patients weighing at least 40 kg).

Depending on the country, the proposed raltegravir product labeling has been updated in relevant sections or alternatively, a specific 600 mg raltegravir product label has been developed to provide details on the appropriate dosage and administration of raltegravir 1200 mg QD (2 x 600 mg tablets) and the available clinical and PK data supporting the raltegravir 1200 mg QD dosing regimen. The raltegravir product labeling has also been revised based on the evaluation of drug-drug interactions with the 1200 mg QD regimen.

The proposed updated raltegravir product labeling, which is submitted with this Application, instructs physicians not to substitute the 400 mg tablet for the 600 mg tablet to create a 1200 mg once daily dose and not to substitute the chewable tablet or the granules for suspension for the 400 mg or 600 mg tablet, because the formulations have different pharmacokinetic profiles. The 400 mg marketed tablet formulation is not intended for QD use and the 600 mg tablet formulation is not intended for BID use.

1.3 Good Clinical Practice

The clinical trials were conducted in accordance with current standard research approaches with regard to the design, conduct, and analysis of such trials including the archiving of essential documents. The Clinical Study Report (CSR) and Statistical Analysis Plan (SAP) for each study were available to prepare this Clinical Overview. All trials were conducted following appropriate Good Clinical Practice standards and considerations for the ethical treatment of human subjects that were in place at the time the trials were performed. Data presented in this Once Daily Application and information presented in this Clinical Overview were subject to audit by Merck Worldwide Quality Assurance Resources groups based on approved Standard Operating Procedures (SOPs) in effect at the time of the audit. Reported protocol deviations can be found in the individual clinical study reports.

After the PN292 Week 48 database lock ([redacted]), the Sponsor identified deviations with Good Clinical Practice (GCP) and Good Documentation Practice (GDP) at Site 157 (enrolled 11 subjects) including delayed reporting of adverse events, which resulted in exclusion of these adverse events from the data included in the database lock for the 48 week CSR. As a result of the identification of these deviations, the Sponsor performed sensitivity analyses of key efficacy and safety endpoints excluding all data from this site, and also reviewed preliminary data on the above noted adverse events. These analyses are provided in a separate sensitivity analysis report [Ref. 5.3.5.1: 04FHKK]. The sensitivity analyses demonstrate that exclusion of study results from this site do not impact the conclusions of the Week 48 PN292 CSR regarding the safety and efficacy of once daily raltegravir. A complete

review of safety data from this site will be included in a Safety Update Report (SUR) and the final Week 96 PN292 CSR.

2 OVERVIEW OF BIOPHARMACEUTICS

A summary of the biopharmaceutic properties of raltegravir evaluated in the Once Daily Development Program is presented in [Sec. 2.7.1]. The studied formulations of the 600 mg tablet differed in the film-coat used in the Phase 1 (PN290, PN291 and PN293), Phase 3 (PN292), and final market image (FMI) formulations. The FMI formulation was used in the 3 DDI studies (PN812, PN823, and PN824). The film-coat change between the Phase 1 to Phase 3 formulations involved the minor change of the addition of coloring agents. The Phase 3 to FMI formulation changes were different OPADRY® non-functional film-coatings, the addition of wax, and debossment. The Phase 3 and FMI tablets demonstrated similar dissolution profiles in comparative dissolution studies [Sec. 2.3.P.2], ([Ref. 5.3.1.1: P290], [Ref. 5.3.1.1: P291], [Ref. 5.3.3.1: P293], [Ref. 5.3.5.1: P292V01], [Ref. 5.3.2.2: P812], [Ref. 5.3.2.2: P823], [Ref. 5.3.2.2: P824]).

The biopharmaceutics of raltegravir 1200 mg QD (either as 3 x 400 mg tablets or 2 x 600 mg tablets) were assessed in two Phase 1 studies (PN290 and PN291) conducted in healthy subjects. The results of these studies, together with modeling and simulation, confirmed the pharmacokinetic profile necessary for efficacy with once daily administration ([Ref. 5.3.1.1: P290], [Ref. 5.3.1.1: P291]).

The effect of food on a single dose of raltegravir 1200 mg QD (2 x 600 mg tablets) was assessed in PN290 [Sec. 2.7.1.2.1.1]. Administration of a low fat meal decreased the rate and extent of absorption of raltegravir 1200 mg QD (2 x 600 mg tablets); on average there was a 42% decrease in $AUC_{0\text{-last}}$, 52% decrease in C_{max}, and 16% decrease in C_{24hr} compared to the fasted state. Administration of a high fat meal decreased the rate but not the extent of absorption of raltegravir 1200 mg QD (2 x 600 mg tablets) (on average, a 1.9% increase in $AUC_{0\text{-last}}$, 28% decrease in C_{max}, and 12% decrease in C_{24hr}). The decrease in raltegravir exposure using 2 x 600 mg tablets observed following a low fat meal is consistent with the food effect observed for the 400 mg BID formulation, while the changes observed following a high fat meal were less than those observed for the 400 mg BID formulation ([Ref. 5.3.1.1: P290]). An integrated analysis using modeling showed that raltegravir 1200 mg QD can be dosed without regard to food [Sec. 2.7.1.3.2], and these were the instructions given in PN292.

In PN291 subjects received multiple daily doses of raltegravir 1200 mg QD (2 x 600 mg tablets) for 5 days, and this resulted in no accumulation in $AUC_{0\text{-}24}$ and C_{max} on Day 5 relative to Day 1. Therefore the PK parameter values observed in this study on Day 5 are similar to those observed in the single dose study PN290 and single dose PK is predictive of steady state exposure.

Results from PN290 and PN291 were instrumental in selecting the raltegravir 600 mg tablet for further clinical development. A viral dynamics PK/PD model, developed using PK and efficacy data from prior raltegravir clinical studies and linking antiviral efficacy to the raltegravir PK profile, was used to assess the probability of demonstrating non-inferiority for

raltegravir 1200 mg QD compared to 400 mg BID. Simulations from the viral dynamics model using PK data from PN290 and PN291 predicted that raltegravir formulated for once daily use, at a dose of 1200 mg QD (2 x 600 mg tablets) will have efficacy similar to raltegravir 400 mg BID. Simulations were also used to explore the impact of the food effect observed in PN290, and indicated that efficacy was likely to be maintained even in a scenario where raltegravir is taken consistently with a low-fat meal [Sec. 2.7.1.3.2]. Consequently, the 600 mg tablet was carried forward into the Phase 3 study PN292, with instructions to dose without regard to food intake. The robust safety and efficacy results from the 1200 mg QD (2 x 600 mg tablets) arm of PN292 support the appropriateness of this dose and formulation for once daily dosing, and that the food effect observed in PN290 is not of clinical importance (that is, once daily raltegravir can be dosed without regard to food intake).

3 OVERVIEW OF CLINICAL PHARMACOLOGY

In this raltegravir Once Daily Application, results from PN290 and PN291 showed that raltegravir at a dose of 1200 mg QD (2 x 600 mg tablets) is rapidly absorbed with median time to maximum plasma concentration (T_{max}) of ~1.5 to 2 hours in the fasted state, and generates a sharper absorption peak with a tendency to higher C_{max} in comparison to raltegravir BID (1 x 400 mg tablet twice daily) [Sec. 2.7.2.3.1]. Relative to raltegravir 400 mg BID (1 x 400 mg tablet), raltegravir 600 mg tablet formulation has higher dose-normalized systemic exposure (greater $AUC_{0\text{-}24hr}$/Dose by approximately 21-66%), and in general, a similar or smaller food effect (see [Sec. 2.5.2] and [Sec. 2.7.1.3.2] for further discussion of food effect). Following oral absorption, the systemic disposition of raltegravir QD (e.g., distribution and elimination kinetics) is comparable to that previously observed from the twice daily development program. The apparent terminal elimination half-life is approximately 9 to 12 hours with a shorter α-phase half-life (~1 hour) accounting for much of the AUC. Steady-state is generally reached in 2 days, with little to no accumulation with multiple dose administration [Sec. 2.7.2.3.1], [Ref. 5.3.1.1: P290, P291] [Ref. 5.3.3.1: P293].

A number of DDI studies were conducted for ISENTRESS® 400 mg BID and the findings can be extended to raltegravir 1200 mg QD, including assessment of raltegravir as a victim or as a perpetrator of drug interactions, though it should be noted that the criteria for a clinically important change in raltegravir PK are different for 1200 mg QD than for 400 mg BID. Raltegravir is not a substrate of CYP enzymes; and therefore it is not expected to be a victim of DDIs via CYP inhibition or induction. Based on in vivo and in vitro studies, raltegravir is eliminated mainly by metabolism via a UGT1A1-mediated glucuronidation pathway and coadministration of UGT1A1 inhibitors or inducers may alter plasma levels of raltegravir. Raltegravir is not a potent inhibitor or inducer of major drug metabolizing enzymes in vitro. Raltegravir did not meaningfully alter the pharmacokinetics of midazolam, providing evidence that raltegravir has a low propensity for perpetrating drug interactions with substrates of CYP3A4. In addition, raltegravir is not a potent inhibitor of drug efflux and uptake transporters in vitro [Sec. 2.7.2.1.2]. Additionally, raltegravir (400 mg BID) was demonstrated not to meaningfully alter the pharmacokinetics of hormonal contraceptives, methadone, tenofovir, lamivudine, etravirine, darunaivr/ritonavir and boceprevir. Additional details on the evaluation of DDIs with raltegravir 1200 mg QD can be found in [Sec. 2.7.2.3.3.1].

The pharmacokinetic profiles are different for raltegravir 1200 mg QD and ISENTRESS® 400 mg BID (higher steady state daily AUC and C_{max} and lower C_{trough} for 1200 mg QD compared to 400 mg BID); therefore, the criteria that define a clinically important change in PK are different. No clinically relevant difference in the efficacy of raltegravir 1200 mg QD is anticipated for factors that decrease raltegravir C_{trough} by <25%; specifically, the lower bound of the 90% confidence interval (CI) of C_{trough} geometric mean ratio (GMR) must be >0.75. Additionally, no clinically relevant difference in the safety of raltegravir 1200 mg QD is anticipated for factors that increase raltegravir AUC_{0-24} by <100%; specifically, the upper bound of the 90% CI of AUC_{0-24} GMR must be <2.00. Details on the comparability bounds established to define a clinically important change in raltegravir 1200 mg QD PK are described in [Sec. 2.7.2.1.3.4].

Evaluations of extrinsic factor effects for raltegravir 1200 mg QD were performed based on dedicated Phase 1 DDI studies, the population pharmacokinetic analysis, and evaluation of data from prior raltegravir submissions, in light of the newly established clinical bounds for raltegravir 1200 mg QD dosing. Based on the data from three DDI studies, a raltegravir/efavirenz interaction study in healthy volunteers (PN812), a raltegravir/atazanavir interaction study in healthy volunteers (PN823), and a raltegravir/antacid interaction study in HIV-infected subjects (PN824), coadministration of raltegravir 1200 mg QD with efavirenz is permitted. However, coadministration of atazanavir or aluminum/magnesium and calcium carbonate antacids (concomitantly or staggered by 12 hours) with raltegravir 1200 mg QD is not recommended.

Population PK analysis of the extrinsic factors were also conducted with detailed discussion in [Ref. 5.3.5.3: 04C39T], [Sec. 2.7.2.3.3]. Two additional types of drug interactions were evaluated in the population PK analysis, TRUVADA™ and proton-pump inhibitors (PPIs) and H2 blockers. Their impact on raltegravir PK is not clinically meaningful (8.8% - 12% change in raltegravir bioavailability). Thus coadministration of raltegravir 1200 mg QD with these agents is permitted. Additionally, the coadministration of raltegravir 1200 mg QD and strong inducers of drug metabolizing enzymes (e.g., rifampin, phenytoin and phenobarbital) or tipranavir/ritonavir is not recommended, due to the potential for clinically meaningful reductions in raltegravir trough concentrations [Sec. 2.7.2.3.3.1.2].

The impact of intrinsic factors including body weight, race, ethnicity, gender, and HIV infection, on the PK of raltegravir 1200 mg QD was assessed through population PK analysis of a pooled dataset containing data from Phase 1 studies and the Phase 3 study PN292 [Ref. 5.3.5.3: 04C39T]. Details are described in [Sec. 2.7.2.2.2] and [Sec. 2.7.2.3.2]. Findings from these analyses were largely consistent with historical data from the raltegravir twice daily development program, where no dose adjustment is needed. Additionally, specific attributes of raltegravir pharmacokinetics from prior raltegravir submissions are considered applicable to the current Once Daily Development Program, including renal impairment, hepatic impairment and effect on QTc. Raltegravir 1200 mg QD has not been evaluated in a pediatric clinical study. However, this dose can be recommended in pediatric patients with a body weight of at least 40 kg and is supported by pediatric simulations, with details described in [Sec. 2.7.2.2.2.4] and [Sec. 2.7.2.3.2.2.1].

Exposure-efficacy analysis was conducted to assess the relationship between PK and efficacy endpoints of both raltegravir treatment arms in PN292 [Ref. 5.3.5.3: 04C3B0]. Details of the analysis and results are described in [Sec. 2.7.2.1.3.2] and [Sec. 2.7.2.2.2.2]. Overall, findings from this analysis showed that the efficacy target in terms of viral suppression is achieved even in the lowest quartile (< 25th percentile) of the C_{trough} values from raltegravir 1200 mg QD. No clinically significant association was found between PK exposures and the primary and secondary efficacy endpoints from PN292. Maximum viral suppression (HIV-1 RNA <40 copies/mL) was achieved at the PK exposure range obtained with these treatment regimens in PN292. This is consistent with previous raltegravir PK/PD findings, which demonstrated that raltegravir efficacy from ISENTRESS® 400 mg BID is at the plateau region of the exposure-efficacy curve.

No clinically meaningful adverse events that were related to raltegravir administration were observed in PN292 [Sec. 2.5.5.2.1]. Exploratory safety analyses based on raltegravir PK quartiles ($AUC_{0\text{-}24h}$ and C_{max}) also confirmed the lack of exposure-safety association within the exposure range of the 1200 mg QD regimen [Sec. 2.7.2.1.3.3] and [Sec. 2.7.2.2.2.3].

3.1 Summary of Human Pharmacokinetic Studies for Once-Daily Raltegravir

A total of six (6) Phase 1 studies were performed in healthy and HIV-infected subjects to evaluate the pharmacokinetics of once daily raltegravir. Three studies (PN290, PN291, and PN293) were performed prior to the initiation of PN292, the large Phase 3 study to establish non-inferior efficacy of raltegravir 1200 mg QD versus raltegravir 400 mg BID in HIV-1 infected treatment naïve subjects. Sparse pharmacokinetic sampling was collected in this Phase 3 study to explore exposure/response relationships. Three other Phase 1 studies were performed during Phase 3 with the final market image product (PN812, PN823, and PN824). Five (5) of the Phase 1 studies were performed in healthy subjects (N = 119) and included a single dose food effect study (PN290), a 5 day multiple dose study (PN291), a 28-day multiple dose study (PN293), a DDI study with efavirenz (PN812), and a DDI study with atazanavir (PN823). One Phase 1 study was performed in HIV-infected subjects (N = 22) and included a DDI study with metal containing antacids (PN824). Data from the biopharmaceutic studies (PN290 and PN291) can be found in [Sec. 2.7.1].

In PN293, a multiple dose PK and safety study was conducted in which subjects received raltegravir 1800 mg QD (3 x 600 mg tablets) or placebo for 28 days. The PK results indicate exposure with raltegravir 1800 mg QD is modestly higher compared to that of raltegravir 1200 mg QD (2 x 600 mg tablets) in the other Phase 1 studies (PN290 and PN291), indicating no further exposure increase with increase in dose ([Ref. 5.3.3.1: P293], [Ref. 5.3.1.1: P290], [Ref. 5.3.1.1: P291]).

In PN812, a drug interaction study was conducted with efavirenz which is known to induce UGT1A1 (a primary elimination pathway for raltegravir) and was selected to assess whether decreases in raltegravir pharmacokinetics at a dose of 1200 mg (2 x 600 mg tablets) were clinically meaningful when coadministered with moderate inducers. Raltegravir was rapidly absorbed with an observed median T_{max} of 1.5 hours following both treatments. The geometric mean apparent terminal $t_{½}$ values were similar following raltegravir alone and raltegravir + efavirenz (8.95 hours and 8.87 hours, respectively). Coadministration with

efavirenz yielded GMRs (raltegravir + efavirenz/raltegravir alone) (90% CIs) for raltegravir $AUC_{0-\infty}$, C_{max}, and C_{24} of 0.86 (0.73, 1.01), 0.91 (0.70, 1.17), and 0.94 (0.76, 1.17), respectively. While the coadministration of efavirenz and raltegravir 1200 mg QD modestly reduces plasma levels of raltegravir, these changes are not considered to be clinically meaningful ([Ref. 5.3.2.2: P812]) and coadministration is permitted.

In PN823, a drug interaction study was conducted with atazanavir, a known inhibitor of UGT1A1. Atazanavir was selected to assess the expected upper limit of increases in raltegravir pharmacokinetics at a dose of 1200 mg (2 x 600 mg tablets) anticipated due to drug interactions. Coadministration with atazanavir yielded GMRs (90% CIs) for raltegravir $AUC_{0-\infty}$, C_{max}, and C_{24} of 1.67 (1.34, 2.10), 1.16 (1.01, 1.33), and 1.26 (1.08, 1.46), respectively [Ref. 5.3.2.2: P823]. The impact of the atazanavir on raltegravir 1200 mg QD PK is significant, with an upper bound of 90% CI of AUC GMR greater than the upper clinical bound of 2.0; thus, coadministration of raltegravir 1200 mg QD and atazanavir is not recommended.

In PN824, a drug interaction study was conducted with metal-cation containing antacids in 22 HIV-infected subjects. The binding of the metal-binding motif in raltegravir with the divalent metal-cation contained in some antacids could result in decreased raltegravir absorption and diminished plasma concentrations at a dose of 1200 mg (2 x 600 mg tablets). Three (3) tablets of TUMS® Ultra Strength 1000 mg given concomitantly with 1200 mg raltegravir yielded GMRs (90% CIs) for raltegravir AUC_{0-24}, C_{max}, and C_{24} of 0.28 (0.24, 0.32), 0.26 (0.21, 0.32), and 0.52 (0.45, 0.61) respectively, compared to 1200 mg raltegravir alone. Twenty (20) mL MAALOX® MS (or generic equivalent) given 12 hours after administration of 1200 mg raltegravir yielded GMRs (90% CIs) for raltegravir AUC_{0-24}, C_{max}, and C_{24} of 0.86 (0.73, 1.03), 0.86 (0.65, 1.15), and 0.42 (0.34, 0.52) respectively, compared to 1200 mg raltegravir alone. Three (3) tablets of TUMS® Ultra Strength 1000 given 12 hours after administration of 1200 mg raltegravir yielded GMRs (90% CIs) for raltegravir AUC_{0-24}, C_{max}, and C_{24} of 0.90 (0.80, 1.03), 0.98 (0.81, 1.17), and 0.43 (0.36, 0.51) respectively, compared to 1200 mg raltegravir alone ([Ref. 5.3.2.2: P824]). The impact of the metal-cation antacids generated clinically meaningful reduction in the plasma trough levels of raltegravir (lower bound of 90% CI of C_{24} GMR is lower than lower clinical bound of 0.75); thus, coadministration of aluminum/magnesium and calcium carbonate containing antacids (concomitantly or staggered by 12 hours) with raltegravir 1200 mg QD is not recommended.

3.2 Clinical Pharmacology Conclusions

1. Following oral absorption, the systemic disposition of raltegravir 1200 mg QD (e.g., distribution and elimination kinetics) is comparable to that previously observed with ISENTRESS® 400 mg BID. Raltegravir 1200 mg QD (2 x 600 mg tablets) has higher systemic exposure (greater AUC_{0-24} by approximately 21-66% compared to 1200 mg QD [3x400 mg tablets] and 2.3-fold compared to 400 mg BID). In Phase 1 studies in healthy adults and adults with HIV infection, both single doses of 1200 mg (administered as 2 x 600 mg tablets) and multiple doses of 1200 mg (administered as 2 x 600 mg tablets) or 1800 mg (administered as 3 x 600 mg tablets) QD were generally well tolerated. The safety profile of the 1200 mg QD regimen is consistent with prior findings in the BID program. The new dosing regimen is supported by the favorable safety profile of raltegravir QD.
2. Exposure-response relationships were characterized based on the results of the Phase 3 non-inferiority study PN292 of raltegravir 1200 mg QD vs. 400 mg BID which provided confirmatory evidence of the potent efficacy and the favorable safety profile of raltegravir 1200 mg QD (administered as 2 x 600 mg tablets).
    a. Based on the efficacy analysis of PN292 by PK exposure quartiles (C_{trough} values), efficacy target in terms of viral suppression (HIV RNA < 40 copies/mL) was achieved even in the lowest quartile (< 25th percentile) of the C_{trough} values from raltegravir 1200 mg QD. No clinically significant association was found between PK exposures and the primary (HIV RNA < 40 copies/mL) and secondary efficacy (change in CD4 cell counts) endpoints for raltegravir QD and BID, and maximum response was likely achieved across the PK exposure range resulting from both QD and BID treatment regimens. Exposure-efficacy analysis of raltegravir supports that continued treatment with raltegravir 1200 mg QD is comparable to continued treatment with raltegravir 400 mg BID; thus, patients suppressed on raltegravir BID can be switched to raltegravir QD, with equivalent virologic outcomes.
    b. No clinically meaningful adverse events that were related to raltegravir administration were observed in PN292. Exploratory safety analyses based on PK exposure quartiles (AUC_{0-24h} and C_{max}) confirmed the lack of any potential increased risks associated with the highest exposures from the raltegravir 1200 mg QD regimen.
3. No clinically relevant difference in the efficacy of raltegravir 1200 mg QD is anticipated for factors that decrease raltegravir C_{trough} by <25%, specifically, the lower bound of the 90% confidence interval (CI) of C_{trough} geometric mean ratio (GMR) must be >0.75. Additionally, no clinically relevant difference in the safety of raltegravir 1200 mg QD is anticipated for factors that increase raltegravir AUC_{0-24} by <100%, specifically, the upper bound of the 90% CI of AUC_{0-24} GMR must be <2.00. Intrinsic and extrinsic factor effects that fall within these clinical comparability bounds are considered not clinically relevant and no alteration in the dosing guidance would be needed for those factors.

4. Raltegravir has a low propensity to be involved in DDIs either as a victim or as a perpetrator. Findings from clinical studies conducted for ISENTRESS® 400 mg BID to evaluate the impact of raltegravir on coadministered drugs, and to evaluate the impact on raltegravir PK by coadministered drugs (e.g., strong inducers of drug metabolizing enzymes) can be extended to raltegravir 1200 mg QD. The impact of strong inducers of drug metabolizing enzymes (e.g., rifampin, phenytoin and phenobarbital), and tipranavir/ritonavir on raltegravir 1200 mg QD are unknown, but given their significant potential to decrease raltegravir trough levels, coadministration of these agents with raltegravir 1200 mg QD is not recommended.
5. DDIs between raltegravir 1200 mg QD and efavirenz, atazanavir or aluminum/ magnesium and calcium carbonate containing antacids (TUMS® and MAALOX®) were investigated in dedicated Phase 1 clinical studies. Interaction with efavirenz was not clinically meaningful, and coadministration of moderate and weak inducers with raltegravir 1200 mg QD is permitted. However, the impact of atazanavir and aluminum/magnesium and calcium carbonate antacids on raltegravir 1200 mg QD pharmacokinetics was significant and their coadministration is not recommended. Findings from population PK analysis demonstrated that raltegravir 1200 mg QD pharmacokinetics did not vary to a clinically meaningful extent with respect to coadministration with TRUVADA™, PPIs, and H2 blockers; therefore, coadministration of these agents with raltegravir 1200 mg QD is permitted.
6. Consistent with conclusions for ISENTRESS® 400 mg BID, raltegravir 1200 mg QD pharmacokinetics in adults do not vary to a clinically meaningful extent with respect to body weight, gender, race, ethnicity, and HIV infection. As such, no specific clinical recommendation regarding these factors is needed for raltegravir 1200 mg (2 x 600 mg) dosing. Additionally, specific attributes of raltegravir pharmacokinetics from the raltegravir twice daily development program are considered applicable to the current Once Daily Development program, including renal impairment, hepatic impairment and effect on QTc.
7. Raltegravir 1200 mg QD has not been evaluated in a pediatric clinical study. However, simulations indicate that this dose and regimen can be recommended in pediatric patients with a body weight of at least 40 kg, and will result in raltegravir exposures within the range observed in adults in PN292.

4 OVERVIEW OF EFFICACY

4.1 Previous Submissions on Raltegravir 400 mg BID

The Original Marketing Applications for raltegravir in 2007 provided compelling efficacy data for raltegravir for twice daily use, which included data from 877 treatment-experienced subjects (PN005, PN018, and PN019) and 198 treatment-naïve subjects (PN004) (Sec. 2.5.4 of Original Application). The approval for the indication in treatment-experienced patients was based primarily on 24-Week data from the 2 pivotal Phase 3 studies, PN018 and PN019. The 48-Week Treatment-Experienced Supplemental Application provided 48-Week efficacy data from these 2 Phase 3 studies and demonstrated durability of the antiretroviral effect of raltegravir in treatment-experienced subjects (Sec. 2.5.4 of 48 Week Treatment Experienced Supplemental Application). The 48 Week Treatment Naïve Supplemental Application

provided 48-week efficacy data of raltegravir in 563 treatment-naïve subjects from PN021 which was supported by 96-week data from 133 subjects from PN004 (Sec. 2.7.3.2.2-hivnaive of 48 Week Treatment Naïve Supplemental Application). The 96 Week Supplemental Application provided additional long term 96-week efficacy data from the 2 treatment-experienced Phase 3 studies, PN018 and PN019, and the Phase 3 treatment-naïve study, PN021, which demonstrated durability of the antiretroviral effect of raltegravir (Sec. 2.5.4 of the 96 Week Supplemental Application). Subsequent applications included the 156-week and final 240-week safety and efficacy data from PN021 (Naïve-3yr Supplemental Application and Naïve-5yr Supplemental Application, respectively). PN021 evaluated treatment naïve subjects and confirmed the long-term durable antiviral efficacy of raltegravir (Sec. 2.5.4 of the Naïve-3 yr and Naïve-5 yr Supplemental Applications). Additionally, two pediatric applications were submitted; Pediatric Application (2 to 18 years) and Pediatric Application (4 weeks to <2 years) which provided data from the IMPAACT P1066 (PN022) study, including the PK, safety and dosing information for 3 different formulations (adult tablet, chewable tablets, and granules for suspension) of raltegravir in children ranging in age from 4 weeks to 18 years.

4.2 Raltegravir Once Daily Program

In this raltegravir Once Daily Application, PN292 is the Phase 3 pivotal clinical study providing 48-week efficacy and safety data in 797 treatment-naïve HIV-1 infected subjects, to support the use of raltegravir 1200 mg QD (2 x 600 mg tablets) for the treatment of HIV-1 infection. This study demonstrated that raltegravir 1200 mg QD (2 x 600 mg tablets) had potent efficacy and is non-inferior to raltegravir 400 mg BID, each in combination with TRUVADA™, through 48 weeks of therapy in HIV-1 treatment-naïve subjects. In this section, the efficacy results are discussed in [Sec. 2.5.4.2.4] after brief comments on the relevance of the subject population (see [Sec. 2.5.4.2.2]), and on the methods for efficacy assessment (see [Sec. 2.5.4.2.3]).

4.2.1 Study Design

The design of the Phase 3 pivotal study, PN292, in treatment-naïve subjects is provided in [Ref. 5.3.5.1: P292V01]. PN292 is a multicenter, double-blind (with in-house blinding), randomized, active-controlled study in treatment-naïve HIV-infected adults. The comparator in PN292 is raltegravir BID (1 x 400 mg tablets twice daily), the approved dose of raltegravir for the treatment of HIV-infected patients, which has documented potent and durable antiretroviral efficacy.[Ref. 5.4: 04C29S]

Subjects were stratified by HIV RNA (≤100,000 copies/mL and >100,000 copies/mL) and by hepatitis status (evidence of hepatitis B surface antigen and/or evidence of hepatitis C virus (HCV) RNA) at screening, then randomly assigned, via an Interactive Voice Response System (IVRS) to 1 of the 2 treatment groups in a 2:1 ratio:

- Group 1 (N=~500) = Raltegravir formulated for once daily use, at a dose of 1200 mg QD (2 x 600 mg tablets) (plus placebo matched to raltegravir 400 mg BID) without regard to food.

- Group 2 (N=~250) = Raltegravir 400 mg BID (plus placebo matched to raltegravir 2 x 600 mg QD) without regard to food.

All subjects also received open label TRUVADA™ QD with food.

The protocol was designed to demonstrate the non-inferior antiretroviral activity of raltegravir 1200 mg QD (2 x 600 mg tablets) compared with raltegravir 400 mg BID at Week 48 and to evaluate the safety, tolerability, and immunological effect of raltegravir 1200 mg QD in treatment-naïve HIV-infected subjects. Raltegravir 1200 mg QD will be concluded non-inferior to raltegravir 400 mg BID if the lower bound of the two-sided 95% CI for the difference in proportion of subjects with HIV RNA<40 copies/mL at Week 48 (QD – BID) is greater than -10 percentage points. The study was well powered to demonstrate non-inferiority, and the non-inferiority design that was employed is well accepted according to regulatory guidance.[Ref. 5.4: 04DT6Q]

Complete Week 48 data for all randomized subjects are currently available, and the study allows for continued double-blind treatment through Week 96.

4.2.2 Description of Subject Population

PN292 included HIV-infected (RNA ≥1000 copies/mL) subjects who had never received antiretroviral therapy. Subjects with documented HIV resistance to raltegravir or the NRTI backbone (tenofovir and emtricitabine) were excluded. (Enrollment and disposition information are provided in [Table 2.7.3-qd1200: 1], [Table 2.7.3-qd1200: 2], [Table 2.7.3-qd1200: 3], [Table 2.7.3-qd1200: 4], [Table 2.7.3-qd1200: 5].) Overall, the study population was 84.6% male and 40.6% non-White, and had baseline mean HIV RNA of 4.6 $\log_{10}$ copies/mL, and mean CD4 count of 415 cells/mm^3. Approximately 28.4% of subjects had HIV RNA >100,000 copies/mL at baseline and 34.0% were infected with non-clade B virus. Overall, there was a broad representation of gender, race, ethnicity, geographic region, age, and viral subtype. Baseline characteristics, concurrent conditions, including AIDS defining conditions, and prior and concomitant medications were reasonably balanced between the treatment groups ([Table 2.7.3-qd1200: 6], [Table 2.7.3-qd1200: 7], [Table 2.7.3-qd1200: 8], [Table 2.7.3-qd1200: 9], [Table 2.7.3-qd1200: 10]) as was compliance ([Table 2.7.3-qd1200: 11] [Table 2.7.3-qd1200: 12]).

4.2.3 Methods for Efficacy Assessment

4.2.3.1 Endpoints

HIV RNA and CD4 cell counts are well accepted surrogate markers for efficacy in clinical studies of HIV therapeutics [Ref. 5.4: 03PZQV, 03Q8DT, 03NSTY] and are used to support the efficacy of raltegravir 1200 mg QD (2 x 600 mg tablets) in this Once Daily Application. The efficacy of raltegravir 1200 mg QD (2 x 600 mg tablets) was demonstrated by focusing on the following at Week 48:

1. Proportion of subjects achieving HIV RNA <40 copies/mL (primary)

2. Proportion of subjects achieving HIV RNA <50 copies/mL (supportive)

3. Proportion of subjects achieving HIV RNA <200 copies/mL (supportive)

4. The change from baseline in CD4 cell count (cells/mm^3) (secondary)

The HIV-1 RNA assay used in PN292 (Abbott RealTime assay) has a lower limit of quantification of 40 copies/mL; therefore, the proportion of subjects achieving HIV-1 RNA < 40 copies/mL was the selected primary efficacy criterion.

Time-to-virologic-response (TVR) was used to compare the potency of the antiretroviral effect of raltegravir 1200 mg QD (2 x 600 mg tablets) with that of raltegravir 400 mg BID, each in combination with TRUVADA™. TVR was defined as the time between randomization and the first of two consecutive HIV RNA values (at least 1 week apart) that were <40 copies/mL. For subjects who did not achieve HIV RNA <40 copies/mL at 2 consecutive visits, TVR was censored at the last available visit.

The durability of the antiretroviral activity of raltegravir 1200 mg QD (2 x 600 mg tablets) as compared to that of raltegravir 400 mg BID, each in combination with TRUVADA™, was also assessed using time-to-loss-of-virologic-response (TLOVR). TLOVR was defined as the time between randomization and the first of two consecutive HIV RNA values above 40 copies/mL for subjects who had confirmed HIV RNA <40 copies/mL at 2 consecutive visits. For subjects who did not achieve HIV RNA <40 copies/mL at 2 consecutive visits, TLOVR is defined as zero.

4.2.3.2 Statistical Methodology

The statistical approaches to analyze the efficacy of raltegravir in this Once Daily Application are consistent with current scientific and regulatory guidelines and are described in detail in the clinical study report for PN292 [Ref. 5.3.5.1: P292V01]. Two approaches were used to address missing values. The primary approach for the analysis of proportion of subjects achieving HIV RNA <40 copies/mL is the Non-Completer=Failure (NC=F) approach as defined by the FDA "snapshot" approach. Under this approach, only those who 1) are on study assigned double-blind-treatment; 2) have an HIV RNA measurement(s) within the time window; and 3) the measurement closest to the target date of the time point is <40 copies/mL can be classified as virologic success at that time point. The other subjects, either with HIV RNA measurement of ≥40 copies/mL or no virologic data within the time window due to intermittent missing or premature discontinuation regardless of reason, were considered as failures in the analyses of proportion of subjects achieving HIV RNA <40 copies/mL at that timepoint.

A second approach, the Observed Failure (OF) approach was performed as a sensitivity analysis for the proportion of subjects achieving HIV RNA<40 copies/mL. Under this approach, monotone (non-intermittent) missing data for subjects who prematurely discontinued assigned treatment due to lack of efficacy are considered as failures thereafter; other types of missing data were excluded from the analyses.

For the proportion of subjects with virologic suppression (HIV RNA <40 copies/mL, <50 copies/mL, and <200 copies/mL), the NC = F analysis is presented (with other methods supportive). For change from baseline in CD4 cell counts and efficacy by prognostic and demographic factors, the OF analysis is presented, as it provides an evaluation focused on virology as opposed to administrative factors such as missing visits or visits outside of the prespecifed time windows.

4.2.4 Efficacy Results

Previous Applications provided compelling evidence of the clinical efficacy of raltegravir 400 mg BID used in combination with other ARTs in HIV-infected subjects. In this Once Daily Application, the 48-week data from PN292 provide similar compelling evidence to support the use of raltegravir 1200 mg QD (2 x 600 mg tablets) in combination with a background antiretroviral regimen for the initial treatment of HIV-1 infected patients. This study demonstrated that raltegravir 1200 mg QD has potent, durable and statistically non-inferior efficacy comparable to raltegravir 400 mg BID in HIV-1 treatment-naïve subjects, each in combination with TRUVADA™. As summarized below, PN292 demonstrated that the efficacy profiles of raltegravir 1200 mg QD and 400 mg BID are virtually identical, including the rapidity of achieving virologic suppression, sustained virologic responses to Week 48, and substantial recovery of CD4 counts. Potent efficacy was observed overall and in key subgroups, including in subjects with high baseline viral load, and this is comparable to other contemporary integrase strand transfer inhibitor (InSTI)-based regimens. The infrequent occurrence of protocol-defined virologic failure and low rates of virologic resistance were also generally comparable with what has been observed for raltegravir 400 mg BID trials, and in general for other contemporary trials of first-line regimens. [Ref. 5.4: 03RJMK, 03QX7X, 03TFV3, 03WQJZ, 042KWT, 042L5D]

In addition to supporting the use of raltegravir 1200 mg QD in treatment-naïve adults, the above data, as well as modeling and simulation, also support the use of raltegravir 1200 mg QD as continued treatment in adult patients who are virologically suppressed on an initial regimen of ISENTRESS® 400 mg BID. In PN292, subjects were required to be treatment-naïve (defined as 0 days of prior antiretroviral treatment), have virus susceptible to the study drugs (raltegravir, tenofovir and emtricitabine), and have screening HIV RNA of at least 1,000 copies/mL. Although virologically suppressed subjects were not enrolled in PN292, full virologic suppression was rapidly achieved in both QD and BID arms, with over 50% reaching HIV RNA <40 copies/mL, and over 85% reaching <200 copies/mL by Week 4; most maintained full suppression through Week 48, as shown by the primary outcomes (HIV RNA <40 copies/mL) of 88.9% and 88.3%, respectively.

Results from exposure-efficacy analysis using data from PN292 demonstrate that maximum viral suppression (HIV RNA <40 copies/mL) is likely achieved across the range of PK exposures obtained from both QD and BID regimens [Sec. 2.7.2.2.2.5], [Sec. 2.7.2.3.2.2.1]. This is consistent with previous raltegravir PK/PD findings, which demonstrated that raltegravir efficacy from ISENTRESS® 400 mg BID is at the plateau region of the exposure-efficacy curve. Therefore, it can be projected that continued treatment with raltegravir 1200 mg QD is comparable to continued treatment with raltegravir 400 mg BID; thus, patients

suppressed on raltegravir BID can be switched to raltegravir QD, with equivalent virologic outcomes.

Finally, PN292 efficacy data and simulation also provided supporting evidence for the use of raltegravir 1200 mg QD in pediatric patients weighing at least 40 kg [Sec. 2.7.2.2.2.4], [Sec. 2.7.2.3.2.2.1].

4.2.4.1 Summary of Antiretroviral and Immunologic Efficacy

Results of the primary and key secondary efficacy analyses at Week 48 are summarized in [Table 2.5: 2]. With respect to the primary efficacy endpoint, the proportion (%) of subjects achieving HIV RNA <40 copies/mL at Week 48 by the FDA Snapshot approach was 88.9% and 88.3% for the raltegravir 1200 mg QD and 400 mg BID groups, respectively. The treatment difference (QD – BID) of 0.510% with associated 95% CI of (-4.204, 5.223) demonstrated non-inferiority (lower bound of 95% CI greater than -10%) of QD compared to BID.

Analyses of the proportions of subjects achieving HIV RNA <40 copies/mL by the OF approach and subjects achieving HIV RNA <50 copies/mL and <200 copies/mL by both missing data approaches showed similar results to the primary analysis.

In addition to potent and non-inferior efficacy, large increases in CD4 cell counts of 232 cells/mm^3 and 234 cells/mm^3 at Week 48 were observed in both raltegravir QD and BID groups, respectively.

Table 2.5: 2
Efficacy Analysis at Week 48

Parameter	Missing Data Approach[†]	Unadjusted Data Summary by Treatment Group		Treatment Difference (QD - BID)[‡]		Conclusion[§]
		Raltegravir 1200 mg QD n/N (%)	Raltegravir 400 mg BID n/N (%)	Estimated Difference	95% CI	
Primary						
Proportion of Patients with HIV RNA <40 copies/mL	Snapshot (NC=F)	472/531 (88.9)	235/266 (88.3)	0.510	(-4.204, 5.223)	Non-inferior
Supportive						
Proportion of Patients with HIV RNA <40 copies/mL	OF	472/501 (94.2)	235/251 (93.6)	0.553	(-3.103, 4.209)	
Proportion of Patients with HIV RNA <50 copies/mL	Snapshot (NC=F)	477/531 (89.8)	240/266 (90.2)	-0.415	(-4.858, 4.027)	
Proportion of Patients with HIV RNA <50 copies/mL	OF	477/501 (95.2)	240/251 (95.6)	-0.432	(-3.633, 2.769)	
Proportion of Patients with HIV RNA <200 copies/mL	Snapshot (NC=F)	484/531 (91.1)	243/266 (91.4)	-0.212	(-4.428, 4.005)	
Proportion of Patients with HIV RNA <200 copies/mL	OF	484/501 (96.6)	243/251 (96.8)	-0.221	(-3.018, 2.576)	
		Mean (95% CI)	Mean (95% CI)	Mean Difference	95% CI	
Secondary						
Change from Baseline in CD4 Cell Count (cells/mm^3)	OF	232.0 (214.6, 249.4)	234.1 (212.8, 255.3)	-2.1	(-30.9, 26.7)	

[†] NC=F: Non-Completer=Failure as defined by FDA snapshot approach; OF: Observed Failure approach.

[‡] The 95% CIs for the treatment differences in percent response were calculated using stratum-adjusted Mantel-Haenszel method with the difference weighted by the harmonic mean of sample size per arm for each stratum (screening HIV-1 RNA <=100,000 copies/mL or HIV-1 RNA >100,000 copies/mL). The 95% CI for mean difference in CD4 change was based on t-distribution.

[§] Raltegravir 1200 mg QD is concluded non-inferior to raltegravir 400 mg BID if the lower bound of the 95% CI for the difference in percent response is above -10 percentage points.

Note: Raltegravir 1200 mg QD and raltegravir 400 mg BID were administered with TRUVADA™

N = Number of subjects in each treatment group.

Data Source: [Ref. 5.3.5.1: P292V01]

The virologic outcomes by the FDA Snapshot method from PN292 are summarized in [Table 2.5: 3] and [Figure 2.5: 1] ([Ref. 5.3.5.1: P292V01]). Of note, by the supportive analyses of proportion of subjects achieving HIV RNA <200 copies/mL, among the subjects being classified as HIV RNA ≥40 copies/mL, approximately half of those (12/29 in the QD group and 8/16 in the BID group) had low level viremia (HIV RNA between 40 and 200 copies/mL) at Week 48 [Table 2.5: 2], [Table 2.7.3-qd1200: 18].

Table 2.5: 3
Virologic Outcome at Week 48
FDA Snapshot Approach

Outcome	Raltegravir 1200 mg QD (N=531) n	(%)	Raltegravir 400 mg BID (N=266) n	(%)
HIV RNA <40 copies/mL	472	(88.9)	235	(88.3)
HIV RNA ≥ 40 copies/mL[†]	29	(5.5)	16	(6.0)
No Virologic Data at Week 48 Window	30	(5.6)	15	(5.6)
Reasons				
Discontinued study due to AE or Death[‡]	6	(1.1)	6	(2.3)
Discontinued study for Other Reasons[§]	20	(3.8)	7	(2.6)
On study but missing data in window	4	(0.8)	2	(0.8)

[†] Includes subjects who changed any component of background therapy to a new drug class or changed background components that were not permitted per protocol or changed any background drug in the regimen because of lack of efficacy (perceived or documented) before Week 48, subjects who discontinued study drug or study before Week 48 for lack or loss of efficacy and subjects with HIV RNA equal to or above 40 copies/mL in the Week 48 window (relative day 295-378).

[‡] Includes subjects who discontinued because of adverse event (AE) or death at any time point from Day 1 through the time window if this resulted in no virologic data on treatment during the specified window.

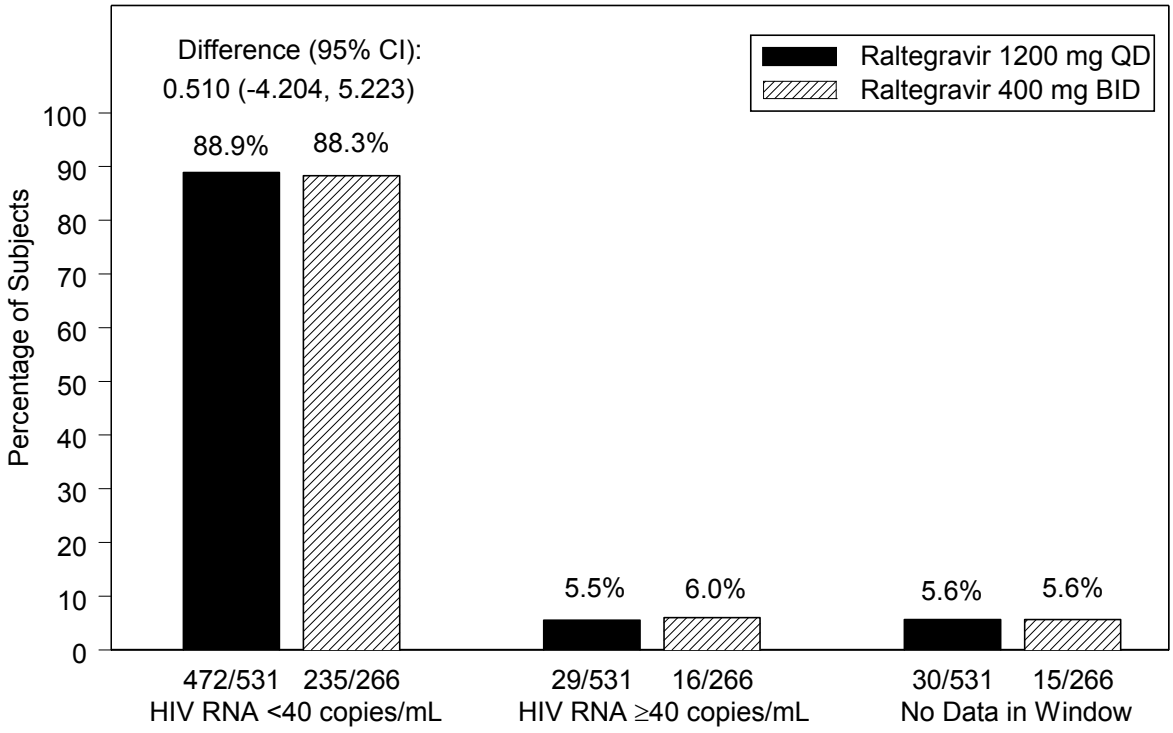
[§] Other Reasons includes: lost to follow-up, non-compliance with study drug, physician decision, pregnancy, withdrawal by subject.

Note: Raltegravir 1200 mg QD and raltegravir 400 mg BID were administered with TRUVADA™.

n (%) = Number (Percent) of subjects in each category.

Data Source: [Ref. 5.3.5.1: P292V01]

Figure 2.5: 1
Virologic Outcome at Week 48
FDA Snapshot Approach



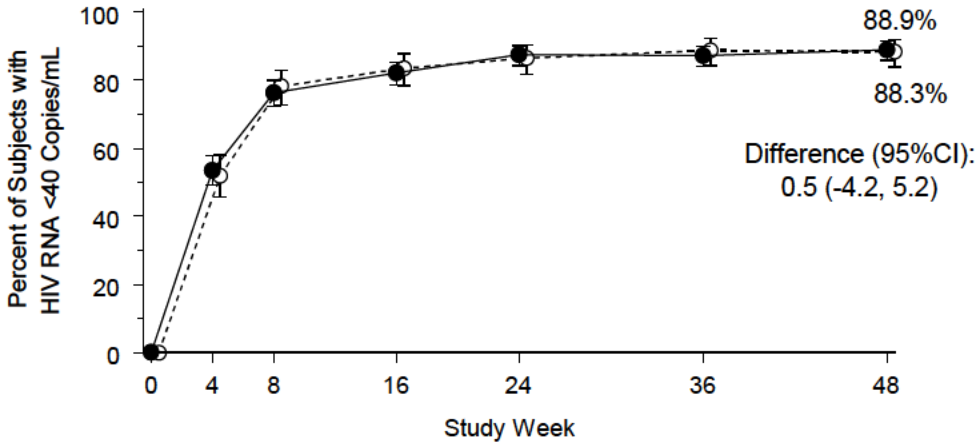
Data Source: [Ref. 5.3.5.1: P292V01]

In summary, raltegravir 1200 mg QD has potent and statistically non-inferior antiretroviral activity compared to raltegravir 400 mg BID at Week 48. Raltegravir 1200 mg QD (2 x 600 mg tablets) has comparable immunological efficacy, as measured by change from baseline in CD4 cell counts, to raltegravir 400 mg BID at Week 48.

4.2.4.2 Antiretroviral Efficacy Over Time

Raltegravir 1200 mg QD (2 x 600 mg tablets) results in rapid viral suppression (HIV RNA <40 copies/mL), comparable to that achieved with raltegravir 400 mg BID, as shown in [Figure 2.5: 2] and [Table 2.5: 4] ([Ref. 5.3.5.1: P292V01], [Table 2.7.3-qd1200: 13], [Figure 2.7.3-qd1200: 1]). Both groups achieved rapid virologic suppression (HIV RNA < 40 copies/mL), (over 50% of subjects by Week 4 and over 75% by Week 8, in both groups).

Figure 2.5: 2
Proportion of Subjects With HIV RNA <40 copies/mL Over Time (95% CI)
Snapshot Approach (Non-Completer = Failure)



Number of Contributing Patients

● RAL 1200 mg QD	531	531	531	531	531	531	531
○ RAL 400 mg BID	266	266	266	266	266	266	266

Data Source: [Ref. 5.3.5.1: P292V01]

Table 2.5: 4
Proportion of Subjects with HIV RNA <40 copies/mL Over Time
FDA Snapshot Approach (Non-Completer = Failure)

Endpoint	Visit	Response				Treatment Difference (QD – BID)[†]	
		Raltegravir 1200 mg QD		Raltegravir 400 mg BID		Difference	95% CI
		n/N	% (95% CI)	n/N	% (95% CI)		
Proportions with HIV RNA <40 copies/mL	Week 4	284/531	53.5 (49.1, 57.8)	138/266	51.9 (45.7, 58.0)	1.3	(-5.1, 7.7)
	Week 8	405/531	76.3 (72.4, 79.8)	208/266	78.2 (72.7, 83.0)	-2.1	(-7.7, 3.4)
	Week 16	436/531	82.1 (78.6, 85.3)	222/266	83.5 (78.4, 87.7)	-1.5	(-6.7, 3.7)
	Week 24	464/531	87.4 (84.3, 90.1)	230/266	86.5 (81.8, 90.3)	0.8	(-4.1, 5.8)
	Week 36	463/531	87.2 (84.0, 89.9)	236/266	88.7 (84.3, 92.3)	-1.6	(-6.3, 3.2)
	Week 48	472/531	88.9 (85.9, 91.4)	235/266	88.3 (83.9, 91.9)	0.5	(-4.2, 5.2)

Approach to handling missing values: Non-Completer = Failure (NC=F) Approach as defined by FDA snapshot approach under which all missing values were counted as failure.

[†]A positive value means raltegravir 1200 mg QD is better than raltegravir 400 mg BID. The 95% CIs for the treatment differences in percent response were calculated using stratum-adjusted Mantel-Haenszel method with the difference weighted by the harmonic mean of sample size per arm for each stratum (screening HIV-1 RNA <=100,000 copies/mL or HIV-1 RNA >100,000 copies/mL).

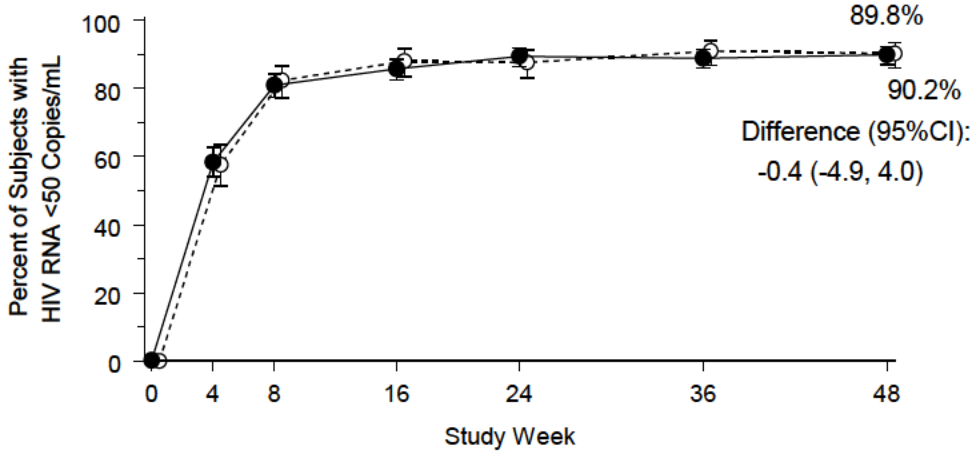
Note: Raltegravir 1200 mg QD and raltegravir 400 mg BID were administered with TRUVADA™.

N = Number of subjects in each treatment group.

Data Source: [Ref. 5.3.5.1: P292V01]

[Figure 2.5: 3] presents the proportion of subjects with HIV RNA <50 copies/mL over time by treatment group using the primary NC=F approach. At Week 48, the QD group had comparable antiretroviral efficacy compared with the BID group based on the 50 copies/mL RNA threshold. The results of additional supportive analyses were consistent ([Ref. 5.3.5.1: P292V01], [Table 2.7.3-qd1200: 14], [Table 2.7.3-qd1200: 15], [Figure 2.7.3-qd1200: 2]).

Figure 2.5: 3
Proportion of Subjects with HIV RNA <50 copies/mL Over Time (95% CI) Snapshot Approach (Non-Completer = Failure)



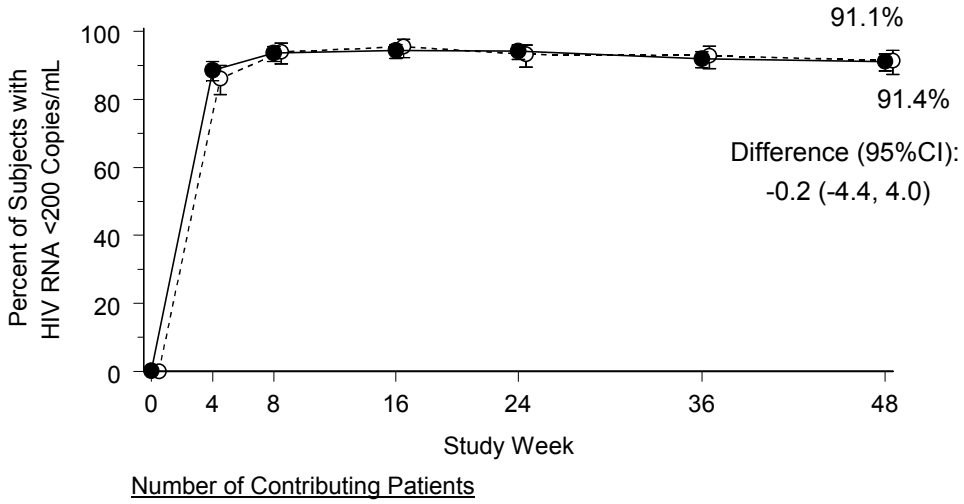
Number of Contributing Patients

● RAL 1200 mg QD	531	531	531	531	531	531	531
○ RAL 400 mg BID	266	266	266	266	266	266	266

Data Source: [Ref. 5.3.5.1: P292V01]

[Figure 2.5: 4] presents the proportion of subjects with HIV RNA <200 copies/mL over time by treatment group using the primary NC=F approach. Both groups demonstrated rapid viral RNA decline with over 85% achieving RNA<200 copies/mL by Week 4. At Week 48, the QD group had comparable antiretroviral efficacy compared with the BID group based on the 200 copies/mL RNA threshold. The results of additional supportive analyses were consistent ([Ref. 5.3.5.1: P292V01], [Table 2.7.3-qd1200: 16], [Table 2.7.3-qd1200: 17], [Figure 2.7.3-qd1200: 3]).

Figure 2.5: 4
Proportion of Subjects with HIV RNA <200 copies/mL Over Time (95% CI)
Snapshot Approach (Non-Completer = Failure)



Number of Contributing Patients

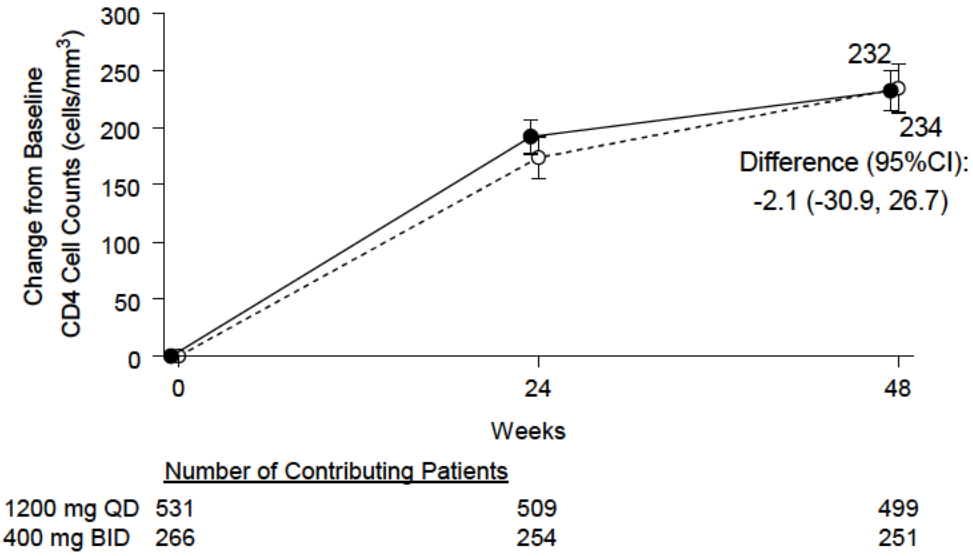
●	RAL 1200 mg QD	531	531	531	531	531	531	531
○	RAL 400 mg BID	266	266	266	266	266	266	266

Data Source: [Ref. 5.3.5.1: P292V01]

4.2.4.3 Immunologic Efficacy Over Time

In addition to rapid and potent antiviral activity [Figure 2.5: 2], raltegravir QD has comparable immunological efficacy, as measured by change from baseline at Week 24 and Week 48 in CD4 cell counts, to raltegravir BID [Figure 2.5: 5]. At Week 48, the mean change from baseline in CD4 cells (cells/mm^3)(95% CI) was 232.0 (214.6, 249.4) and 234.1 (212.8, 255.3) in the QD and BID groups, respectively ([Ref. 5.3.5.1: P292V01], [Table 2.7.3-qd1200: 19]).

Figure 2.5: 5
Change from Baseline in CD4 Cell Count (Cells/mm^3) Over Time (95% CI) Observed Failure Approach



Number of Contributing Patients

●	RAL 1200 mg QD	531	509	499
○	RAL 400 mg BID	266	254	251

Data Source: [Ref. 5.3.5.1: P292V01]

4.2.4.4 Time to Virologic Response and Time to Loss of Virologic Response

Analysis of time to virologic response and time to loss of virologic response demonstrated that raltegravir 1200 mg QD (2 x 600 mg tablets) results in rapid virologic suppression and durable antiretroviral effect similar to raltegravir 400 mg BID [Table 2.7.3-qd1200: 20], [Table 2.7.3-qd1200: 21], [Figure 2.7.3-qd1200: 4], [Table 2.7.3-qd1200: 22], [Table 2.7.3-qd1200: 23], [Figure 2.7.3-qd1200: 5], [Table 2.7.3-qd1200: 24], [Table 2.7.3-qd1200: 25].

4.2.4.5 Efficacy by Subgroups

Subgroup analyses evaluating the efficacy of raltegravir 1200 mg QD (2 x 600 mg tablets) by important baseline prognostic and stratification factors, and demographic factors demonstrated consistent efficacy across all these factors, acknowledging that some of the subgroups are small and thus have very wide confidence intervals. [Table 2.7.3-qd1200: 26], [Table 2.7.3-qd1200: 27], [Table 2.7.3-qd1200: 28], [Table 2.7.3-qd1200: 29], [Table 2.7.3-qd1200: 32], [Table 2.7.3-qd1200: 33], [Figure 2.7.3-qd1200: 6], [Figure 2.7.3-qd1200: 7], [Figure 2.7.3-qd1200: 8], [Figure 2.7.3-qd1200: 9].

Baseline prognostic and stratification factors:

- Baseline plasma HIV RNA (≤100,000 or >100,000 copies/ml)
- Baseline plasma HIV RNA (≤500,000 or >500,000 copies/ml)

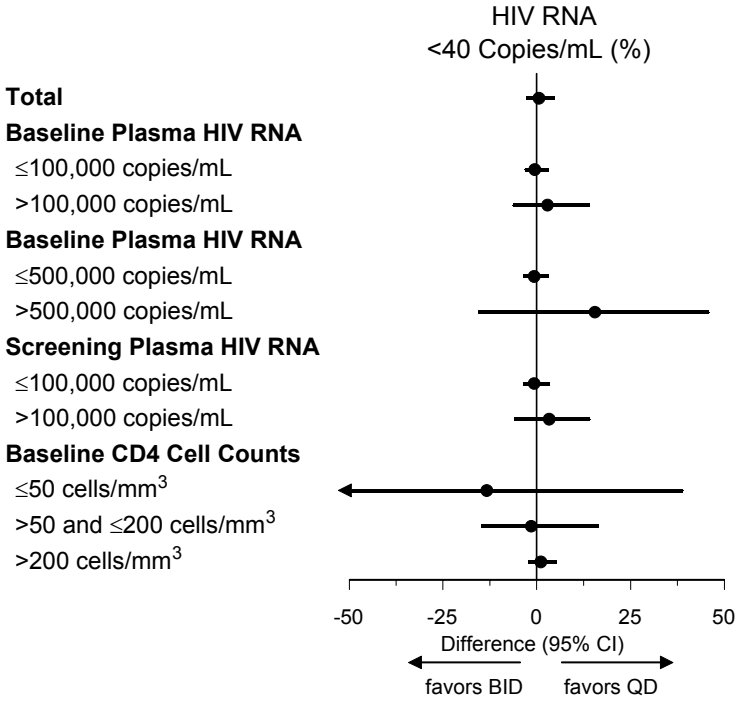
- Screening plasma HIV RNA (≤100,000 or >100,000 copies/ml)
- Baseline CD4 cell counts (≤50 or >50 and ≤200 or >200 cells/mm^3)
- Hepatitis status (Hepatitis B and/or C positive vs. Both Hepatitis B and Hepatitis C negative)
- Use of proton pump inhibitors/H_2 blockers (yes/no)

Demographic factors:

- Age (<65 years vs ≥65 years, ≤median vs >median, with median age of 34 years)
- Gender (male, female)
- Race (White, Black, American Indian, Asian, and Multiracial)
- Ethnicity (Hispanic vs. non-Hispanic)
- Region (Africa, Asia/Pacific, Europe, Latin America, North America)
- Viral subtype (clade B vs. non-clade B)

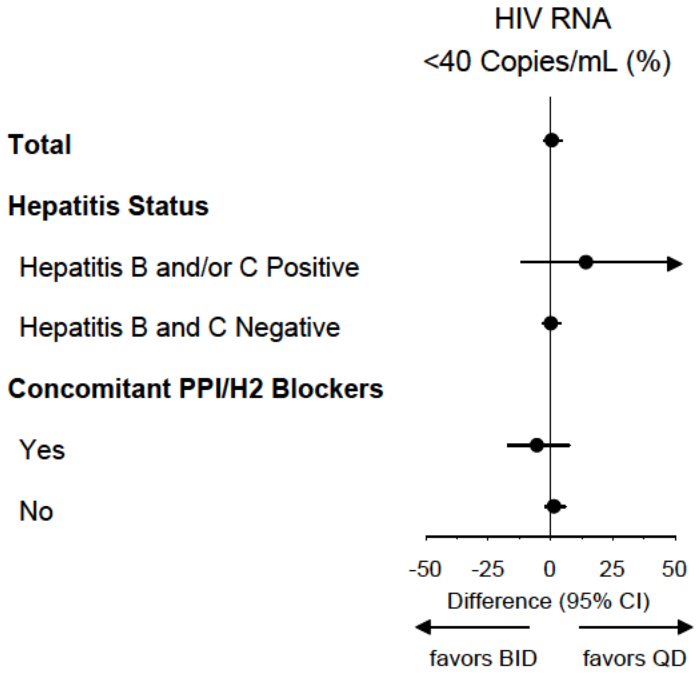
[Figure 2.5: 6], [Figure 2.5: 7], [Figure 2.5: 8], and [Figure 2.5: 9] show the primary efficacy analysis endpoint (HIV RNA < 40 copies/mL) at Week 48 by the above prognostic and demographic factors, using the Observed Failure Approach. Figures displaying secondary efficacy endpoints (HIV RNA <50 copies/mL, HIV RNA < 200 copies/mL, and CD4 cell count [cells/mm^3]), can be found in [Figure 2.7.3-qd1200: 6], [Figure 2.7.3-qd1200: 7], [Figure 2.7.3-qd1200: 8], [Figure 2.7.3-qd1200: 9].

Figure 2.5: 6
Proportion of Subjects with Plasma HIV RNA <40 Copies/mL at Week 48 by Baseline and Screening HIV RNA (copies/mL) and Baseline CD4 Cell Count (cells/mm^3) Categories
Difference Between Treatment Groups (QD-BID)
Observed Failure Approach



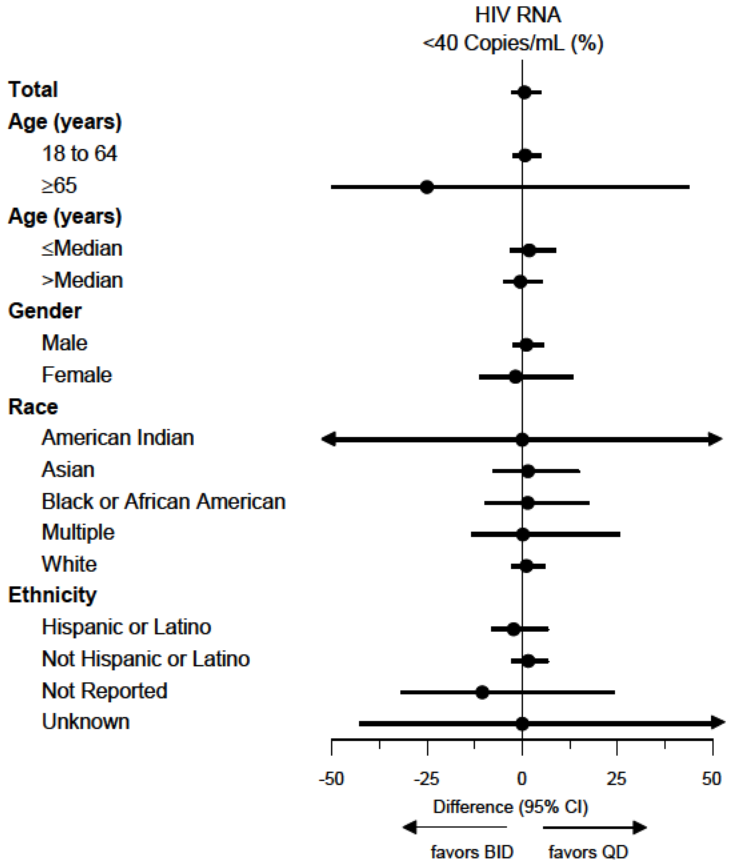
Data Source: [Ref. 5.3.5.1: P292V01]

Figure 2.5: 7
Proportion of Subjects with Plasma HIV RNA <40 Copies/mL at Week 48 by Hepatitis Status and Proton Pump Inhibitor/H2 Blocker Use
Difference Between Treatment Groups (QD-BID)
Observed Failure Approach



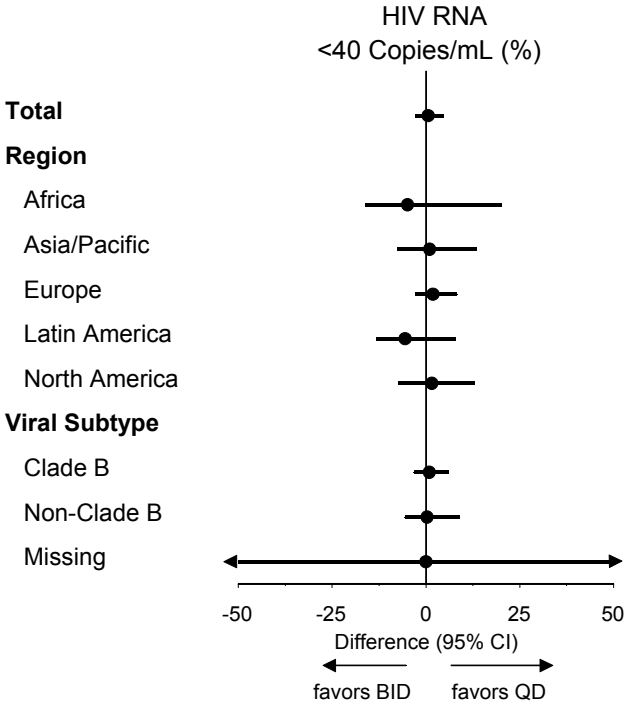
Data Source: [Ref. 5.3.5.1: P292V01]

Figure 2.5: 8
Proportion of Subjects with Plasma HIV RNA <40 Copies/mL at Week 48 by Age, Gender, Race, and Ethnicity
Difference Between Treatment Groups (QD-BID)
Observed Failure Approach



Data Source: [Ref. 5.3.5.1: P292V01]

Figure 2.5: 9
Proportion of Subjects with Plasma HIV RNA <40 Copies/mL at Week 48 by Region and Viral Subtype
Difference Between Treatment Groups (QD-BID)
Observed Failure Approach



Data Source: [Ref. 5.3.5.1: P292V01]

4.2.4.6 Subjects with Protocol Defined Virologic Failure and Virologic Resistance

The protocol was designed to carefully detect and evaluate subjects who did not achieve virologic suppression or that had achieved suppression and then had subsequent elevations of HIV RNA. Protocol defined virologic failure (PDVF) was used to identify subjects for resistance testing (which required HIV RNA ≥500 copies/mL as the laboratory threshold for resistance testing). There were few PDVFs and virologic resistance was rare.

The protocol definition of virologic failure was (1) those subjects who never achieved HIV-1 RNA <40 copies/mL by Week 24 (nonresponder); or (2) those subjects who had two consecutive measurements of HIV 1 RNA ≥40 copies/mL at least one week apart after initial response of HIV 1 RNA <40 copies/mL (rebounder). By Week 48, 36/531 (6.8%) subjects in the raltegravir QD group and 18/266 (6.8%) subjects in the raltegravir BID group were identified as PDVFs. In both treatment groups, half of the PDVFs were non-responders and half were rebounders [Table 2.5: 5].

A substantial proportion of subjects who met PDVF criteria continued in the study and subsequently achieved virologic suppression. In the QD group, 27 of the 36 subjects (75.0%) who met PDVF criteria later suppressed (non-responders) or re-suppressed (rebounders) below 40 copies/mL and 20 of the 36 subjects (55.6%) were considered successes at the Week 48 primary analysis. In the BID group, similarly, 13 of the 18 subjects (72.2%) who met PDVF criteria later suppressed or re-suppressed and 8 of the 18 subjects (44.4%) were considered successes at the Week 48 primary analysis. [Table 2.7.3-qd1200: 30], [Ref. 5.3.5.1: P292V01]

Table 2.5: 5
Number of Subjects with Protocol Defined Virologic Failure
(Weeks 0-48)

	Raltegravir 1200 mg QD N=(531) n (%)	Raltegravir 400 mg BID N=(266) n (%)
Virologic Failure (confirmed)† by Week 24		
Non-responder	18 (3.4)	9 (3.4)
Rebounder	12 (2.3)	7 (2.6)
Virologic Failure (confirmed)† by Week 48		
Non-responder	18 (3.4)	9 (3.4)
Rebounder	18 (3.4)	9 (3.4)

† Virologic failure is defined as 1) Non-responder: Subjects who never achieved HIV RNA <40 copies/mL by Week 24, OR 2) Rebounder: Subjects who have two consecutive measurements of HIV-1 RNA ≥40 copies/mL at least one week apart after initial response of HIV-1 RNA <40 copies/mL.

Note: Raltegravir 1200 mg QD and raltegravir 400 mg BID were administered with TRUVADA™.

N = Number of subjects in each treatment group.

Data Source: [Ref. 5.3.5.1: P292V01]

Among the subjects with protocol-defined virologic failure (36 [6.8%] in the QD group and 18 [6.8%] in the BID group), specimens from 14 subjects in the QD group and 3 subjects in the BID group were subjected to resistance testing [Table 2.7.3-qd1200: 31]. The overall rate of resistance to any agent among subjects in the QD group was 5/531 or 0.9%; 5 had resistance to raltegravir and/or emtricitabine (FTC): 4 of the 5 had resistance to both raltegravir and FTC, and 1 had resistance to FTC only. The 4 subjects with raltegravir and FTC resistance had integrase mutations in N155H/I203M, V151I/N155H, N155H, L74M/E92Q as well as RT mutations in M184, either M184V or M184M/I/V. The subject with the L74M/E92Q mutation discontinued the study for lack of efficacy; this subject's HIV RNA levels were suppressed to <40 copies/mL at the 14-day follow-up visit. The subject with FTC resistance only had M184V and V118I mutations; this subject remained on study treatment and HIV RNA was re-suppressed to <40 copies/mL at Weeks 36 and 48. No TDF mutations were observed. Among the 3 subjects in the BID group with virologic failure who had resistance testing performed, no raltegravir mutations were found. In all subjects with resistance mutations, compliance was at least 94%.

Overall the resistance rate and pattern were similar to those described previously in the Phase 2 and 3 clinical studies of raltegravir BID conducted in treatment-naïve and treatment-experienced subjects [Ref. 5.4: 03QX7X, 04D0C0, 03RJMK]. In particular, in previous studies with raltegravir 400 mg BID in treatment naïve subjects, typical rates of resistance were in the range of 2% to 6% [Ref. 5.4: 03QX7X, 04D0C0, 03RJMK], whereas, in PN071, the observed rate of resistance was 5.2% in the 800 mg (2 x 400 mg) QD arm [Ref. 5.4: 03RJMK].

In summary, the proportion of subjects with detected resistance observed in both QD and BID groups in this study were consistent, indeed at the lower end, of that observed with raltegravir 400 mg BID in previous studies and lower than what was observed with raltegravir 800 mg QD in PN071.

4.2.5 Efficacy Conclusions

Raltegravir 1200 mg QD has potent and durable efficacy comparable to raltegravir 400 mg BID in HIV-1 treatment-naïve subjects, each in combination with TRUVADA™. In particular, raltegravir 1200 mg QD:

- Has statistically non-inferior antiretroviral activity (HIV RNA <40 copies/mL) compared with raltegravir 400 mg BID at Week 48 with
  - similar rapid viral suppression,
  - similar potent efficacy, regardless of demographic or prognostic factors, including baseline RNA and CD4 count,
  - a low frequency of resistance to raltegravir, similar to the frequency observed with raltegravir BID.
- Has comparable and robust immunologic efficacy, as measured by increases at Week 48 from baseline CD4 cell counts.

5 OVERVIEW OF SAFETY

Previous applications have provided considerable data demonstrating the favorable safety profile of twice daily (BID) raltegravir at a dose of 400 mg BID, including data from 462 treatment-experienced and 281 treatment-naïve subjects treated for up to 5 years in long-term Phase 3 studies [Ref. 5.4: 03RSF2]. In addition to post-marketing exposure [Sec. 2.5.5.5] and exposure to other forms of raltegravir [Sec. 2.5.1.1.2], at least 1274 treatment-naïve and treatment-experienced subjects have been exposed to raltegravir 400 mg BID in large external trials.[Ref. 5.4: 04D0C0, 04DXV3, 04DXV8, 04DXVF] This Once Daily Application provides 48-week data from the Phase 3 pivotal study of raltegravir 1200 mg QD (2 x 600 mg tablets) versus raltegravir 400 mg BID in 797 treatment-naïve subjects (PN292), demonstrating the favorable safety profile of raltegravir once daily (QD) (N = 531), as observed with raltegravir 400 mg BID (N = 266). This Application also provides safety data from the Phase 1 single- and multiple-dose studies in healthy volunteers and HIV-infected subjects, which included 133 subjects ([Sec. 2.7.2.3.4]; [Ref. 5.3.1.1: P290], [Ref. 5.3.1.1: P291], [Ref. 5.3.3.1: P293], [Ref. 5.3.2.2: P812], [Ref. 5.3.2.2: P823], [Ref. 5.3.2.2: P824], [Ref. 5.3.5.1: P292V01]).

The overall safety evaluation plan is similar to that in previous raltegravir applications, which for PN292 included a detailed review of adverse events by organ system/syndrome, including the assessment of the immune reconstitution syndrome (IRS), AIDS defining conditions, and events of clinical interest (ECI). In addition, a comprehensive review of safety in special groups and situations (i.e., age, gender, race, ethnicity, proton pump inhibitor/H_2 blocker use, and hepatitis B and/or C co-infection) was also performed ([Ref. 5.3.5.1: P292V01]).

The comprehensive review of safety data in this Once Daily Application confirms raltegravir QD was generally well tolerated with a similar overall safety profile to raltegravir BID when given as initial treatment in HIV-infected subjects.

No new potential or identified risks for raltegravir QD or BID have been identified. The established risk profile for raltegravir remains the same ([Ref. 5.3.5.1: P292V01]).

5.1 Study Population and Extent of Exposure

5.1.1 Phase 1 Studies

One hundred and thirty-three (133) subjects (39 female; 94 male) received at least one dose of raltegravir 1200 mg or 1800 mg QD in six Phase 1 studies (PN290, PN291, PN293, PN812, PN823, PN824). Raltegravir QD was generally well tolerated after single doses of 1200 mg and multiple dose administration of 1200 mg and 1800 mg up to 28 days, when given alone or in combination with antacids, atazanavir or efavirenz. The counts of all adverse events (≥5% incidence) by system organ class (SOC) for the 6 pooled Phase 1 studies are in [Table 2.7.2: 3]. The most commonly reported adverse events (those occurring at an incidence ≥5%) for raltegravir alone were: headache (15%), hypertension (6.8%), myalgia (6%), and abdominal pain (5.3%), and for raltegravir + other were: diarrhea (6%) and upper respiratory tract infection (6%). There was no apparent correlation between increasing exposure and the incidence of adverse events.

A summary of safety from these 6 Phase 1 studies can be found in ([Sec. 2.7.2.3.4]) ([Ref. 5.3.1.1: P290], [Ref. 5.3.1.1: P291], [Ref. 5.3.3.1: P293], [Ref. 5.3.2.2: P812], [Ref. 5.3.2.2: P823], [Ref. 5.3.2.2: P824]).

5.1.2 Phase 3 Study

The evaluation of the safety of raltegravir 1200 mg QD (2 x 600 mg tablets) versus raltegravir 400 mg BID in HIV-infected subjects presented in this document includes data from PN292 ([Ref. 5.3.5.1: P292V01]). In PN292, 531 subjects received raltegravir 1200 mg QD and 266 subjects received raltegravir 400 mg BID for 48 weeks [Table 2.7.3-qd1200: 1], [Table 2.7.3-qd1200: 2] [Table 2.7.4: 1], [Table 2.7.4: 2]. The majority of subjects were young (median age: 34 years), male (84.6%), White (59.3%), not Hispanic/Latino (77.7%), and mostly from North America and Europe (63.4%), with no history of AIDS (86.6%). Concurrent conditions, ADCs, and concomitant therapies were balanced across treatment groups. The two treatment groups were generally well balanced with regard to baseline demographic and prognostic factors [Table 2.7.3-qd1200: 6], [Table 2.7.3-qd1200: 7], [Table 2.7.3-qd1200: 8], [Table 2.7.3-qd1200: 9], [Table 2.7.3-qd1200: 10]) as was compliance ([Table 2.7.3-qd1200: 11], [Table 2.7.3-qd1200: 12], [Ref. 5.3.5.1: P292V01].

There were no significant findings for vital signs and they are not further discussed [Table 2.7.4: 69].

5.2 Analysis of Adverse Events

The overall safety evaluation plan is described in the clinical study report for PN292 ([Ref. 5.3.5.1: P292V01]). Briefly, monitoring of safety was done by the investigator(s) at each study visit. Subjects who completed the study (none at the time of the database lock for the present analysis) or discontinued early were requested to return for a 14-day post-therapy follow-up visit. Clinical adverse events were graded as mild, moderate, or severe intensity

by the investigator. A drug-related adverse event was one that the investigator regarded as related to study therapy; each drug-related adverse event was further specified as related to raltegravir either alone or in combination with TRUVADA™, or related to TRUVADA™ alone. An adverse event was considered serious if it fulfilled any of the following criteria: resulted in death; was life threatening; resulted in a persistent or significant disability/incapacity; resulted in or prolonged an existing inpatient hospitalization; or was a congenital anomaly/birth defect, other important medical event, cancer or overdose. In addition to the investigators' evaluation of laboratory adverse events, all post-baseline laboratory values outside the normal range were assessed regardless of whether or not they were considered by the investigator to be an adverse event. Guidelines for grading the severity of laboratory abnormalities are based on Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS Criteria [Ref. 5.4: 03Q0NV]).

5.2.1 Analysis of Adverse Events Through Week 48

Analyses discussed in this section support the safety of raltegravir 1200 mg QD (2 x 600 mg tablets) and demonstrate that the overall safety profile of raltegravir 1200 mg QD (2 x 600 mg tablets) in treatment-naïve subjects was similar to that of raltegravir 400 mg BID in PN292, with few serious drug-related adverse events and very few discontinuations due to adverse events through 48 weeks.

Overall, the safety profile of raltegravir 1200 mg QD (2 x 600 mg tablets) is similar to the established safety profile of ISENTRESS® BID in HIV-infected subjects.

5.2.1.1 Clinical Adverse Events

The overall clinical adverse event profile of raltegravir 1200 mg QD (2 x 600 mg tablets) was consistent with that observed in the raltegravir 400 mg BID arm and also consistent with the data in previous Applications. [Table 2.5: 6] shows a summary of clinical adverse events (AEs) in PN292. The proportions (%) of subjects with AEs and with drug-related AEs in the QD group were similar to those in the BID group. There were 3 fatal AEs in the study: tuberculosis and immunoblastic lymphoma in the QD group, and AIDS (worsening) in the BID group. An important measure of the overall safety profile is the proportion of subjects who discontinued study therapy due to an adverse event. There were few discontinuations due to AEs in both treatment groups, 0.8% versus 2.3% for QD and BID, respectively [Table 2.7.4: 3], [Table 2.7.4: 4].

Table 2.5: 6
Analysis of Adverse Event Summary
Clinical Adverse Events
Weeks 0-48

	Raltegravir 1200 mg QD		Raltegravir 400 mg BID		Difference in % vs Raltegravir 400 mg BID
	n	(%)	n	(%)	Estimate (95% CI)[†]
Subjects in population	531		266		
with one or more adverse events	439	(82.7)	231	(86.8)	-4.2 (-9.2, 1.3)
with no adverse events	92	(17.3)	35	(13.2)	4.2 (-1.3, 9.2)
with drug-related[‡] adverse events	130	(24.5)	68	(25.6)	-1.1 (-7.6, 5.1)
with serious adverse events	31	(5.8)	25	(9.4)	-3.6 (-8.0, 0.2)
with serious drug-related adverse events	1	(0.2)	2	(0.8)	-0.6 (-2.5, 0.4)
who died	2	(0.4)	1	(0.4)	0.0 (-1.7, 1.0)
discontinued[§] due to an adverse event	4	(0.8)	6	(2.3)	-1.5 (-4.1, 0.1)
discontinued due to a drug-related adverse event	0	(0.0)	2	(0.8)	-0.8 (-2.7, -0.0)
discontinued due to a serious adverse event	3	(0.6)	2	(0.8)	-0.2 (-2.2, 1.0)
discontinued due to a serious drug-related adverse event	0	(0.0)	0	(0.0)	0.0 (-1.4, 0.7)

[†] Based on Miettinen & Nurminen method.
[‡] Determined by the investigator to be related to the drug.
[§] Study medication withdrawn.
Estimated differences and confidence intervals are provided in accordance with the statistical analysis plan.
Note: Raltegravir 1200 mg QD and raltegravir 400 mg BID were administered with TRUVADA™.

Data Source: [Ref. 5.3.5.1: P292V01]

In general, the frequency of individual clinical AE preferred terms was similar in both treatment groups. The most frequently reported clinical AEs (reported in ≥10% of subjects in one or more treatment groups), including those of all intensity and regardless of drug relationship, in the QD and BID groups, respectively, were: headache (13.4%, 10.9%), nausea (11.3%, 9.8%) and diarrhea (10.9%, 11.3%) [Table 2.7.4: 5], [Table 2.7.4: 6], [Table 2.7.4: 7].

The frequency of drug-related clinical AEs of any intensity was low in both treatment groups. The most frequently reported (incidence >2%) drug-related AEs in either group (shown as % for QD, % for BID) were nausea (7.3%, 6.8%), headache (3.0%, 4.5%), and dizziness (2.3%, 3.0%) [Table 2.7.4: 9]. No individual drug-related clinical AE of moderate or severe intensity was reported in more than 2% of subjects in either group [Table 2.7.4: 8], [Table 2.7.4: 9], [Table 2.7.4: 10], [Table 2.7.4: 11], [Table 2.7.4: 12], [Table 2.7.4: 13].

5.2.1.1.1 Deaths, Serious Adverse Events, and Discontinuations

The incidences of deaths (0.4% QD, 0.4% BID), serious adverse events (5.8% QD; 9.4% BID), and discontinuations due to clinical AEs (0.8% QD, 2.3% BID) were low and similar in both raltegravir 1200 mg QD (2 x 600 mg tablets) and raltegravir 400 mg BID groups ([Ref. 5.3.5.1: P292V01]).

There were 3 fatal AEs in the study: 2 (0.4%; tuberculosis and immunoblastic lymphoma) in the QD group; 1 (0.4%; AIDS) in the BID group. Each of these AEs was early onset (by Day

36 of the study) and may represent immue reconstitution system (IRS), although not reported as such by the investigator. The case of tuberculosis occurred in a subject with prior pulmonary TB, the case of immunoblastic lymphoma was newly diagnosed in the region of the kidney in a subject with lumbar pain at study entry, and the case of AIDS presented as progression of cryptococcal meningitis in a subject reported as having inadequately treated prior cryptococcal meningitis. None of these fatal adverse events was considered to be drug related [Table 2.7.4: 20]. [Ref. 5.3.5.1: P292V01]

In this Once Daily Application, serious clinical adverse events occurred in comparable frequencies for the raltegravir 1200 mg QD (2 x 600 mg tablets) and raltegravir 400 mg BID groups (5.8% QD; 9.4% BID) [Table 2.5: 6], [Table 2.7.4: 13], [Table 2.7.4: 14], [Table 2.7.4: 15], [Table 2.7.4: 16], [Table 2.7.4: 17], [Table 2.7.4: 18].

Serious drug-related clinical AEs were very infrequent (1/531 [0.2%] QD; 2/266 [0.8%] BID). The 1 serious drug-related AE in the QD group was headache, and was considered related to TRUVADA™ and not raltegravir. The 2 serious drug-related AEs in the BID group included a transient increase in RNA (drug ineffective), and vomiting considered related to an overdose (2 extra tablets of placebo). No subjects discontinued from the study due to serious drug-related adverse events.

Clinical AEs leading to discontinuation (0.8% QD, 2.3% BID) or clinical AEs associated with IRS (2.1% QD, 1.1% BID) or AIDS defining condition (1.3% QD, 2.3% BID) occurred at similar and low frequencies in both treatment groups [Table 2.7.4: 21], [Table 2.7.4: 23], [Table 2.7.4: 24], [Table 2.7.4: 25], [Table 2.7.4: 26].

In summary, the review of cases of deaths, serious adverse events, and adverse events leading to discontinuation in PN292 showed no findings of clinical concern and raise no new safety issues for raltegravir 1200 mg QD (2 x 600 mg).

5.2.1.2 Laboratory Adverse Events and Laboratory Values

The frequencies of treatment-emergent laboratory abnormalities were similar for raltegravir 1200 mg QD (2 x 600 mg tablets) and raltegravir 400 mg BID, including parameters of hepatic safety ([Ref. 5.3.5.1: P292V01]).

Results of safety laboratory tests were assessed by 3 different approaches: (1) investigator-reported adverse events, including investigator assessment of potential causality; (2) review of changes from baseline of laboratory values using Predefined Limits of Change (PDLC) according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS Criteria) [Ref. 5.4: 03Q0NV]; and (3) review of study therapy discontinuations due to laboratory adverse events. Overall, with respect to laboratory parameters, raltegravir 1200 mg QD (2 x 600 mg tablets) demonstrates a favorable safety profile that is consistent with that observed with raltegravir 400 mg BID.

Laboratory adverse events (7.0% QD; 11.3% BID) and drug-related laboratory adverse event (1.5% QD; 1.5% BID) were reported at low and comparable frequencies in the raltegravir 1200 mg QD (2 x 600 mg tablets) and raltegravir 400 mg BID groups [Table 2.7.4: 28], [Table 2.7.4: 29], [Table 2.7.4: 30], [Table 2.7.4: 31], [Table 2.7.4: 32], [Table 2.7.4: 33],

[Table 2.7.4: 34]. The frequencies of serious laboratory adverse events and discontinuations due to a laboratory adverse event were low in both treatment groups [Table 2.7.4: 19], [Table 2.7.4: 22], [Table 2.7.4: 35], [Table 2.7.4: 36]. There were no deaths due to laboratory adverse events in either group. Of the tests performed in routine monitoring, the most frequently (≥2% of subjects in one or more treatment groups) reported laboratory adverse events, regardless of drug relationship, were blood creatine phosphokinase increased (3.4%, 6.4%), and AST increased (2.6%, 1.9%) in the QD and BID groups, respectively [Table 2.7.4: 28].

Summary statistics (baseline and change from baseline) for protocol-specified laboratory tests within each of the categories of laboratory measurements (serum chemistry, hematology, and urinalysis) are in [Table 2.7.4: 27]. There were no clinically significant differences over time in either treatment group.

In general, laboratory abnormalities exceeding the predefined limits of change were similar in both groups, not of clinical significance, and occurred at similar frequencies in both treatment groups [Table 2.7.4: 37], [Table 2.7.4: 38], [Table 2.7.4: 39], [Table 2.7.4: 40]. A summary of the number and percent of subjects with laboratory abnormalities exceeding the predefined limits of change for all selected parameters is presented in [Table 2.7.4: 40].

Overall the frequencies of Grade 3 and 4 laboratory abnormalities were similar in the two groups: AST (8/530 [1.5%] QD, 1/266 [0.4%] BID), ALT (7/530 [1.3%] QD, 1/266 [0.4%] BID), and CPK (16/530 [3.0%] QD, 11/266 [4.1%] BID) occurred at similar frequencies in both treatment groups. Grade 3 or 4 ALT elevations occurred concurrently with Grade 2, 3 or 4 AST in a number of subjects in both groups (7/530 [1.3%] QD; 1/266 [0.4%]). In most cases, Grade 3 or 4 ALT elevations (with or without AST elevations) were self limited and did not recur or require treatment interruption or had alternative etiologies, such as viral hepatitis or use of hepatotoxic drugs [Ref. 5.3.5.1: P292V01].

Of the 7 cases of ALT elevations to Grade 3 or above in the QD group:

- Three cases were associated with viral hepatitis – 2 with acute hepatitis C infection (which, in one case, led to discontinuation), and 1 with flare of hepatitis B infection (discontinued).

- AN P3001* (*Grade 4 AST and Grade 4 ALT*), is a 31-year-old [redacted] in the 1200 mg QD treatment group with a history of hepatitis B. Screening serologies were positive for hepatitis B surface antigen and hepatitis B e antigen and negative for hepatitis B surface antibody and negative for hepatitis C. No concomitant medications were reported. At screening both AST, ALT, and bilirbubin were within normal limits (AST, 26 IU/L; ALT, 30 IU/L; total bilirubin, 0.6 mg/dL). On Day 1, an AE of worsening hepatitis B (severe intensity) was reported with Grade 3 elevations noted for both AST (215 IU/L) and ALT (338 IU/L), without bilirubin elevation (0.7 mg/dL). AST and ALT values rose to Grade 4 on Day 8 (AST: 459 IU/L and Grade 4 ALT: 566 IU/L); bilirubin increased (1.1 mg/dL) but remained within the normal range on Day 8. On Day 15, the subject experienced Grade 4 AST (565 IU/L) and Grade 4 ALT (998 IU/L) values, with Grade 2 bilirubin elevation (2.8 mg/dL). At this point the subject was considered to have met potential DILI criteria. However, due to the flare of pre-existing hepatitis B beginning on Day 1, the Sponsor does not consider this case a true DILI; this case was also reviewed by the eDMC. Study therapy was discontinued on Day 17 due to worsening hepatitis B. On Day 28, AST, ALT, and bilirubin values were Grade 4 (AST, 683 IU/L; ALT, 1001 IU/L; bilirubin, 7.6 mg/dL). On Day 43, at the post treatment study visit, AST, ALT and bilirubin values returned toward normal range (AST, 43 IU/L; ALT, 103 IU/L; bilirubin, 0.8 mg/dL); the AE of worsening hepatitis B was considered resolved. Please note this event was not reported as an ECI due to the identified viral hepatitis etiology. It was also not reported by the investigator as IRS but potentially may have been a hepatitis flare exacerbated by IRS.
- AN P3002* (*Grade 4 AST and Grade 4 ALT*), a 46 year-old [redacted] was randomized to the QD group and had no relevant medical history. Screening serology showed resolved hepatitis B (HBSAb positive; HBSAg negative) and was negative for hepatitis C. On Day 1, AST (30 IU/L) and ALT (24 IU/L) levels were within normal range. No concomitant medications were reported. On Day 119, the subject was found to have Grade 4 elevations in AST (810 IU/L) and ALT (1265 IU/L), without bilirubin elevations. The subject was found to have hepatitis C (AE reported on Day 121). The subject was found to be hepatitis C antibody (Ab) positive; hepatitis C RNA was reported as 4191858 IU/mL. The study physician decided to discontinue the subject due to hepatitis C diagnosis.
- AN P3003* *(Grade 3 ALT)*, a 20 year-old [redacted] was randomized to the QD group and had no relevant medical history. Screening serology showed resolved hepatitis B (HBSAb positive; HBSAg negative) and was negative for hepatitis C. On Day 1, AST (17 IU/L) and ALT (13 IU/L) levels were within normal range. No concomitant medications were reported. On Day 339, the subject was found to have Grade 2 AST (184 IU/L) and Grade 3 ALT (268 IU/L) levels, without bilirubin elevations. The subject was found to have acute hepatitis C (mild intensity) on Day 339 and continuing (hepatitis C antibody positive; polymerase chain reaction [PCR] test not done). Study therapy was not interrupted. Subsequent values on Day 351 were Grade 1 AST (86 IU/L) and Grade 2 ALT (131 IU/L).

- One case with hepatic steatosis (entered the study with Grade 2 ALT; discontinued).

- AN P3004* *(Grade 3 ALT)*, a 31 year-old [redacted] was randomized to the QD group. He had a prior history of gonorrhea, chlamydia, and herpes simplex virus infections. Screening serology showed resolved hepatitis B (HBSAb positive; HBSAg negative) and was negative for hepatitis C. On Day 1, the subject was found to have Grade 1 AST (59 IU/L) and Grade 2 ALT (152 IU/L) elevations. No concomitant medications were reported. On Day 169, the subject was found to have Grade 1 AST (90 IU/L) and Grade 3 ALT (282 IU/L) levels. These elevations were not accompanied by bilirubin elevations. The subject had the following concurrent AE reported: hepatic steatosis (moderate intensity) on Day 197; the hepatic steatosis did not resolve as of the data cutoff date. Diagnosis was made by abdominal MRI. Subsequent values on Day 232 were Grade 1 AST (86 IU/L) and Grade 3 ALT (285 IU/L). Study therapy was discontinued due to increased AST and ALT. No associated bilirubin elevations were observed.

- One case had elevated ALT and AST of several months duration in association with use of isoniazid for tuberculosis prophylaxis; the abnormalities resolved after isoniazid was stopped.
  - AN P3005* *(AST Grade 3 and ALT Grade 3, CPK Grade 4)*, a 33 year-old [redacted] was randomized to the QD group and had a history of alcoholism and positive purified protein derivative test. Screening serology was negative for hepatitis B (HBSAb negative; HBSAg negative) and negative for hepatitis C. Day 1 values were AST (36 IU/L), ALT (50 IU/L), ALP (100 IU/L), BILI (0.5mg/dL), and CPK (265 IU/L). Concomitant medications included isoniazid and pyridoxine (both from Day 78 to Day 120). Omeprazole was started on Day 120 and continued. On Day 108 the subject was found to have Grade 2 AST (171 IU/L), Grade 3 ALT (250 IU/L), and Grade 4 CPK (7046 IU/L) levels. Concurrently, ALP (98 IU/L) and BILI (0.3 mg/dL) were within normal range. The subject had the following concurrent clinical AEs reported: night sweats of mild intensity (started Day 41 and continuing) and gastrooesophageal reflux disease of mild intensity (started Day 93 and continuing). Study therapy was not interrupted. On Day 120, CPK (227 IU/L) returned to normal and did not exceed Grade 2 through Day 512. On Day 340 (after discontinuation of isoniazid), AST (50 IU/L) and ALT (47 IU/L) levels returned to baseline and remained within the normal range through Day 512. No associated bilirubin elevations were observed.

- One case had an adverse event of nonspecific hepatitis which resolved, and 1 case had a Grade 4 ALT not associated with clinical AE, which resolved.

- AN P3006* *(Grade 3 AST, Grade 3 ALT)*, a 38 year-old [redacted] was randomized to the QD group and had a history of past hepatitis B infection and hepatitis C. Screening serology showed resolved hepatitis B (HBSAb positive; HBSAg negative) and was positive for hepatitis C (hepatitis C virus [HCV] PCR less than 15 IU/ML). Day 1 AST (21 IU/L) and ALT (20 IU/L) levels were within normal range. Concomitant medications included cefuroxime and metronidazole. Omeprazole was taken from Day 171 to Day 172. On Day 169, the subject was found to have Grade 3 AST (232 IU/L) and Grade 3 ALT (329 IU/L) levels. The subject was found to have acute hepatitis on Days 162 and 169 (moderate intensity; duration 35 days). Ultrasound was normal. HBsAg was negative; HCV RNA was not done. Study therapy was not interrupted. On Day 197, AST (27 IU/L) and ALT (26 IU/L) levels returned to normal range. All subsequent AST, ALT, ALP, and BILI values through Day 423 were within the normal range. No associated bilirubin elevations were observed.
- AN P3007* *(Grade 3 ALT)*, a 34 year-old [redacted] was randomized to the QD group and had a history of tachycardia. Screening serology was negative for hepatitis B (HBSAb negative; HBSAg negative) and negative for hepatitis C. Concomitant medications included ibuprofen, alprazolam, omeprazole, and atenolol. Day 1 values were slightly elevated (AST 44 IU/L and ALT 57 IU/L). On Day 57, the subject was found to have Grade 2 AST (144 IU/L) and Grade 3 ALT (249 IU/L) levels. No concurrent adverse events were reported. Study therapy was not interrupted. On Day 113, values returned to baseline, AST (42 IU/L) and ALT (63 IU/L). All subsequent AST and ALT values through Day 333 did not exceed Grade 2. No associated bilirubin elevations were observed.

There was 1/266 (0.4%) subject in the BID group with Grade 3 ALT which was associated with a Grade 2 AST. This was transient and resolved on study.

Thus, most cases of Grade 3 or 4 AST and/or ALT elevations had underlying causes identified, and although 1 case (AN P3001* met Hy's law laboratory criteria, a flare of hepatitis B as early as Day 1 of the study was considered to be the etiology of these laboratory abnormalities.

Grade 3 or 4 CPK elevations occurred concurrently with Grade 2, 3, or 4 AST elevations in a number of subjects in both groups (6/530 [0.7%] QD; 4/266 [0.4%]). In most cases, Grade 3 or 4 CPK elevations (with or without AST elevations) were self-limited and did not recur or require treatment interruption. There were no cases associated with significant muscular conditions such as myositis or rhabdomyolysis. One subject in the QD group with Grade 3 or 4 CPK was discontinued due to recurrent CPK elevation without any associated clinical findings.

While Grade 3 and 4 lipase elevations were observed in both groups (13/530 [2.4%] QD; 1/266 [0.4%]), this was generally clinically silent, other than one subject in the QD group who had Grade 3 lipase with a concurrent diagnosis of pancreatits, which persisted after resolution of the elevated lipase. No specific symptomatology was reported, no imaging was performed and amylase was not reported.

Thus, a detailed review revealed that the occurrence of aminotransferase, CPK, and lipase elevations was comparable in the QD and BID groups and did not raise new clinical concerns.

In summary, detailed review of the laboratory safety in PN292 demonstrated that the laboratory safety profile of raltegravir 1200 mg QD (2 x 600 mg tablets) was similar to that of raltegravir 400 mg BID in treatment-naïve subjects, and was consistent with the safety profile of raltegravir 400 mg BID reported in previous Applications.

5.3 Safety in Special Groups and Situations

As in the previous Applications, safety of raltegravir 1200 mg QD in special groups and situations was evaluated in PN292 in various subgroups of interest. Data in this Once Daily Application demonstrate a safety profile consistent with the safety profile of raltegravir 400 mg BID in the special groups noted.

5.3.1 Intrinsic Factors

In the subgroups of gender (male and female), age (<65 and ≥65 years), ethnicity (Hispanic vs. non-Hispanic), and race (White, Black, Native Hawaiian/Pacific Islander, Asian, and Multiracial) raltegravir 1200 mg QD (2 x 600 mg tablets) was generally well tolerated (taking into account very small sample sizes for some categories). These results were consistent with those for raltegravir 400 mg BID [Table 2.7.4: 41], [Table 2.7.4: 42], [Table 2.7.4: 43], [Table 2.7.4: 44], [Table 2.7.4: 45], [Table 2.7.4: 46], [Table 2.7.4: 47], [Table 2.7.4: 48], [Table 2.7.4: 49], [Table 2.7.4: 50], [Table 2.7.4: 51], [Table 2.7.4: 52] [Ref. 5.3.5.1: P292V01], and also consistent with the profile of raltegravir 400 mg BID as reported in the previous Applications.

5.3.2 Extrinsic Factors

Safety data were reviewed in subjects with hepatitis B and/or C virus co-infection and in those using gastric proton pump inhibitors and H_2 blockers such as omeprazole and famotidine.

The safety profile of raltegravir QD was not affected by the presence of chronic hepatitis B and/or C virus co-infection, or by the use of gastric proton pump inhibitors and H_2 blockers. Raltegravir 1200 mg QD (2 x 600 mg tablets) was generally well tolerated in these subgroups [Table 2.7.4: 53], [Table 2.7.4: 54], [Table 2.7.4: 55], [Table 2.7.4: 56], [Table 2.7.4: 57], [Table 2.7.4: 58], [Table 2.7.4: 59], [Table 2.7.4: 60], [Table 2.7.4: 61], [Table 2.7.4: 62], [Table 2.7.4: 63], [Table 2.7.4: 64], [Ref. 5.3.5.1: P292V01]. These results were consistent with those for raltegravir 400 mg BID, and also consistent with the profile of raltegravir 400 mg BID as reported in the previous Applications.

The safety profile of raltegravir QD was also not associated with any particular PK parameter or exposure. Raltegravir 1200 mg QD (2 x 600 mg tablets) was generally well tolerated regardless of C_{max} or AUC [Table 2.7.4: 65], [Table 2.7.4: 66], [Table 2.7.4: 67], [Table 2.7.4: 68], [Ref. 5.3.5.1: P292V01].

5.3.3 Overdose

No specific information is available on the treatment of overdosage with ISENTRESS®. Multiple doses as high as 1800 mg (3 x 600 mg) QD for 28 days were studied in Phase 1 (P293) and occasional doses of 2400 mg per day were taken in PN292 without evidence of toxicity.

In [Ref. 5.3.5.1: P292V01], overdoses of blinded study drug (3 or more 600 mg or placebo to 600 mg tablets, 4 or more 400 mg or placebo to 400 mg tablets, or 2 or more Truvada™ tablets) without AE were reported in 4.1% and 3.8% of subjects in the QD and BID groups, respectively. After unblinding, actual overdoses of raltegravir, i.e., a total daily dose of more than 1200 mg, were found to have occurred in 1.5% of subjects in the QD group, with total daily doses not exceeding 2400 mg in any one subject for more than 1 day at a time. There were no actual overdoses of raltegravir in the BID group. These findings are consistent with safety results from [Ref. 5.3.3.1: P293] in which raltegravir dosed at1800 mg QD for 28 days was generally well tolerated [Table 2.7.4: 70] ([Ref. 5.3.5.1: P292V01]).

Based upon available data, raltegravir appears to be well tolerated at prescribed total daily doses up to 1200 mg and when administered with drugs that increase exposure by 50% to 70% (such as tenofovir and atazanavir) [Sec. 2.7.2].

5.4 Limitations of the Safety Database

The current database focuses on safety finding through 48 weeks of therapy in Protocol 292. This study will continue through Week 96 of therapy; additional safety findings from this longer duration of follow-up will be provided in a future submission.

While pediatric subjects were not studied in PN292, the use of 1200 mg QD in pediatric patients weighing at least 40 kg is supported by simulation [Sec. 2.7.2.2.2.4], [Sec. 2.7.2.3.2.2.1] and the available safety data in pediatric subjects with the approved pediatric twice daily formulations. The daily raltegravir AUC values obtained with 1200 mg QD in PN292 are the highest attained in any long-term raltegravir clinical study to date, and higher than those from ISENTRESS® 400 mg BID. Safety analysis conducted based on PK exposure quartiles (AUC_{0-24}, C_{max}) using data from raltegravir 1200 mg QD in PN292 demonstrated no relationship between PK and clinical or laboratory adverse events, and importantly, no increased risks associated with the highest PK exposure quartiles [Table 2.7.4: 65], [Table 2.7.4: 66], [Table 2.7.4: 67], [Table 2.7.4: 68], [Ref. 5.3.5.1: P292V01]. Thus the safety database from ISENTRESS® 400 mg BID development program can be considered supportive for the raltegravir 1200 mg QD program.

5.4.1 Risk Management Plan

An updated version (V11.0) of the Raltegravir Risk Management Plan has been prepared to support this application. The assessment of the safety data from PN292 has demonstrated that the safety profile for raltegravir QD is consistent with that established for raltegravir BID with no new important potential or identified risks identified.

5.5 Worldwide Marketing Experience

The raltegravir 600 mg tablet for once daily use has not been licensed in any country and therefore no post-marketing data are available. However, as of 31-December-2015, a total of 848,082,853 of the 400 mg tablets have been sold for use in HIV-infected patients, with a total estimated exposure of 1,160,962 patient-years.

5.6 Safety Conclusions

5.6.1 Phase 1 Studies

Raltegravir QD was generally well tolerated after single doses of 1200 mg and multiple dose administration of 1200 mg and 1800 mg up to 28 days, when given alone or in combination with antacids, atazanavir or efavirenz.

5.6.2 Phase 3 Study

- Raltegravir 1200 mg QD has a favorable safety profile, which is similar to that of raltegravir 400 mg BID in HIV-1 treatment-naïve subjects in this study, and consistent with the established safety profile of ISENTRESS® BID. There are no new safety concerns for the raltegravir 1200 mg QD regimen.
- The most frequently reported (incidence >2%) drug-related AEs in either group (shown as % for QD, % for BID) were nausea (7.3%, 6.8%), headache (3.0%, 4.5%), and dizziness (2.3%, 3.0%).
- No deaths were considered related to study drug, and serious drug-related AEs and AEs leading to discontinuation were rare.
- The rates of treatment-emergent laboratory abnormalities are low and generally similar for raltegravir 1200 mg QD and raltegravir 400 mg BID.
- Both raltegravir 1200 mg QD and raltegravir 400 mg BID have favorable safety profiles in key baseline demographic or prognostic groups.
- Exploratory safety analysis based on PK exposure quartiles ($AUC_{0\text{-}24h}$ and C_{max}) confirmed the lack of any potential increased risks associated with the highest exposures from the raltegravir 1200 mg QD regimen. Additionally, the safety profile of raltegravir 1200 mg QD is comparable among subjects in the lowest and highest PK quartiles.

6 BENEFIT AND RISK CONCLUSIONS

Raltegravir, an HIV integrase strand transfer inhibitor, continues to provide strong clinical evidence of its benefits in HIV-1 infected patients. There is well-established evidence of the efficacy and safety of rategravir BID in the Applicant's clinical development program as well as in studies conducted by others and in real world use. Raltegravir 400 mg BID is currently listed as one of the preferred agents to be used in a combination regimen for initiation of treatment in HIV-1 infected patients in multiple national and international guidelines

including US DHHS and EACS. Raltegravir 400 mg BID use is not restricted by renal function, has limited potential for DDIs, and can be administered without regard to food, allowing its use in the setting of comorbid conditions and concomitant medications.

In this submission, data demonstrating that raltegravir 1200 mg QD has potent and non-inferior efficacy and comparable safety to the 400 mg BID regimen are provided. Raltegravir as a QD agent can provide the added benefit of simplified dosing, facilitating adherence which is likely to translate into sustained virologic suppression and control of disease progression. Thus, this Once Daily Application demonstrates that there is a favorable benefit/risk ratio for the use of raltegravir 1200 mg QD (2 x 600 mg tablets) in HIV-1 infected treatment-naïve patients and for continued treatment in patients who are virologically suppressed on an initial regimen of ISENTRESS® 400 mg BID.

6.1 Benefits

Protocol 292 demonstrated that 48 weeks of therapy with a regimen of raltegravir 1200 mg QD (2 x 600 mg tablets) plus TRUVADA™ was equally efficacious to the standard of care regimen of raltegravir 400 mg BID plus TRUVADA™, as currently recommended in US DHHS and other national and regional guidelines for initial treatment of HIV-1 infection [Ref. 5.4: 04DK0G, 04DK20]. Raltegravir 1200 mg QD (2 x 600 mg tablets) leads to rapid viral suppression (HIV RNA<40 copies/mL) similar to that with raltegravir 400 mg BID. The raltegravir 1200 mg QD (2 x 600 mg tablets) regimen resulted in similar immunologic efficacy as measured by the increases in CD4 cell count compared to the raltegravir 400 mg BID regimen. Consistent efficacy was observed across important prognostic subgroups, including those with high baseline viral load, as well as across various demographic variables including race and gender. Both the QD and BID raltegravir regimens in PN292 were generally well tolerated with similar safety profiles. The overall safety of raltegravir 1200 mg QD (2 x 600 mg tablets) is consistent with the established safety profile for raltegravir 400 mg BID ([Ref. 5.3.5.1: P292V01]).

Raltegravir 1200 mg as a new once daily option for pediatric patients weighing at least 40 kg is of particular potential benefit in adolescents with recent, horizontally acquired infection, who may have multiple potential barriers to medication adherence [Ref. 5.4: 04DK0G]. Modeling and simulation data support the use of raltegravir 1200 mg QD in pediatric patients weighing at least 40 kg.

Findings from exposure-efficacy analysis using raltegravir data from PN292 demonstrate that maximum viral suppression (HIV RNA <40 copies/mL) is likely achieved across the range of PK exposures obtained from both QD and BID regimens. This is consistent with previous raltegravir PK/PD findings, which demonstrated that raltegravir efficacy from ISENTRESS® 400 mg BID is at the plateau region of the exposure-efficacy curve. Therefore, it can be projected that continued treatment with raltegravir 1200 mg QD is comparable to continued treatment with raltegravir 400 mg BID, and therefore patients suppressed on an initial regimen of raltegravir BID can be switched to raltegravir QD, with equivalent virologic outcomes.

Overall, raltegravir 1200 mg QD (2 x 600 mg tablets) has demonstrated potent and durable antiretroviral and immunologic efficacy in treatment-naïve subjects. Raltegravir 1200 mg QD was generally well tolerated. These results establish that raltegravir QD has statistically non-inferior efficacy compared to raltegravir BID at Week 48 in treatment-naïve subjects with a similar favorable safety profile. The results from PN292 along with PK and modeling and simulation data indicate that raltegravir 1200 mg QD (2 x 600 mg tablets) is an important simplified dosing regimen that can be used both for HIV-1 infected treatment-naïve patients and patients who are virologically suppressed on an initial regimen of ISENTRESS® 400 mg BID including adult and pediatric patients weighing at least 40 kg.

6.2 Risks

Raltegravir 1200 mg QD (2 x 600 mg tablets) demonstrates a favorable tolerability and safety profile with low rates of discontinuations due to adverse events similar to that observed for raltegravir 400 mg BID (Sec. 2.5.5 of 48 Week Treatment Experienced Supplemental Application) (Sec. 2.5.5 of 48 Week Treatment Naïve Supplemental Application) (Sec. 2.5.5 of 96 Week Treatment Naïve and Treatment Experienced Supplemental Filing). During the Once Daily Development program for raltegravir 1200 mg QD, there have been no new risks identified beyond those that were recognized and described in the product labeling of the approved BID formulation.

In summary, raltegravir 1200 mg QD (2 x 600 mg tablets) has a positive benefit/risk profile. Raltegravir 1200 mg QD (2 x 600 mg tablets) would expand the once daily treatment options for HIV-1 infected treatment-naïve patients and patients who are virologically suppressed on an initial regimen of ISENTRESS® 400 mg BID including adult and pediatric patients weighing at least 40 kg. This regimen simplification offers a new treatment option that may increase the likelihood of adherence to ART, and maximize the probability of achieving and maintaining optimal virologic suppression and immune reconstitution with first-line regimens.

7 APPENDICES

Appendix 2.5: 1
Module 5 Sections Omitted in the 48 Week Raltegravir Once Daily Application

Omitted Section	Justification for the omission
5.3.1 Reports of Biopharmaceutic Studies	
5.3.1.2 Comparative BA and Bioequivalence (BE) Study Reports	No absolute BA or BE studies were performed in support of this Application. Two comparative BA studies (PN290 and PN291) were performed and the clinical study reports are included in [Sec. 5.3.1.1].
5.3.1.3 *In vitro-In vivo* Correlation Study Reports	No in vitro- in vivo correlation study was conducted in support of this Application.
5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies	Bioanalytical reports for the Phase 1 studies and Phase 3 study are provided as appendices to the clinical study reports in [Sec. 5.3.1.1] (P290, P291), [Sec. 5.3.5.1] (P292V01), [Sec. 5.3.3.1] (P293), and [Sec. 5.3.2.2] (P812, P823, P824).
5.3.2 Reports of Studies Pertinent to Pharmacokinetics using Human Biomaterials No new nonclinical studies were conducted in support of this Application. Reports of all non-clinical studies were submitted in the Original Application for ISENTRESS® in Module 4 and a reference describing assessment of the effect of raltegravir on human drug transporters is included in [Sec. 4.3].	
5.3.2.1 Plasma Protein Binding Study Reports	No new plasma protein binding studies were conducted in support of this Application.
5.3.2.3 Reports of Studies Using Other Human Biomaterials	No new studies using human biomaterials studies were conducted in support of this Application. A reference describing assessment of the effect of raltegravir on human drug transporters is included in [Sec. 4.3].
5.3.3 Reports of human pharmacokinetic (PK) studies	
5.3.3.2 Patient PK and Initial Tolerability Study Reports	Patient PK and safety was evaluated in the Phase 1 study PN824 (clinical study report is in [Sec. 5.3.2.2]) and in the Phase 3 study PN292 (clinical study report in [Sec. 5.3.5.1]).
5.3.3.3 Intrinsic Factor PK Study Reports	The effect of intrinsic factors on the PK of the raltegravir 1200 mg QD dose was examined in PN292/using population PK modeling. The population PK report is in [Sec. 5.3.5.3.4].

Omitted Section	Justification for the omission
5.3.3.4 Extrinsic Factor PK Study Reports	The effect of extrinsic factors on the PK of the raltegravir 1200 mg QD dose was examined in the Phase 1 studies (PN812, PN823 and PN824) and in PN292, using population PK modeling. The population PK report is in [Sec. 5.3.5.3.4].
5.3.3.5 Population PK Study Reports	Three population PK analysis reports are included in this Application and all are included in [Sec. 5.3.5.3.4]: population PK report, pediatric simulation report, and exposure- efficacy report.
5.3.4 Reports of human pharmacodynamic (PD) studies	
5.3.4.1 Healthy Subject PD and PK/PD Study Reports	No healthy subject PD or PK/PD studies were conducted in support of this Application.
5.3.4.2 Patient PD and PK/PD Study Reports	Data and discussion of patient PD and PK/PD can be found in the PN292 clinical study report in [Sec. 5.3.5.1] and the exposure-efficacy report in [Sec. 5.3.5.3.4].
5.3.5 Reports of efficacy and safety studies	
5.3.5.2 Study Reports of Uncontrolled Clinical Studies	No uncontrolled clinical studies of the 1200 mg QD dose were performed in support of this Application.
5.3.6 Reports of post-marketing experience	The raltegravir 600 mg tablet for once daily use has not been licensed in any country and therefore no post-marketing data are available.

8 LITERATURE REFERENCES

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