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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	22-145
Supplement #:	36
Drug Name:	Isentress® HD (raltegravir potassium) 600 mg film-coated tablet
Indication(s):	Treatment of HIV-1 in treatment-naïve patients (adults and pediatrics weighing at least 40 kg) or patients who are virologically suppressed on an initial regimen of ISENTRESS 400 mg twice daily
Applicant:	Merck Sharp & Dohme Co.
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Table of Contents

1 EXECUTIVE SUMMARY....4

2 INTRODUCTION....5

2.1 OVERVIEW....7
2.2 DATA SOURCES....7

3 STATISTICAL EVALUATION....7

3.1 DATA AND ANALYSIS QUALITY....7
3.2 EVALUATION OF EFFICACY FOR TRIAL PN292....8
3.2.1 Trial Design and Endpoints....8
3.2.2 Statistical Methodologies....10
3.2.3 Patient Disposition, Demographic and Baseline Characteristics....13
3.2.4 Results and Conclusions....18
3.3 EVALUATION OF SAFETY....22

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS....22

4.1 GENDER, RACE, AGE, AND GEOGRAPHIC REGION....22
4.2 OTHER BASELINE CHARACTERISTICS....23

5 SUMMARY AND CONCLUSIONS....26

5.1 STATISTICAL ISSUES....26
5.2 COLLECTIVE EVIDENCE....27
5.3 CONCLUSIONS AND RECOMMENDATIONS....27
5.4 LABELING RECOMMENDATIONS....28

LIST OF TABLES

Table 1: PN292 Trial Summary....6
Table 2: Trial Time Points....12
Table 3: Randomization Stratification Distribution....14
Table 4: Subject Disposition the FAS (Week 48)....15
Table 5: Baseline Subject Demographics and Characteristics (FAS)....16
Table 6: Primary Analysis of W48 HIV-1 RNA....18
Table 7: Secondary Efficacy Endpoints....19
Table 8: Treatment Compliance....21
Table 9: Concordance between Screening and Baseline HIV-1 RNA Categorization....21
Table 10: Virologic Success (NC=F) by Gender, Race and Age....23
Table 11: Week 48 HIV-RNA <40 c/mL by Subgroup (NC=F)....24

LIST OF FIGURES

Table 1: PN292 Trial Summary....6
Table 2: Trial Time Points....12
Table 3: Randomization Stratification Distribution....14
Table 4: Subject Disposition the FAS (Week 48)....15
Table 5: Baseline Subject Demographics and Characteristics (FAS)....16
Table 6: Primary Analysis of W48 HIV-1 RNA....18
Table 7: Secondary Efficacy Endpoints....19
Table 8: Treatment Compliance....21
Table 9: Concordance between Screening and Baseline HIV-1 RNA Categorization....21
Table 10: Virologic Success (NC=F) by Gender, Race and Age....23
Table 11: Week 48 HIV-RNA <40 c/mL by Subgroup (NC=F)....24

1 EXECUTIVE SUMMARY

Isentress® (raltegravir) 400 mg is FDA approved for marketing as a twice-daily (BID) treatment given in combination with other antiretroviral agents for treating HIV-1 infection in treatment-naïve and treatment-experienced patients with evidence of ongoing viral replication. There remains a continued need for alternative dosing to increase patient compliance to maximize the long-term virologic suppression of HIV-1 infection. This supplemental New Drug Application (sNDA) contains new safety and efficacy data intended to support Merck's proposed alternative raltegravir treatment regimen for HIV-1 infection. The proposed regimen is a once-daily (QD) dosing of raltegravir 1200 mg (2 x 600 mg film-coated tablets), ISENTRESS® HD, for use in adult and pediatric patients weighing at least 40 kg who are antiretroviral treatment (ART) naïve or already virologically suppressed on a 400 mg twice-daily (BID) ISENTRESS ® regimen. Specifically, this sNDA contains data from six Phase 1 studies and one pivotal Phase 3 trial (PN292); however, this review covers PN292 only.

PN292 was a Phase 3 trial designed to evaluate the safety and efficacy of raltegravir 1200 mg QD versus raltegravir 400 mg BID, both administered in combination with TRUVADA™ (emtricitabine (FTC) plus tenofovir (TDF)), in treatment-naïve (TN) HIV-1 infected adult subjects. PN292 was a randomized (2:1; 1200 mg QD:400 mg BID), multinational, double-blind trial, based on a non-inferiority objective using a 10% margin. The trial duration was 98 weeks, which included 96 weeks of treatment followed by two weeks of follow-up. The primary efficacy endpoint, virologic suppression defined as achieving an HIV-1 RNA <40 copies/mL analyzed via the FDA Snapshot approach, was measured at Week 48 in all randomized subjects. Interim data through Week 48 were submitted to support this sNDA; however, the trial was ongoing at the time of the submission.

Overall, among 797 ART treatment-naive, HIV-1 infected adults randomized to treatment (n=531 QD; n=266 BID), the majority were male (85%), had an average age at screening of 36 years, 59% White race, 17% Black race, 15% Asian race, and 7.5% with multiple race. At baseline, the mean CD4 count was 414 cells/mm^3 with 87% of all subjects entering the trial with a CD4 count greater than 200 cells/mm^3. More than 71% of all subjects had baseline HIV-1 RNA of 100,000 c/mL or fewer, 66% were infected with Clade B HIV-1, and few (less than 5%) subjects were co-infected with either HCV or HBV. Overall, baseline factors were balanced between randomized groups with the exception of HIV-1 subtype; however, this factor did not appear to influence outcome.

The proportion of subjects in the full analysis set (all randomized and treated) who were virologically suppressed at Week 48 was 88.9% (472/531) and 88.3% (235/266) in the QD and BID groups, respectively, yielding a difference (QD-BID) of 0.51% and corresponding 95% CI of -4.20% to 5.22% (FDA Snapshot approach). The proportion of subjects in each group with an HIV-1 RNA ≥ 40 c/mL at W48 was 5.5% and 6% in the QD and BID groups, respectively. The remaining failures were due to missing values. The 95% lower confidence bound around the

difference in virologic suppression falls within the pre-specified -10% non-inferiority margin and the point estimates commensurate with the expected proportion of virologic suppression providing evidence that the 1200 mg QD raltegravir regimen is effective for treating HIV-1 infection in TN adults. Specifically, these results suggest that the QD regimen is as much as 4.2% worse than or as much as 5.2% better than the already-approved BID raltegravir regimen. Differences between groups were maintained across a series of secondary endpoints considering different virologic cut points and missing data approaches supporting a finding of non-inferiority. However, this trial did not enroll HIV-1 infected subjects who were virologically suppressed at baseline; therefore there is no statistical evidence from this trial to support use of the QD regimen as a switch regimen. Furthermore, this trial did not enroll adolescent or pediatric subjects, thus preventing statistical assessment in these subgroups. Finally, despite the multi-national distribution of clinical sites the majority of trial subjects were male thus limiting the ability to fully extrapolate trial findings to the larger population of females infected with HIV. Greater attempts are needed to ensure a more balanced distribution by gender in future HIV treatment trials.

Given that raltegravir 400 mg BID is an already-approved regimen for treating HIV-1 infection in TN and virologically-suppressed adults and pediatrics, evidence from a single trial was viewed as sufficient for this reformulated regimen. Findings from the single, confirmatory, non-inferiority trial PN292 support the proposed labeling revisions to include reformulated raltegravir 1200 mg QD, ISENTRESS® HD, regimen for treatment of HIV-1 infected, treatment-naive, adult subjects. Trial PN292 did not enroll virologically-suppressed HIV-1 infected subjects and therefore it does not provide statistical evidence to support Merck's proposed dosing and administration of 1200 mg QD raltegravir in virologically suppressed patients already taking raltegravir 400 mg BID.

2 INTRODUCTION

The complicated HIV-1 viral replication process in the human cell largely relies on several enzymes including integrase, which catalyzes the stepwise process of viral integration into the host cell genome. Raltegravir was the first-in-class integrase inhibitor approved by FDA (original approval on 10/12/2007; NDA 22145) for treating HIV-1 infection in treatment-experienced adult patients with evidence of viral replication and HIV-1 strains resistant to multiple antiretroviral agents. The approved formulation is a 400 mg film-coated tablet taken twice-daily. Subsequent to the original approval, raltegravir was approved for treating HIV infection in treatment-naïve adult and pediatric patients. The approved dosage is 400 mg administered twice daily for adults, children and adolescents weighing at least 25 kilograms. Chewable (NDA 203045, approval 12/21/2011) and oral suspension (NDA 205786, approved 12/20/2013) formulations are also available for children and adolescents unable to swallow the film-coated 400 mg tablet and/or weigh less than 25 kilograms.

Previously, Merck (the applicant) conducted trial PN071, which was a large Phase 3, randomized, active-controlled, non-inferiority (10% margin) trial to compare the efficacy of a

800 mg (2 x 400 mg tablets) QD raltegravir regimen versus the marketed 400 mg tablet BID regimen of raltegravir both given in combination with TRUVADA in adult, treatment-naïve HIV-1 infected subjects. Trial PN071 was prematurely terminated after analysis of Week 48 (W48) primary endpoint revealed that the raltegravir 800 mg QD regimen failed to achieve non-inferiority against the raltegravir 400 mg BID regimen. Specifically, the treatment difference in the proportion of subjects achieving an HIV-1 RNA <50 c/mL at W48 was -5.7% (QD-BID) with a 95% CI of -10.7% to -0.83% showing inferiority as the lower bound exceeded -10% and the interval excluded zero. Using data from PN071, Merck performed additional Phase 1 studies to better characterize the PK profile of a 600 mg tablet administered at varying doses up to 1800 mg QD.

In this supplemental NDA (sNDA), Merck submits data from a new Phase 3, active-controlled trial, PN292 (Table 1). These data are in support of the proposed reformulated raltegravir 600 mg film-coated tablet for the proposed dosage and administration of 1200 mg (2 x 600 mg tablets) QD for treating HIV-1 infection in adult and pediatric (weighing at least 40 kg) patients who are treatment-naïve or who are virologically suppressed on an initial regimen of ISENTRESS 400 mg twice daily. ***Note that this sNDA also contains six Phase 1 studies, which are not covered in this review as they focused on biopharmaceutics in healthy volunteers (PN290, PN291 and PN293) and drug-drug interaction in healthy volunteers (PN812 and PN823) and HIV-infected subjects (PN824). Refer to the review by Dr. Mario Sampson for details from the clinical pharmacology assessment.***

Table 1: PN292 Trial Summary

Trial	Design*	Treatment (n)	Endpoint/Analysis	Findings
PN292	R, MN, DB, AC, NI trial (10% margin) in HIV-1 treatment-naïve adults (≥18 yrs) w/ baseline HIV RNA ≥1000 c/mL 2:1 rand ratio, stratification factors: HIV RNA** and Hepatitis (B and/or C) status	Raltegravir 1200 mg once (QD) daily + TRUVADA QD (n=531) Raltegravir 400 mg twice daily (BID) + TRUVADA QD (n=266) 797 total in FAS	Primary: Proportion achieving HIV RNA <40 c/mL at **W48** Mantel-Haenszel method (stratum-adjusted) weighted by the harmonic mean of the sample size use to compare proportions achieving primary endpoint in the FAS, non-completer = failure using FDA "Snapshot' approach Key Secondary: Change from BL in CD4 at W48	***Primary***: W48: 88.9% (472/531) and 88.3% (235/266) for QD and BID, respectively. Treatment difference (QD – BID) 0.51%, 95% CI of (-4.20, 5.22). ***Secondary***: Mean change from BL in CD4 of 232 cells/mm3 in the QD group compared with 234 cells/mm3 in the BID group; treatment difference (95% CI) of -2.1 (-30.9, 26.7)

* MN: multi-national, R: randomized, DB: double-blind, NI: non-inferiority, PC: placebo controlled, AC: active controlled, QD: once-daily dosing; BID: twice-daily dosing; ** ≤100,000 c/mL and >100,000 c/mL, FAS: full analysis set including all randomized subjects who have taken at least one dose of study medication and have baseline data (for analyses requiring baseline data)

2.1 Overview

2.2 Data Sources

The sNDA was submitted electronically and located internally at the FDA server: \\CDSESUB1\evsprod\NDA022145\0325. In addition, clarification was sought by the review team regarding the reported protocol deviations in trial PN292. In addition, the team requested copies of reports presented to the DMC and the DRC minutes. The Applicant's response to these requests is located at: \\CDSESUB1\evsprod\NDA022145\0329.

This submission contains the Week 48 primary findings; however, the trial is ongoing at the time of the sNDA submission. The database lock for purposes of the Week 48 analyses occurred on 2/10/16.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

There were 17 (14 QD and 3 BID) subjects who were randomized to an incorrect stratum based on analysis of the locked data bases. In seven cases, the screening viral RNA was incorrectly reported in the IVRS (by the clinical site) leading to incorrect classification of the subject. This misclassification was not corrected for in the analyses, that is, the subject was analyzed in the stratum to which they were randomized. There were eight cases where subjects were incorrectly stratified according to HCV and/or HBV co-infection. These misclassifications were corrected for in the analysis (i.e. analyzed per result) based on the actual laboratory result obtained. The Applicant's justification for the approach to manage incorrect stratification is that baseline HIV-1 RNA is related to efficacy outcome and therefore analysis was as per the ITT principle. In contrast, baseline hepatitis is related to safety and therefore analysis was based on an as-treated principle.

Reviewer's Comment: The approach to analyze subjects as randomized based on screening viral RNA is preferred as to preserve the overall randomization structure. While the reviewer disagrees with the approach to correct for the incorrect strata assignment by co-infection status, due to the overall low proportion of subjects randomized in the trial with co-infection (n=39; 4.9%), the applicant's primary analysis using the stratum-adjusted Mantel-Haenszel method with difference weighted by the harmonic mean of sample size per stratum only included screening HIV-1 RNA as a strata. Therefore, the primary efficacy analysis was not impacted by the few misclassifications by co-infection status.

In addition, one subject received the incorrect study medication for 12 days (active 600 mg raltegravir instead of matching placebo where the matching placebo was used to ensure a double-

blind, double-dummy approach (see section 3.2.1.1 for specific on the blinding approach)) but was analyzed as randomized. Given that this incorrect treatment occurred for only 12 days (out of 48 weeks) and among one subject it is unlikely to greatly impact the overall findings.

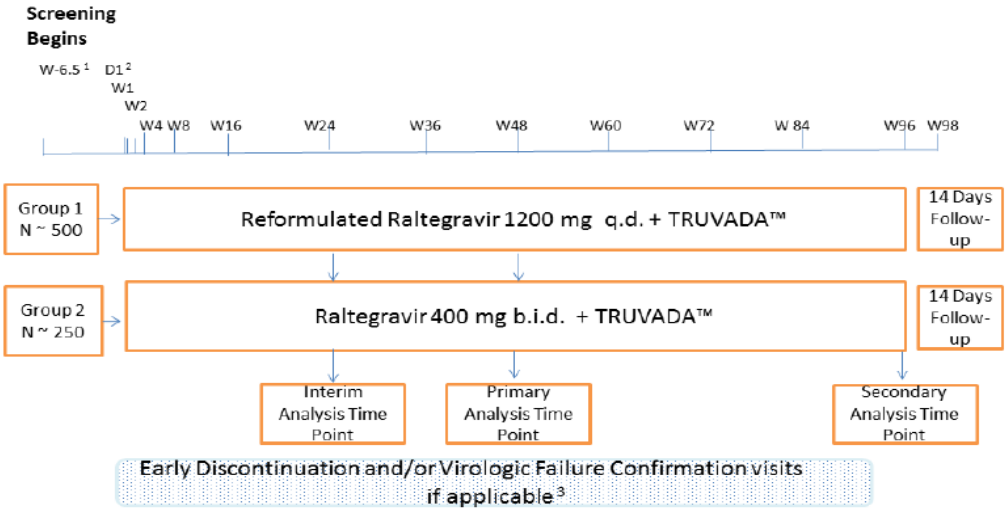
The applicant reports that there were numerous protocol deviations relating to the Informed Consent Form, which were reviewed and found to be minor errors not impacting the overall trial quality and results.

3.2 Evaluation of Efficacy for Trial PN292

There were two protocol amendments during the trial leading to changes and/or clarifications none of which were related to the overall trial design and analyses.

3.2.1 Trial Design and Endpoints

PN292 was a multinational, double-blind, randomized, parallel, two-arm, 98 week, non-inferiority trial including 96 weeks of treatment and a follow-up visit at week 98, two weeks post-treatment discontinuation (Figure 1).



[1] W-6.5 - Screening period is 45 days (~ 6.5 weeks) prior to randomization.
W = Week so, W1 = Week 1, etc..
[2] D1 = Day 1.
[3] Virologic failure or relapse is confirmed with 2 consecutive measurements of HIV-1 –RNA at least one week apart.

Figure 1: PN292 Trial Design (exacted from page 12 of the PN292-00 protocol)

The key trial eligibility criteria included:

Inclusion criteria:

- Male/female adults at least 18 years of age at time of screening
- Screening HIV-1 RNA ≥1000 c/mL within 60 days prior to treatment phase
- Antiretroviral treatment-naïve
- Screening creatinine ≤2 x upper limit of normal (ULN); alkaline phosphatase ≤3 x ULN; AST and ALT ≤5 x ULN

Exclusion criteria:

- History of condition, therapy or abnormalities felt to interfere with current therapy
- Use of illicit drugs and or alcohol abuse history
- Treatment for another viral infection such as HBV at time of screening (previous treatment for HBV is acceptable)
- Active diagnosis of acute hepatitis
- Breastfeeding, pregnant or planning to conceive during study period

Overall, the trial inclusion/exclusion criteria for this study were reasonable and commensurate with other confirmatory trials for treating HIV-1 infection in treatment-naïve subjects.

Subjects were randomized to one of the following treatment regimens in a 2:1 (QD:BID) fashion:

- Group 1: Reformulated raltegravir 1200 mg (2 x 600 mg) oral (PO) QD + TRUVADA QD
- Group 2: Raltegravir 400 mg PO BID + TRUVADA QD

Randomization was performed via an interactive voice response system (IVRS)/integrated web response and stratified according to the following two factors leading to four possible randomization strata:

- Screening HIV-1 RNA (≤100,000 or >100,000 copies/mL)
- Chronic HBV and/or HCV infection defined as serologic evidence of cHBV surface antigen and/or evidence of HCV RNA by PCR.

3.2.1.1 Dosing and Blinding Approach

To maintain a double-blind, double-dummy design following randomization, each subject was issued two bottles, A and B, and instructed to take tablets as follows:

- Bottle A (reformulated raltegravir or matching placebo): Take two tablets at the same time once a day (QD)
- Bottle B (raltegravir or matching placebo): Take one tablet twice a day (BID)

For each subject (depending on randomization assignment), either Bottle A or Bottle B contained active raltegravir; the other bottle contained placebo. In addition, subjects were provided with a third bottle, Bottle C, containing open-label TRUVADA for which subjects were instructed to take one tablet daily.

3.2.1.2 Efficacy Endpoints

The primary efficacy endpoint was the proportion of subjects achieving an HIV-1 RNA < 40 copies/mL at Week 48 (W48) measured using the Abbott RealTime® HIV-1 assay (virologic success). This primary efficacy endpoint is commensurate with current FDA guidelines on developing therapies to treat HIV infection.

Secondary Efficacy Endpoints included the following:
- Proportion achieving HIV-1 RNA <50 copies/mL at W48
- Proportion achieving HIV-1 RNA<200 copies/mL at W48
- Change from baseline in CD4 cell count at W48
- Time to virologic response (TVR) for subjects achieving an HIV-1 RNA <40 c/mL at W48
- Time to loss of virologic response (TLOVR) among subjects achieving virologic response

3.2.2 Statistical Methodologies

Trial Hypothesis

The primary trial null hypothesis was that the proportion of subjects achieving virologic success in the raltegravir 1200 mg QD arm is inferior to raltegravir 400 mg BID, each in combination with TRUVADA. Inferiority is based on achieving a lower bound around the difference (QD-BID) at or below -10 percentage points.

Alternatively, non-inferiority was concluded if the lower bound of the 95% confidence interval calculated using the stratum-adjusted Mantel Haenszel method around the difference (QD-BID) is above -10 percentage points.

Sample Size Determination

Given the following assumptions, the trial with a targeted sample size of 750 subjects randomized in a double-blind 2:1 ratio of QD versus BID raltegravir had at least 90% power to achieve the primary non-inferiority objective given:

- 10% non-inferiority margin
- 1-sided Type-I error of 0.025
- Assumed true response rate of 85% at Week48 for raltegravir 400 mg BID arm
- ≤1% lower response rate in the raltegravir 1200 mg QD arm

Reviewer's Comments:

1) ***The 10% NI margin is in accordance with current regulatory views on an acceptable margin required to demonstrate non-inferiority of new regimen for treating HIV infection in a TN population. This margin is considered the clinical margin or M2 as M1, the effect size of the active comparator, is quite large, e.g. at least 80%. This is based on the premise that TRUVADA (a two-NRTI regimen) alone would confer little, to no virologic suppression at W48. The addition of a third agent, raltegravir to TRUVADA leads to a high suppression rate and the amount of loss of virologic suppression that has been viewed acceptable for regulatory purposes is around 10% for treatment-naïve populations.***
2) ***In trial PN021, which was a confirmatory randomized, double-blind, active-controlled trial that supported the efficacy of raltegravir 400 mg BID dosing, the W48 proportion of subjects achieving a HIV-1 RNA < 50 copies/ml (40 copies/mL was not an endpoint in this trial) was 86% (241/280). It is therefore reasonable to estimate that the W48 proportion <40 c/mL is 85% given findings from the prior trial of a lower-overall daily dose of raltegravir.***

Primary Analysis

The Full Analysis Set (FAS), comprising all randomized subjects who received at least one dose of study treatment and had baseline data for the analyses requiring baseline data (i.e. this include HIV-1 RNA and co-infection with HCV/HBV for the primary analysis), served as the primary set for analyses of efficacy. A secondary analysis set, observed=failure (OF) served as secondary.

The proportion of subjects achieving virologic success, defined as a HIV RNA < 40 copies/mL at Week 48 (W48), was compared between treatment groups using a stratum-adjusted Mantel-Haenszel (MH) method with the difference weighted by the harmonic mean of sample size per

arm per stratum (Appendix 1). Randomization was stratified by screening HIV RNA ≤100,000 copies/mL versus HIV RNA >100,000 copies/mL. All missing primary endpoint assessments, regardless of cause, were treated as virologic failures in the FAS.

The following table extracted from the protocol specifies the time windows and target days for each planned analysis. Day 337 (window: 295 to 378) served as the target day for the W48 analysis. When more than one measurement was obtained during the window, the closest measurement to the target day was chosen.

Table 2: Trial Time Points

Treatment Phase	Treatment Period	Protocol Time	Day-Range Rules	Target Day†	CSR Time‡	Visit Number
Pre-treatment	Baseline	Day 1 (Baseline)	≤1	1	Day 1	2
Treatment	Double-Blind	Week 4	>1 and ≤42	29	Week 4	5
		Week 8	≥43 and ≤84	57	Week 8	6
		Week 16	≥85 and ≤140	113	Week 16	7
		Week 24	≥141and ≤210	169	Week 24	8
		Week 36	≥211 and ≤294	253	Week 36	9
		Week 48	≥295 and ≤ 378	337	Week 48	10
		Week 60	≥379 and ≤ 462	421	Week 60	11
		Week 72	≥463 and ≤ 546	505	Week 72	12
		Week 84	≥547 and ≤ 630	589	Week 84	13
		Week 96	≥631 and ≤ 714	673	Week 96	14

† Relative days and target day are counted from the first day of study medication.
‡ The clinical study report (CSR) time is the time label to be used in the analysis tables.

Source: Page 58 of the 292-00 protocol

Handling of Missing Values

The types of missing data included:

- intermittent missing due to missed or skipped visit or due to inadequate sample
- monotone missing values due to premature discontinuations for treatment-related reasons
- monotone missing values due to premature discontinuations due to other reasons unrelated to treatment effect

The approach to handling missing in the primary analysis was to treat missing as failure (non-complete=failure (NC=F)) as defined via the FDA's Snapshot approach. A secondary approach, defined as the Observed Failure (OF) whereby monotone missing for subjects who prematurely discontinued due to lack of efficacy, were treated as failures and other missing were excluded in this analysis.

Reviewer's Comment: The reviewer considers the OF a secondary population, which likely suffers from bias given the exclusion of missing values due to reasons unrelated to treatment.

Secondary and Sensitivity Analyses

Secondary analysis included comparing the time to virologic response and time to loss of virologic response between groups using standard Kaplan-Meier methods with comparisons between groups by means of log rank tests.

A sensitivity analysis using only observed failure data where monotone missing data for subjects who prematurely discontinued treatment due to lack of efficacy were counted as failures was also performed on the W48 endpoint.

Interim analysis

An interim analysis (IA) was planned when approximately 375 of randomized subjects completed the Week 24 visit or prematurely discontinued before the Week 24 visit. This analysis was performed merely for purposes of futility and hence there was no adjustments made to the overall type-I error. This analysis was set up such that if the conditional power for demonstrating NI at Week 48 was less than 20%, then the trial was to be halted. Alongside, the type-I error of prematurely stopping the trial for futility was 8.9%, i.e. a 9% chance of stopping the trial by incorrectly concluding inferiority.

The external Data Monitoring Committee (eDMC) meeting for the planned IA occurred on 6/30/15 and the recommendations were to continue the trial, as planned. The data generated for this analysis were provided by the sponsor's external unblinded statistical vendor who provided a blinded (pooled) report to the sponsor and the eDMC along with a closed report (unblinded data) to only the eDMC.

There were three additional eDMC meetings for purposes of periodic safety monitoring. These meetings occurred on 3/11/14, 3/13/15, and 11/18/15. The sponsor provided copies of the open reports and the open session meeting minutes to the NDA (SDN 329). These reports appear to be satisfactory coincident with the eDMC charter and do not reveal details about treatment assignment. The closed reports were not included in the submission to the FDA.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Out of 913 screened subjects, 802 subjects were randomized of which 531 and 266 received at least one dose of study drug in the QD and BID raltegravir groups, respectively. The first and last subjects were randomized on 6/25/14 and 1/16/15, respectively. Approximately 71% of all FAS subjects were enrolled with a screening HIV-1 RNA ≤100,000 copies/mL and only 5% and 4% of subjects were HBV- or HCV- positive at screening in the QD and BID groups, respectively. The majority (72%) of subjects had a HIV-1 RNA ≤100,000 c/mL AND where HCV/HBV negative at screening (Table 3).

Table 3: Randomization Stratification Distribution

	Reformulated Raltegravir 1200 mg QD + TRUVADA		**Raltegravir 400 mg BID + TRUVADA**	
	n	%	n	%
Randomized	533	100	269	100
Full Analysis Set (FAS)	531	99.62	266	98.88
Randomization Strata in FAS				
Screening HIV RNA ≤100,000 c/mL	382	71.94	190	71.4
Screening HIV RNA >100,000 c/mL	149	28.06	76	28.57
Negative HBV and negative HCV	503	94.73	255	95.86
Positive HBV or HCV	28	5.27	11	4.13
HIV-RNA >100,000 c/mL w/ HBV/HCV	6	1.13	3	1.13
HIV-1 RNA > 100,000 c/mL w/o HBV/HCV	143	26.93	73	27.44
HIV-RNA ≤100,000 c/mL w/ HBV/HCV	22	4.14	8	3.01
HIV-1 RNA ≤ 100,000 c/mL w/o HBV/HCV	360	67.8	182	68.42

When the database was locked for purposes of the W48 primary analysis over 90% of FAS subjects were still participating in the trial with no apparent differences between groups in causes for premature discontinuation (Table 4).

Table 4: Subject Disposition the FAS (Week 48)

	Reformulated Raltegravir 1200 mg QD + TRUVADA (N=531)		Raltegravir 400 mg BID + TRUVADA (N=266)	
	n	%	n	%
Ongoing in Trial	490	92.28	242	90.98
Prematurely Discontinued from Trial	41	7.72	24	9.02
Adverse event	6	1.13	6	2.26
Death	0	0.00	1	0.38
Lack of efficacy	4	0.75	1	0.38
Lost to follow-up	8	1.51	4	1.50
Non-compliance	5	0.94	4	1.50
Physician's Decision	4	0.75	0	0.00
Pregnancy	2	0.38	0	0.00
Subject Withdrawal	12	2.26	8	3.01

The majority of randomized and treated (FAS) subjects were male (85%), on average were 36 years old and were of White race (59%) and were non-Hispanic/Latino (73%). The mean baseline CD4 cell count was 414 cells/mm^3 and 72% of subjects had an HIV-1 RNA ≤100,000 c/mL. There were no differences between treatment groups with the exception of proportion of subjects with Clade B HIV subtype, which was higher in the BID regimen (71%) versus the QD regimen (63%).

Subjects were enrolled across 130 sites in 23 different countries. Almost 40% of all trial subjects were enrolled in clinical sites across Europe, followed by 24% in North America. The majority of subjects in North America were enrolled in the United States (89%). There were 173 subjects enrolled in sites located in the United States (21.7% of all countries) of which all but 15 (8.7%) were males.

Reviewer's Comment: Per the CDC, based on 2013 data, 23% of all Americans living with HIV were female[1]. Worldwide, 51% of all adults living with HIV are female[2]. As stated, the

[1] https://www.cdc.gov/hiv/group/gender/women/index html
[2] http://www.unwomen.org/en/what-we-do/hiv-and-aids/facts-and-figures

trial included a large proportion of subjects enrolled outside of the US. Therefore the overall proportion of enrolled females (15%) is considerably low calling into question how accurately trial results may predict outcomes once extrapolated to the intended population.

Table 5: Baseline Subject Demographics and Characteristics (FAS)

Full Analysis Set	**Reformulated Raltegravir 1200 mg QD + TRUVADA (n=531)**		**Raltegravir 400 mg BID + TRUVADA (n=266)**		**Total (n=797)**	
Baseline Characteristic	n	%	n	%	n	%
Male	440	82.86	234	87.97	674	84.6
Female	91	17.14	32	12.03	123	15.4
Age						
Mean (SD) Age	35.38 (10.29)		36.85 (10.97)		35.87 (10.53)	
Age 18-64	527	99.25	263	98.87	790	99.12
Age ≥65	4	0.75	3	1.13	7	0.88
Race						
White	301	56.69	174	64.68	473	59.35
Black	98	18.46	36	13.53	134	16.81
Asian	83	15.63	40	15.04	123	15.43
Multiple	46	8.66	14	5.26	60	7.53
American Indian/Alaska Native	3	0.56	3	1.13	6	0.75
Native Hawaiian or Other Islander	0	0	1	0.38	1	0.12
Ethnicity						
Not Hispanic or Latino	380	71.56	205	77.07	585	73.40
Hispanic or Latino	126	23.73	52	19.55	178	22.33
Not Reported	19	3.58	8	3.01	27	3.29
Unknown	6	1.13	1	0.38	7	0.88
CD4 cell count/mm^3						
Mean CD4 (SD)	407 (213)		429 (217)		414 (215)	
Median CD4	380		415.5		390	
CD4 ≤50	9	1.69	6	2.256	15	1.88

CD4 >50 and ≤200	60	11.3	31	11.65	91	11.42
CD4 >200	462	87.01	229	86.09	691	86.70
HIV-1 RNA copies/mL						
Mean (SD)	132757 (316174)		120976 (218852)		128825 (287292)	
log_{10} c/mL	4.61 (0.69)		4.61 (0.68)		4.61 (0.69)	
HIV RNA ≤100,000	382	71.94	189	71.05	571	71.65
HIV RNA >100,000	149	28.06	77	28.95	226	28.35
HIV RNA ≤500,000	506	95.29	251	94.36	757	94.98
HIV RNA >500,000	25	4.71	15	5.64	40	5.02
Clade						
B	335	63.33	186	70.72	521	65.78
Non-B	194	36.67	77	29.28	271	34.22
Co-Infection/AIDS						
HBV Positive	11	2.07	4	1.50	15	1.88
HCV Positive	4	0.75	5	1.88	9	1.13
HBV or HCV Positive*	15	2.8	8	3.0	23	2.89
Reported Hx of AIDS	79	14.88	28	10.53	107	13.42
Region						
Europe	200	37.66	112	42.10	312	39.15
North America	125	23.54	69	25.94	194	24.34
Asia/Pacific	86	16.19	46	17.29	132	16.56
Latin America	77	14.50	26	9.77	103	12.92
Africa	43	8.10	13	4.89	6	7.03

*One subject positive for HCV and HBV infection; % are column percentages

3.2.4 Results and Conclusions

Primary Endpoint: HIV RNA < 40 c/mL at W48 in FAS (Snapshot Method)
Due to small numbers of enrolled HBV and/or HCV co-infected subjects (39 in total), the primary analysis was only stratified by screening HIV-1 RNA (≤100,000 or >100,000 copies/mL). At W48, the proportions achieving an HIV RNA < 40 c/mL was 88.9% and 88.3% in the QD and BID groups, respectively, leading to a difference of 0.5% (QD-BID), and stratum adjusted 95% CI of -4.2% to 5.2%. The proportions of subjects failing to achieve the target HIV RNA level was 5.5% and 6% in the QD and BID groups, respectively. The remainder of subjects failed to achieve the primary endpoint due to missing values at the W48 assessment for the reasons listed below (Table 6).

The lower bound of the 95% CI is within the -10% NI bound and therefore demonstrative of NI of the QD regimen to the approved-BID regimen. Considering a more conservative confidence interval of 97.5%, the lower bound becomes -4.9%, again easily falling within the -10% NI margin. In addition, the achieved rate of virologic suppression in the active-control regimen is consistent with expectations (i.e. 85%) based on prior clinical trials of the BID regimen. This suggests that constancy of the treatment effect was maintained in this trial compared to the prior trial.

Table 6: Primary Analysis of W48 HIV-1 RNA

Based on FDA Snapshot analysis approach	**Reformulated Raltegravir 1200 mg QD + TRUVADA (n=531)**		**Raltegravir 400 mg BID + TRUVADA (n=266)**		**Diff (QD-BID)* 95% CI**
	n	%	n	%	
HIV-1 RNA <40 c/mL at W48	**472**	**88.9**	235	88.3	**0.51 (-4.22, 5.20)**
HIV-1 RNA ≥40 c/mL at W48	29	5.5	16	6.0	
No HIV-1 RNA measured at W48	30	5.6	15	5.6	
Discontinued prior to W48 due to AE/death	6	1.1	6	2.3	
On trial but missing W48 assessment	4	0.7	2	0.8	
Discontinued prior to W48 due other reasons#	20	3.8	7	2.6	

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

The results of the secondary analyses comparing proportions of subjects achieving HIV RNA < 50 c/mL, < 200 c/mL when imputing missing as failures (NC=F) are provided below. Overall, the differences between treatment groups are less than 1% regardless of endpoint. Similarly, when evaluating the primary and secondary endpoints using an observed=failure only approach, the differences between group is maintained at less than 1% and all lower bounds of 95% CIs around differences fall well within the pre-specified -10% margin of non-inferiority (unadjusted for multiple endpoints). Therefore, regardless of endpoint chosen, the virologic success of the QD regimen was in line with that of the standard, BID regimen when using a 10% non-inferiority criterion.

Reviewer's Comment: The proportion of subjects missing the W48 visit was equal (5.6%) and small. These subjects are omitted from the secondary analysis of the OF population.

Mean changes from baseline CD4 with or without imputation for missing were also similar between groups yielding differences (QD-BID) between -3 and -2 cells/mm^3 and corresponding confidence intervals including zero suggestive of no statistically significant or clinically relevant differences between regimens.

Table 7: Secondary Efficacy Endpoints

Week 48 Assessment	**Reformulated Raltegravir 1200 mg QD + TRUVADA**		**Raltegravir 400 mg BID + TRUVADA**		**Diff (QD-BID)* 95% CI**
	n/N	*%*	n/N	*%*	
HIV-1 RNA <**50** c/mL (NC=F)	477/531	*89.9*	240/266	*90.2*	-0.41 (-4.9, 4.0)
HIV-1 RNA <**200** c/mL (NC=F)	484/531	*91.1*	243/266	*91.3*	-0.21 (-4.4, 4.0)
HIV-1 RNA <**40** c/mL (OF)	472/501	*94.2*	235/251	*93.6*	0.55 (-3.1, 4.2)
HIV-1 RNA <**50** c/mL (OF)	477/501	*95.2*	240/251	*95.6*	-0.43 (-3.6, 2.8)
HIV-1 RNA <**200** c/mL (OF)	484/501	*96.6*	243/251	*96.8*	-0.22 (-3.0, 2.6)
	Mean (95% CI)		Mean (95% CI)		Diff (QD-BID) 95% CI
Change from Baseline in CD4 cells/mm^3 (NC=F)	218.0 (201.6, 234.3)		220.8 (197.8, 243, 9)		-2.87 (-31.1, 25.4)
Change from Baseline in CD4 cells/mm^3 (OF) (n=499 QD; n=251 QD)	232.0 (214.5, 249.4)		234.0 (212.8, 255.3)		-2.09 (-29.5, 25.3)

*stratum-adjusted MH difference in proportion with harmonic mean of sample size per group for each stratum (screening HIV-1 RNA ≤100000 c/mL or HIV-RNA >100000 c/mL), 95% CI around difference in change from baseline based on the t-distribution; OF=observed failures, NC=Not collected imputed as a failure

The proportion of subjects with an HIV-1 RNA < 40 copies/mL by trial week is shown in the figure below suggesting that for those subjects who achieved virologic suppression, i.e. 88-89%, the majority achieved it by Week 24 and this was maintained through Week 48. Again, this trial assessed outcomes out to Week 98 and these results will be submitted once available.

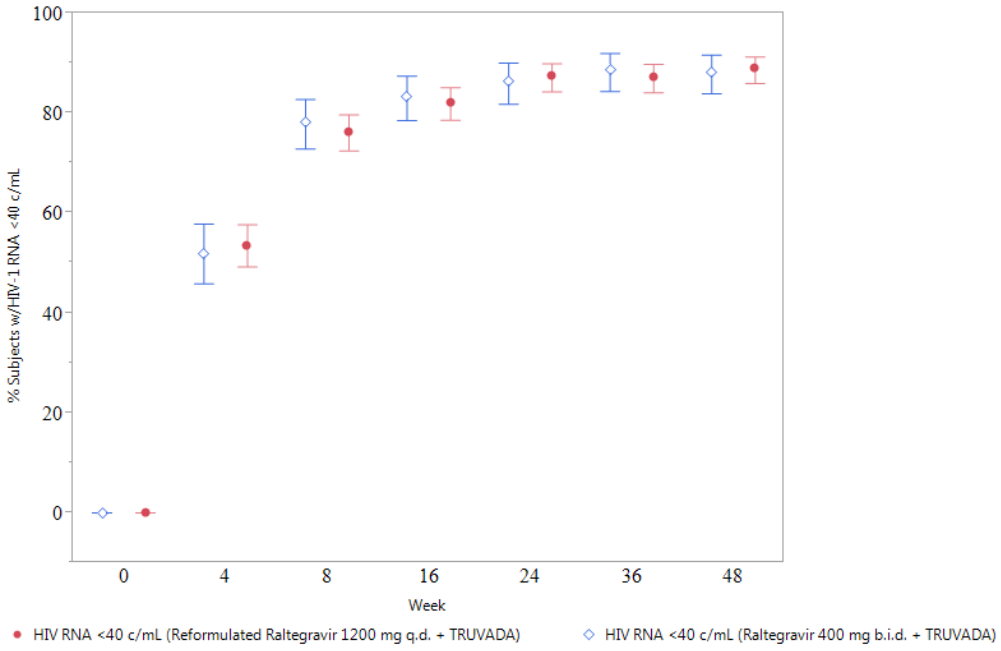


Figure 2: HIV-1 RNA < 40 c/mL by Visit by Treatment

Analysis of Treatment Compliance

Treatment compliance was self-reported by the subject by means of an electronic study medication diary (eDiary). Average days of treatment duration were similar between groups and were approximately 390 days (Table 8). The applicant contends that a once-daily treatment option of raltegravir will provide a more-convenient dosing option over the currently-approved, twice-daily regimen. However, due to the double-blind, double-dummy design in which all subjects received the same number of tablets, this trial is unable to compare or assess overall treatment compliance as it relates to a QD versus a BID regimen. Therefore, data from this trial does not allow us to conclude increased compliance with a once-a-day regimen versus a twice-a-day regimen.

Table 8: Treatment Compliance

Days of Study Treatment*	**Reformulated Raltegravir 1200 mg QD + TRUVADA (N=531)**	**Raltegravir 400 mg BID + TRUVADA (N=266)**
Mean (SD)	391.5 (89.3)	390.4 (91.8)
Median (range)	405 (9-515)	405 (7-518)

*based on data at time of database lock for purposes of the W48 analyses

Analysis by baseline HIV-1 RNA

Screening HIV-1 RNA was used in the randomization stratfication factor where this value could have been obtained within 45 days of randomization. The reviewer assessed the concordance between screening and baseline HIV-1 RNA and found discordance in approximately 13% and 11% of subjects in the QD and BID groups, respectively (Table 9).

Table 9: Concordance between Screening and Baseline HIV-1 RNA Categorization

	Reformulated Raltegravir 1200 mg QD + TRUVADA (n=531)		**Raltegravir 400 mg BID + TRUVADA (n=266)**	
	BL VL≤100K	BL VL >100K	BL VL≤100K	BL VL >100K
Screening VL ≤100K	346 (90.6)	36 (9.4)	175 (92.1)	15 (7.9)
Screening VL >100K	36 (24.2)	113 (75.8)	14 (18.4)	62 (81.6)

Given the discordance between screening and baseline HIV RNA category, the reviewer performed a sensitivity analysis of the primary endpoint of Week 48 HIV-1 RNA < 40 c/mL to calculate the stratum-adjusted MH difference in proportion with harmonic mean of sample size per group for each stratum based on baseline HIV-1 RNA category instead of screening HIV-1 RNA. In this analysis, the adjusted difference between groups in subjects achieving an HIV-1 RNA < 40 c/mL (NC=F) was 4.6%, adjusted 95% CI, (-4.23, 5.16).

An additional sensitivity analysis included only subjects with concordance between screening and baseline HIV-1 RNA. This is a subset of the overall randomized set and includes 459 QD and 237 BID subjects of which 89.5% and 88.2% achieved an HIV-1 RNA < 40 c/mL at Week 48 leading to an adjusted difference of 1.2% and a 95% CI of -3.7 to 6.2. Hence, overall these discordant values do not seem to impact the overall conclusions.

3.3 Evaluation of Safety

There were two (0.4%) and 1 (0.4%) deaths in the QD and BID groups, respectively by Week 48. One patient (AN 101970) was a 44 year old Black female in the QD group enrolled with comorbid conditions including AIDS and a history of pulmonary TB. The reported cause of death for this subject was miliary TB. A second patient (AN 100269) was a 31 year old multi-racial male enrolled in the QD group had concurrent hypertension, bilateral lumbar pain, hyperuricemia and a history of anal condylom and appendicitis. Study medication was stopped on day 36, and the patient expired on day 70 with the cause of death reported as lymphatic system neoplasm. The third patient (AN 100156) who was in the BID group was a 20 y.o. white male with a history of AIDS and cryptococcal meningitis. The subjects stopped treatment on Day 32 and expired on Day 50 most likely due to multiple opportunistic infections due to an AIDS diagnosis. ***Refer to the clinical review by Dr. Sarita Boyd for a more-detailed assessment of these patient deaths and any other safety-related assessments.***

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

Virologic success was numerically greater in the QD regimen compared to the BID regimen among males; however, the opposite trend was observed among female subjects. A test for interaction between treatment and gender was not significant; however, due to the small sample size of female subjects this test is likely underpowered to detect an interaction. Given the relatively few females enrolled (15%) in PN292, the confidence interval around the treatment difference was notably wide ranging from -15% to 11%.

No evidence for an interaction between median age of 35 years or race and treatment was found. However, virologic success was numerically lower in both treatment groups among Black subjects compared to other racial groups (Table 10).

Table 10: Virologic Success (NC=F) by Gender, Race and Age

	Reformulated Raltegravir 1200 mg QD + TRUVADA (n=531)		Raltegravir 400 mg BID + TRUVADA (n=266)		Diff (95% CI)
	n		n		
Males	440	393 (89.3)	234	206 (88.0)	1.3 (-3.7, 6.5)
Females	91	79 (86.8)	32	29 (90.6)	-3.8 (-15.1, 10.7)
Baseline Age (median of 35 years)					
BL Age < 35	251	230 (91.6)	139	127 (91.4)	0.3 (-5.4, 6.4)
BL Age ≥ 35	280	242 (86.4)	127	108 (85.0)	1.4 (-5.7, 9.1)
Race					
Asian	83	76 (91.6)	40	36 (90.0)	1.6 (-9.1, 14.1)
Black/AA	98	83 (84.7)	36	29 (80.6)	4.1 (-9.8, 19.9)
Other	49	43 (87.8)	18	17 (94.4)	-6.7 (-19.9, 12.5)
White/Caucasian	301	270 (89.7)	172	153 (89.0)	0.7 (-4.9, 6.8)

4.2 Other Baseline Characteristics

Virologic success was lower in both treatment groups in the subset of subjects enrolled in North American sites compared to subjects enrolled in other regions suggesting some regional differences (Table 11). Virologic failure (HIV RNA ≥40 c/mL at W48) was 11/125 (8.8%) and 7/69 (10.1%) in the QD and BID regimens, respectively among subjects enrolled in North American sites. In comparison, virologic failure was 7/200 (3.5%) and 6/112 (5.4%) in the QD and BID subjects enrolled in European sites, which comprised the largest region for subject enrollment. Exploratory analysis of HIV subtype, baseline RNA viral load, gender, and race did not reveal any factors strongly contributing to this lower observed efficacy among subjects in both treatment groups enrolled in sites in North America.

There was no evidence of a treatment interaction according to baseline HIV-1 RNA level (≤100,000 c/mL, >100,000 c/mL) though virologic suppression was lower in both groups in the subset of subjects entering the trial with a higher viral load as expected. Similarly, no interaction was observed when considering HIV subtype (clade B versus non-clade B) or baseline CD4 cell

count. These analyses are illustrated in forest plots (QD-BID with 95% CIs (unadjusted)) in Figure 3, Figure 4, and Figure 5 imputing missing as failures.

Table 11: Week 48 HIV-RNA <40 c/mL by Subgroup (NC=F)

	Reformulated Raltegravir 1200 mg QD + TRUVADA (n=531)		Raltegravir 400 mg BID + TRUVADA (n=266)		Diff (95% CI)
	n		n		
Geographic Region					
Africa	43	39 (90.7)	13	12 (92.3)	-1.6 (-17.2, 21.7)
Virologic Failure		*2/43 (4.6)*		*0/13*	
Asia	86	79 (91.9)	46	40 (87)	4.9 (-6.1, 17.1)
Virologic Failure		*5/86 (5.8)*		*3/46 (6.5)*	
Europe	200	183 (91.5)	112	102 (91.1)	0.4 (-6.0, 7.4)
Virologic Failure		*7/200 (3.5)*		*6/112 (5.4)*	
North America	125	102 (81.6)	69	55 (79.7)	1.9 (-9.4, 13.9)
Virologic Failure		*11/125 (8.8)*		*7/69 (10.1)*	
Latin America	77	69 (89.6)	26	26 (100)	-10.4 (-17.6, 2.0)
Virologic Failure		*4/77(5.2)*		*0/26*	
Baseline CD4 Cells/mm3					
≤50	9	6 (66.7)	6	4 (66.7)	0 (-42.8, 45.1)
>50 and ≤200	60	51 (85)	31	25 (80.6)	4.3 (-11.6, 21.8)
>200	462	415 (89.8)	229	206 (90)	-0.1 (-4.8, 4.8)
Baseline HIV-1 RNA					
≤ 100,000 c/mL	382	348 (91.1)	189	173 (91.5)	-0.4 (-5.2, 4.7)
>100,000 c/mL	149	124 (83.2)	77	62 (80.5)	2.7 (-7.7, 13.7)
≤ 4 $\log_{10}$	91	79 (86.8)	47	44 (93.6)	-6.8 (-16.2, 4.6)
≤ 5 $\log_{10}$	291	269 (92.4)	142	129 (90.8)	1.6 (-3.9, 7.6)
≤ 6 $\log_{10}$	134	116 (86.6)	73	60 (82.2)	4.4 (-5.9, 15.3)

≤ 7 $\log_{10}$	15	8 (53.3)	4	2 (50)	3.3 (-43.6, 49.4)
Clade					
Clade B	335	296 (88.4)	186	164 (88.2)	0.2 (-5.4, 6.2)
Non-Clade B	194	175 (90.2)	77	69 (89.6)	0.6 (-7.0, 9.4)
Missing	2	1 (50.0)	3	2 (66.7)	-16.7 (-75.1, 55.1)

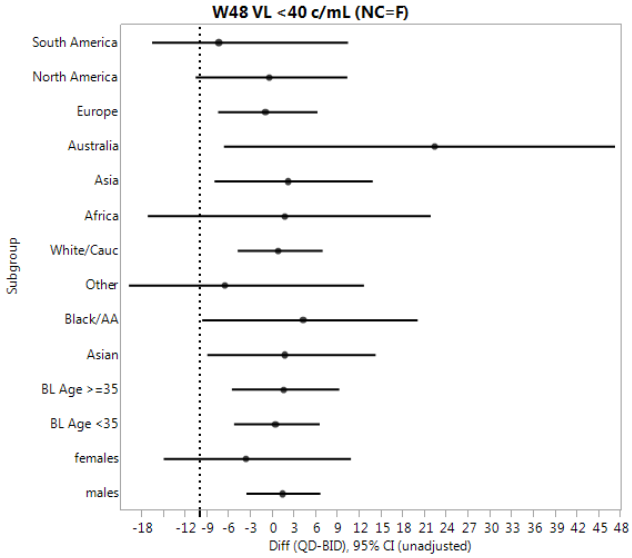


Figure 3: Difference (QD-BID) in W48 HIV-1 RNA < 40 c/mL by Baseline Characteristic (NC=F)

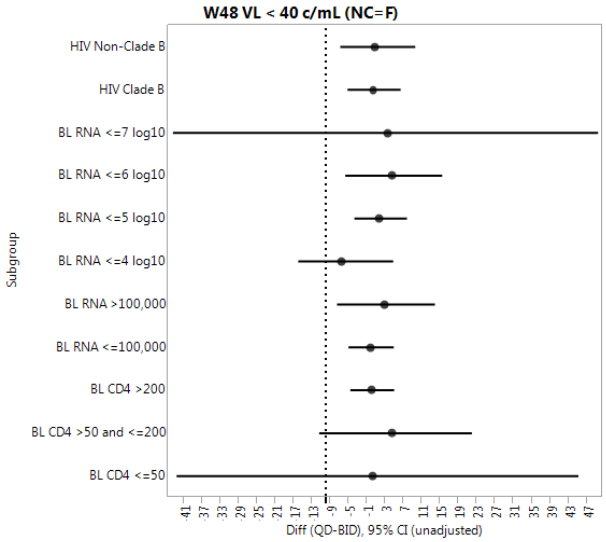


Figure 4: Difference (QD-BID) in W48 HIV-1 RNA < 40 c/mL by Baseline Characteristic (NC=F)

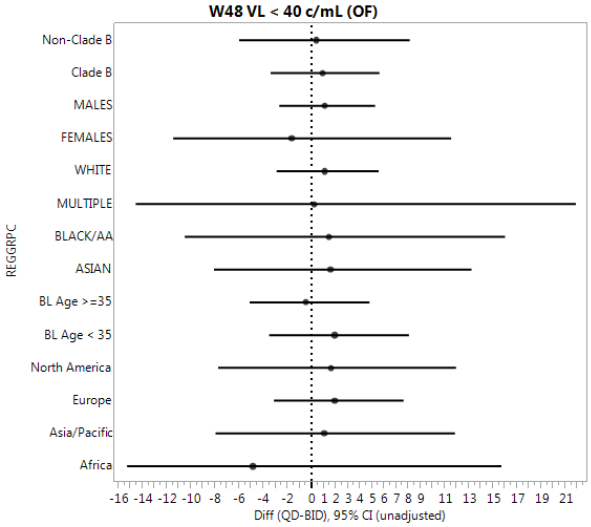


Figure 5: Difference (QD-BID) in W48 HIV-1 RNA < 40 c/mL by Baseline Characteristic (OF)

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

Given that trial PN292 did not enroll virologically suppressed HIV-1 infected adults, data from this trial do not provide evidence to support the applicant's proposed dosing and administration of raltegravir 1200 mg QD (2 x 600 mg tablets) in virologically-suppressed HIV-1infected adults already receiving 400 mg BID raltegravir.

The trial enrollment largely favored men (85% of all randomized) thereby greatly limiting the ability to generalize findings to women who globally comprise 51% of all living adults infected with HIV.

Virologic success was lower in both treatment groups in the subset of subjects enrolled in North American sites compared to subjects enrolled in other regions suggesting some regional differences. Virologic failure was 11/125 (8.8%) and 7/69 (10.1%) in the QD and BID regimens, respectively among subjects enrolled in North American sites. In comparison, virologic failure was 7/200 (3.5%) and 6/112 (5.4%) in the QD and BID subjects enrolled in European sites, which comprised the largest region for subject enrollment.

Due to the double-blind, double-dummy design in which all subjects in both groups received the same number of tablets, this trial is unable to compare or assess overall treatment compliance as

it relates to a QD versus a BID regimen. Therefore, findings from this trial cannot be used to draw conclusions that the QD regimen will confer greater compliance than the existing BID regimen.

The non-inferiority margin is commensurate with the current FDA guidance to industry on developing antiretroviral drugs for treatment of HIV infection[3]. Specifically, the guidance states that the NI margin for comparing a potent anchor drug or third drug in regimens for HIV treatment-naïve patients is 10-12%. While PN292 was designed around a -10% NI margin, the trial was essentially comparing two formulations of the same drug, raltegravir, given with TRUVADA and therefore a more conservative margin could have been considered. That said, the trial results suggest that the reformulated QD regimen is no worse than the currently-approved BID regimen within 5%, which is half the pre-specified 10% margin.

5.2 Collective Evidence

The collective evidence supporting this sNDA for a reformulated regimen of raltegravir for 1200 mg QD comes from a single, large, well-designed, randomized, double-blind, non-inferiority confirmatory trial, PN292. The trial primary objective was to demonstrate non-inferiority of a reformulated regimen of raltegravir with a once-daily dosing of 1200 mg (2 x 600 mg tablets) to an already-approved 400 mg BID raltegravir regimen. The primary endpoint for determination of non-inferiority was virologic suppression (defined as an HIV RNA less than 40 copies/mL) measured at treatment Week 48. The trial enrolled and treated 797 HIV-1 treatment-naïve, adult subjects, in a 2:1 ratio to the QD and BID regimens, respectively. By Week 48, over 90% of the ITT population was still participating in the trial with few subjects lost to follow-up (1.5%) and only one subject death. Demographically, the trial sample comprised mostly male adults (85%), White race (59%), infected with Clade B HIV (66%), and not co-infected with HBV or HCV (95%). The proportion of subjects in the full analysis set who achieved virologic suppression at Week 48, treating all non-completers as failures, was 88.9% (472/531) and 88.3% (235/266) in the QD and BID groups, respectively yielding a risk difference (QD-BID) of 0.51% and corresponding 95% CI of -4.20% to 5.22%. Results of a secondary analysis imputing only missing due to lack of efficacy as failures were consistent with the primary results. Changes from baseline in CD4 were 218 and 221 cells/mm^3 in the QD and BID groups, respectively yielding a difference of -2.9 cells/mm^3, 95% CI (-31.1 25.4) between groups, which is neither clinically nor statistically relevant. Subgroup analyses by gender revealed a difference between groups in Week 48 virologic suppression favoring the QD regimen among males with the reverse pattern seen among the smaller subset of females albeit not significant for interaction.

5.3 Conclusions and Recommendations

In the PN292 trial, the proportion of subjects in the full analysis set who achieved virologic suppression at Week 48 was 88.9% (472/531) and 88.3% (235/266) in the QD and BID groups,

[3] https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm355128.pdf

respectively yielding a risk difference (QD-BID) of 0.51% and corresponding 95% CI of -4.20% to 5.22%. Since the 95% lower confidence bound around the difference in incidences of virologic suppression falls within the pre-specified -10% non-inferiority margin, and the point estimates are commensurate with the expected proportion of virologic suppression, PN292 provides evidence that the 1200 mg QD regimen is non-inferior to the 400 mg BID regimen for treating HIV-1 infection in TN, adult patients. This conclusion of efficacy is further supported by assessing a myriad of secondary endpoints including different virologic cut-points and approaches to handling missing data.

Given that raltegravir 400 mg BID is an already-approved regimen for treating HIV-1 infection in TN and VS adults and pediatrics, evidence from a single trial is adequate to support the efficacy and safety of the reformulated regimen for use in the as-studied (in trial PN292), TN adult population. However, the PN292 trial neither enrolled virologically-suppressed (at baseline) subjects nor pediatric or adolescent subjects. Therefore, there are no clinical efficacy data to allow for a statistical evaluation in these subgroups of HIV-1 infected patients. Finally, 85% of randomized and treated subjects were male greatly limiting the ability to extrapolate and generalize these findings to a larger population of HIV-1 infected TN female adults.

5.4 Labeling Recommendations

With this supplement, the sponsor proposes the new dosing and administration as follows (sections 2.2 and 2.3 of the label). To streamline the information provided in Section 14, the reviewer (in concordance with the clinical reviewer) recommends summarizing the information contained in proposed Table 14 into a paragraph. The information provided in proposed Table 15 has been verifed by the reviewer and should be included in the revised label along with proposed Figure 1; however, with modification (see below in track changes). As already noted, the reformulated raltegravir 1200 mg QD regimen was not evaluted in pediatric patients therefore there is nothing included in Section 14 for this population for the QD regimen. Refer to the clinical pharmacology and clinical reviews regarding the specifics pertaining to pharmacokinetic and safety assessments for the proposed pediatric regimen.

2.2 Adults

For the treatment of adult patients with HIV-1 infection, the dosage of ISENTRESS is as follows:

Dosing Recommendations for ISENTRESS in Adults with HIV 1 infection	
Population	**Recommended Dose**
Treatment-naïve patients or patients who are virologically suppressed on an initial regimen of ISENTRESS 400 mg twice daily	*1200 mg (2 x 600mg) once daily or 400 mg twice daily
Treatment-experienced patients	400 mg twice daily
Co-administration with rifampin	800 mg (2 x 400 mg) twice daily

*Do not substitute the 400 mg tablet for the 600 mg tablet to create a 1200 mg once daily dose.

2.3 Pediatrics

(b) (4)

[redacted]

Table 1: Alternative Dose* with ISENTRESS Chewable Tablets for Pediatric Patients Weighing at Least 25 kg

Body Weight (kg)	Dose	Number of Chewable Tablets
25 to less than 28	150 mg twice daily	1.5 x 100 mg† twice daily
28 to less than 40	200 mg twice daily	2 x 100 mg twice daily
At least 40	300 mg twice daily	3 x 100 mg twice daily

*The weight-based dosing recommendation for the chewable tablet is based on approximately 6 mg/kg/dose twice daily *[see Clinical Pharmacology (12.3)]*.
†The 100 mg chewable tablet can be divided into equal halves.

Table 2: Recommended Dose* for ISENTRESS For Oral Suspension and Chewable Tablets in Pediatric Patients at least 4 weeks of age and weighing Less than 25 kg

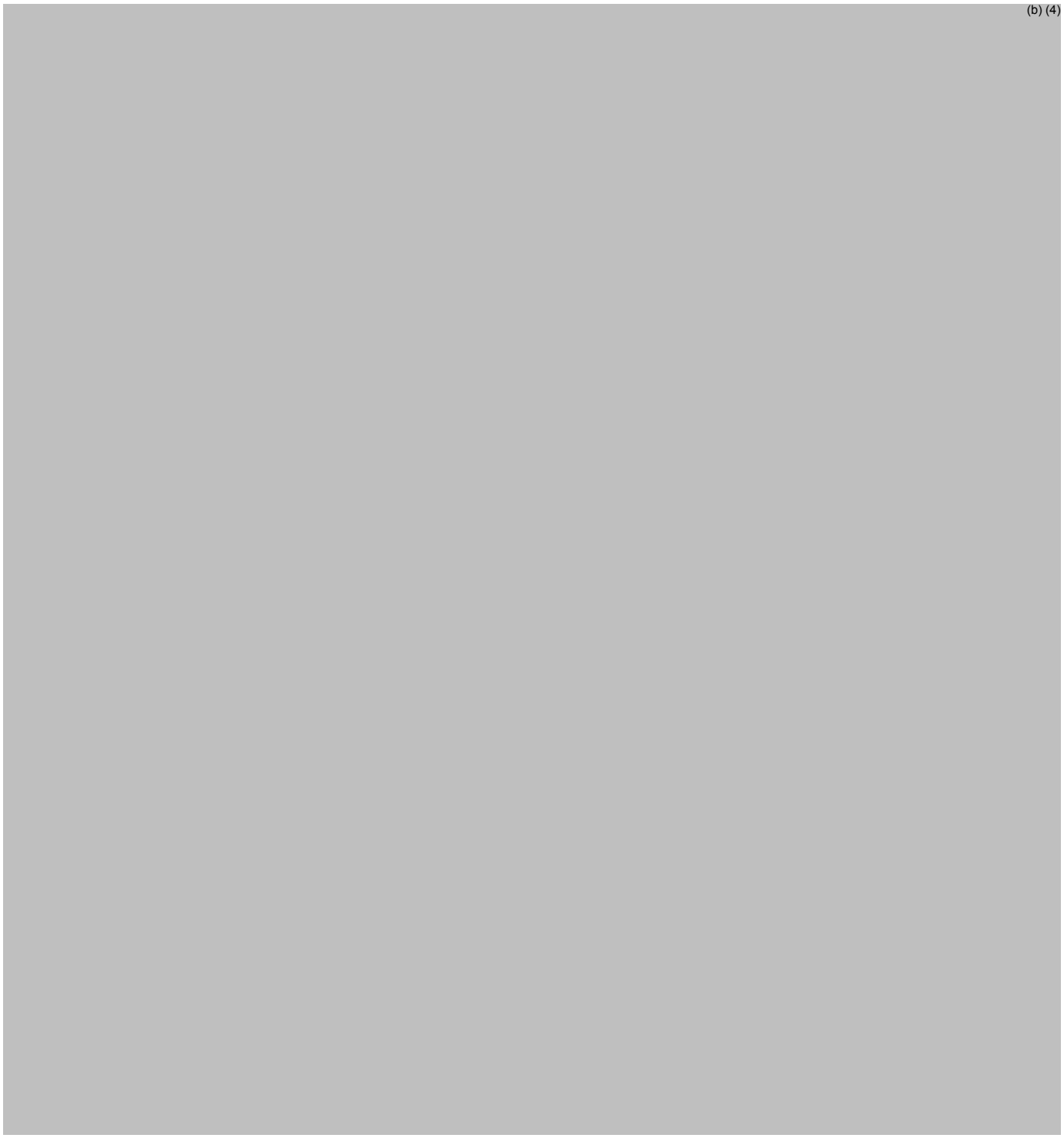
Body Weight (kg)	Volume (Dose) of Suspension to be Administered	Number of Chewable Tablets
3 to less than 4	1 mL (20 mg) twice daily	
4 to less than 6	1.5 mL (30 mg) twice daily	
6 to less than 8	2 mL (40 mg) twice daily	
8 to less than 11	3 mL (60 mg) twice daily	
11 to less than 14†	4 mL (80 mg) twice daily	3 x 25 mg twice daily
14 to less than 20†	5 mL (100 mg) twice daily	1 x 100 mg twice daily
20 to less than 25		1.5 x 100 mg‡ twice daily

*The weight-based dosing recommendation for the chewable tablet and oral suspension is based on approximately 6 mg/kg/dose twice daily *[see Clinical Pharmacology (12.3)]*.
†For weight between 11 and 20 kg either formulation can be used.
Note: The chewable tablets are available as 25 mg and 100 mg tablets.
‡The 100 mg chewable tablet can be divided into equal halves.

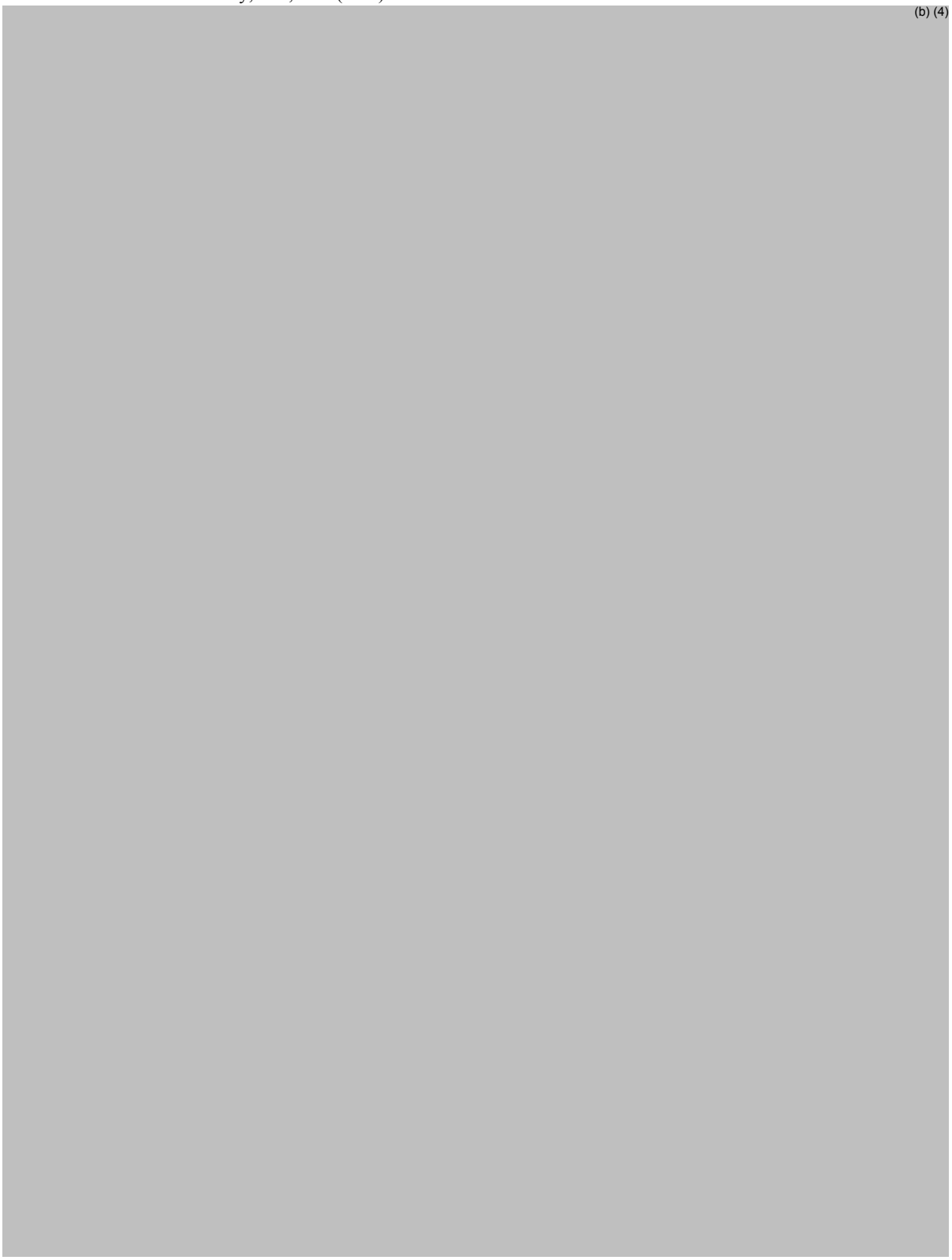
Patients can remain on the granules for suspension formulation as long as their weight is below 20 kg.

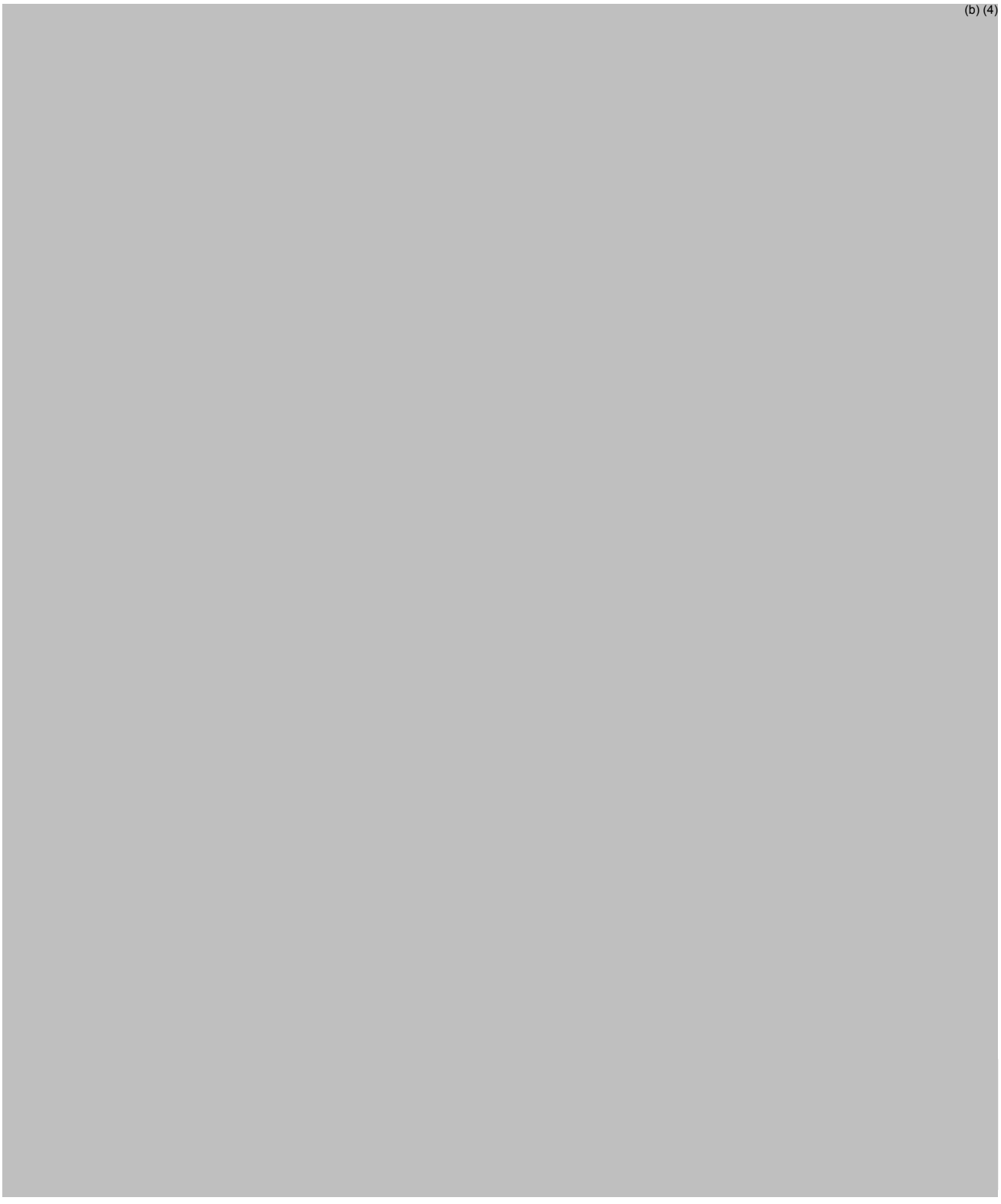
The sponsor proposes to insert the following new language into Section 14. Clinical Studies.

(b) (4)

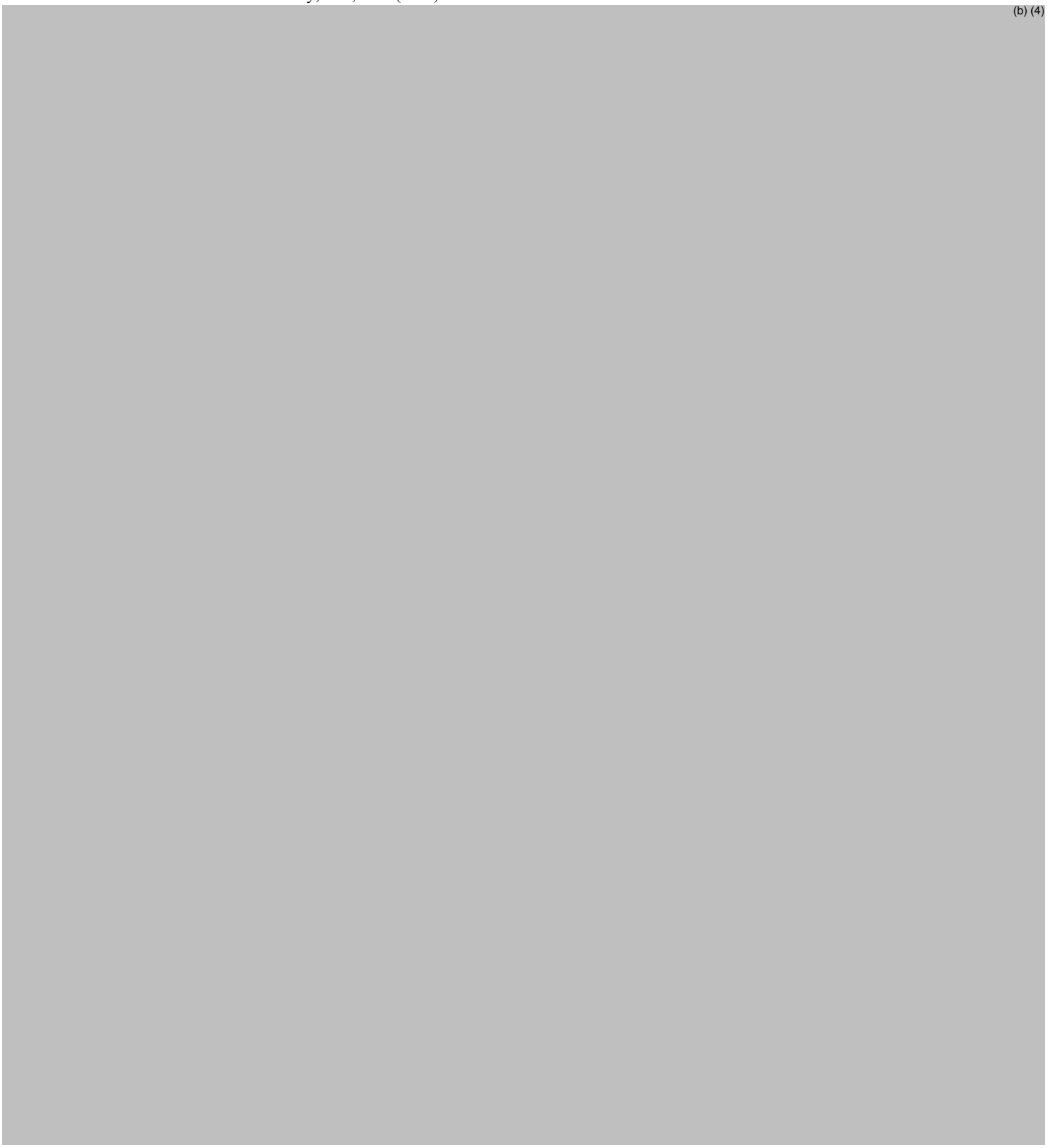


(b) (4)





(b) (4)



(b) (4)

Appendix 1

Computation of the stratum-adjusted MH proportion as per Koch et al., 1989

If n1h and n2h are the sample size of the two treatment groups, 1 and 2 in stratum h, then the weight is

$$w_h = \frac{n_{1h} n_{2h}}{n_{1h} + n_{2h}}$$ is the stratum-specific weight.

Let dh=p1h-p2h be the differnece in proportions in group 1 and 2, then the stratum-adjusted MH proportion is

$$d = \frac{\sum w_h d_h}{\sum w_h}$$ and the continuity-corrected variance is

$$\frac{\sum w_h^2 \left(\frac{p^*_{1h}(1-p^*_{1h})}{n_{1h}-1} + \frac{p^*_{2h}(1-p^*_{2h})}{n_{2h}-1}\right)}{\left(\sum w_h\right)^2}$$

Where $p^*_{1h} = \frac{m_{1h}+0.5}{n_{1h}+1}$ and $p^*_{2h} = \frac{m_{2h}+0.5}{n_{2h}+1}$ and m1h and m2h are the responders in group 1 and 2, respectively.

In Koch et al, the variance is not continuity-corrected, i.e.

$$\frac{\sum w_h^2 \left(\frac{p_{1h}(1-p_{1h})}{n_{1h}-1} + \frac{p_{2h}(1-p_{2h})}{n_{2h}-1}\right)}{\left(\sum w_h\right)^2}$$

where $p_{1h} = \frac{m_{1h}}{n_{1h}}$ and $p_{2h} = \frac{m_{2h}}{n_{2h}}$.

Koch, G.G., Carr, G.J., Amara, I.A., Stokes, M.E.. and Uryniak, T.J. (1989). Categorical Data Analysis. Chapter 13 in Berry, D.A. (ed.), Statistical Methodology in the Pharmaceutical Sciences, Marcel Dekker, New York, pp. 414-421.

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