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APPLICATION NUMBER:

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MICROBIOLOGY REVIEW(S)

DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)

VIROLOGY REVIEW

NDA: 203-045 SDN: 001 DATE REVIEWED: 10/28/11

NDA: 022-145 SDN: 230

Clinical Virology Reviewer: Sung S. Rhee, Ph.D.

NDA #: 203-045

Supporting Document Number: 001

NDA #: 022-145

Supporting Document Number: 230

Applicant Name and Address: Merck Sharp & Dohme Corp.
126 E. Lincoln Avenue, P.O. Box 2000, RY 33-212
Rahway, NJ 07065-0900

Reviewer's Name(s): Sung S. Rhee, Ph.D.

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Product Name(s):

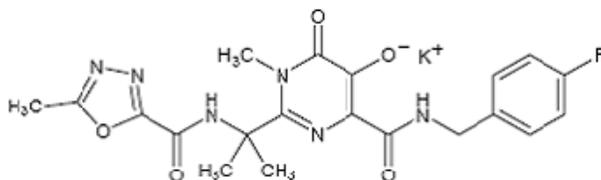
Proprietary: ISENTRESS®

Non-Proprietary/USAN: Raltegravir potassium

Code Name/Number: MK-0518

Chemical Name: N-[(4-fluorophenyl)methyl]-1,6-dihydro-5-hydroxy-1-methyl-2-[1-methyl-1-[[[(5-methyl-1,3,4-oxadiazol-2-yl)carbonyl]amino]ethyl]-6-oxo-4-pyrimidinecarboxamide monopotassium salt

Structural Formula:



Raltegravir (RAL)

Molecular Formula: C₂₀H₂₀FKN₆O₅

Molecular Weight: 482.51

Dosage Form(s): 400 mg Tablet; 25 mg and 100 mg Chewable Tablets

Route(s) of Administration: Oral

Indication(s): Treatment of HIV-1 infection in combination with other antiretroviral agents

Recommended Dosage:

- 400 mg tablet twice daily for adults, adolescents (12 through 18 years of age), and children (6 through 11 years of age and weighing at least 25 kg)
- Weight based to maximum dose 300 mg chewable tablet twice daily for children (2 through 11 years of age)

Dispensed: Rx OTC (Discipline relevant)

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Abbreviations: ARV, antiretroviral; BID, *bis in die* (twice a day); CLIA, clinical laboratory improvement amendments; DAIDS, Division of AIDS; EC₅₀, effective concentration inhibiting viral replication by 50%; (b) (4); HIV-1, human immunodeficiency virus type 1; IN, HIV-1 integrase; INSTI, HIV-1 integrase strand transfer inhibitor; LLOQ, lower limit of quantification; NDA, new drug application; NIAID, National Institute of Allergy and Infectious Diseases; NRTI, nucleoside reverse transcriptase inhibitor; OBR, optimized background regimen; OBT, optimized background therapy; PK, pharmacokinetic; PR, HIV-1 protease; RAL, raltegravir; RAL^R, RAL resistance; RT, reverse transcriptase; RTI, reverse transcriptase inhibitor; ULOQ, upper limit of quantification

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Figure 2: HIV-1 Viral Load in Subjects 501124 and 5037598
Figure 3: RAL Resistance and Replication Capacity of HIV-1 Variant Harboring Q95K
(Source: Fun *et al.*, 2010)11

EXECUTIVE SUMMARY

Raltegravir (RAL; MK-0518, ISENTRESS™) is an HIV-1 integrase (IN) inhibitor that specifically inhibits the strand transfer reaction of HIV-1 IN, and thereby prevents the covalent insertion (integration) of unintegrated linear HIV-1 DNA during the early phase of viral infection into the host cell genome resulting in the formation of the provirus. The integration of viral DNA into host chromosomal DNA is one of the essential steps in the HIV-1 life cycle. RAL 400 mg BID for the oral tablet formulation was approved by the FDA for the treatment of HIV-1 infection in combination with other antiretroviral agents in treatment-experienced adult patients in October, 2007 (BENCHMRK trials, NDA 22-145) and for treatment-naïve adult patients in July, 2009 (STARTMRK trial, NDA 22-145, SE5-004).

In support of a labeling update for RAL to include information on pediatric use of RAL in patients aged from 2 to <19 years old, the applicant submitted two NDA applications, NDA 22-245 SDN 230 and NDA 203045 SDN 001, for two formulations of RAL (adult tablet and chewable tablet, respectively). These two submissions include results from a single pediatric study (IMPAACT P1066, also referred to as Merck Protocol 022) that was conducted to address the requirements of the Pediatric Written Request for RAL. Study P1066 is an ongoing Phase 1/2, multicenter, open-label, noncomparative, multiple cohort (defined by age and RAL formulation) study in HIV-1-infected children and adolescents, ≥4 weeks to <19 years of age to evaluate the safety, tolerability, pharmacokinetic (PK) parameters, and efficacy of RAL in combination with an optimized background regimen. This study was designed to determine the appropriate dose for three RAL formulations (film-coated tablet, also referred to as the adult tablet, chewable tablet, and oral granules for suspension) for each cohort based on the intensive PK and short-term safety data. This study however was not designed or powered to demonstrate efficacy but, after dose selection, efficacy and viral resistance as well as longer-term safety and population PK data were evaluated.

These two applications provide study results from cohorts of HIV-infected children and adolescents (2 through 18 years of age) receiving either the chewable or adult tablet formulation. Overall results from the study support the use of RAL at the age-appropriate recommended doses of either the adult or chewable tablet, given in combination with an OBT, in this HIV-infected pediatric population. Please refer to the reviews by Medical Officer Tafadzwa Vargas-Kasambira, M.D. and Statistician Lei Nie, Ph.D. for detailed safety and efficacy analyses. Of note, the third RAL formulation, oral granules for suspension in water, is available to permit study of children ≥4 weeks to <2 years of age in Study P1066. (b) (4)

To date, three independent RAL resistance pathways, through the emergence of Y143C/H/R, Q148H/K/R, or N155H substitutions within the HIV-1 integrase protein, were identified. These 3 amino acid substitutions were highly associated with virologic failure and virologic rebound to RAL therapy, detectable in 64% and 67% of evaluable virologic failures and rebounders,

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respectively, at Week 48 in the treatment-experienced BENCHMARK trials (Virology review N022145.SE7-001). The cell-based phenotypic studies demonstrated that each of these three substitutions conferred significantly reduced susceptibility to RAL. Increases in EC₅₀ values for failure isolates harboring the Y143C/H/R, Q148H/K/R, or N155H substitution were observed with median increases of 39-fold, 117-fold, and 37-fold, respectively, compared to the corresponding baseline isolates. By Weeks 48 and 96, the emergence of these substitutions was observed cumulatively in isolates from 15.2 % and 17% of the treatment-experienced, RAL recipients in the BENCHMARK trials, and 1.1% and 1.4% of the treatment-naïve RAL recipients in the STARTMARK trial, respectively (Virology review N022145.SE8-011 &-012). Each of these three substitutions was usually accompanied by one or more of 11 secondary substitutions, L74M, E92Q, T97A, E138A/K, G140A/S, V151I, G163R, H183P, Y226C/D/F/H, S230R, and D232N.

As observed in the HIV-1-infected adult population, 42% of the RAL-treatment failure pediatric subjects with evaluable genotypic resistance data developed HIV-1 variants harboring at least one of the 3 primary RAL resistance-associated substitutions. Most (92%) of these HIV-1 variants were less sensitive to RAL (5 to >180-fold, compared to the subject's pre-treatment isolate and/or wild-type reference HIV-1). Secondary RAL resistance-associated substitutions were also detectable in most (77%) of those isolates with emerging primary RAL resistance-associated substitutions. HIV-1 variants with the primary RAL resistance-associated substitutions emerged in a significantly greater proportion of the failures who did not receive the final selected dose of RAL compared to those who received the final selected dose (75% versus 30%). Suboptimal dosing of RAL may contribute to the increased emergence rate of RAL resistant variants during treatment in some of the failures in the non-recommended dose population: 3 of the 6 subjects received RAL 200 or 300 mg BID (the recommended dose of RAL is 400 mg BID for those 3 subjects).

Genotypic resistance analysis of pooled data from multiple studies of RAL (BENCHMRK, STARTMARK, SWITCHMRK, and P1066) revealed that HIV-1 IN Q95K/R substitution was found exclusively in the same virus population harboring the primary RAL resistance-associated substitutions. Currently, 11 RAL-treatment failures were identified from 4 trials to develop HIV-1 variants harboring a substitution at IN Q95 (changed to H [n=1], K [n=3], N [n=2], and R [n=5]) which emerged while on RAL, and the primary RAL^R substitutions were detectable in all 11 isolates. In a cell-based study by Fun *et al.* (2010), Q95K was shown to enhance N155H-mediated RAL resistance and improve the impaired replication of the N155H mutant virus. Thus, it is recommended that Q95K/R be included in the list of the secondary RAL resistance-associated substitutions that may contribute to RAL resistance in the presence of the primary RAL resistance-associated substitutions.

1. Recommendations

- 1.1. Recommendation and Conclusion on Approvability:** Approval of these pediatric new drug applications (NDA 203-045 and sNDA 22-145 SDN 230) for the ISENTRESS™ tablet (400 mg) and chewable tablet (25 and 100 mg) formulations is recommended with respect to Clinical Microbiology for the treatment of HIV-1 infection in combination with other antiretroviral agents in children and adolescents aged from 2 to <19 years old.

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1.2. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, If Approvable: None

2. Summary of Clinical Virology Assessments: Raltegravir Resistance Analysis

In Study P1066, genotypic and phenotypic resistance testing was performed to monitor the emergence of RAL treatment-resistance viruses in subjects who experienced confirmed virologic failure at Week 24 or later (see below for definition) and had plasma HIV-1 RNA >1,000 copies/mL at the time of virologic failure. In addition, virus samples with HIV-1 RNA >1,000 copies/mL at the time of discontinuation from subjects who were not confirmed virologic failure but discontinued the study at or after Week 24 were tested.

Virologic failure was defined in this study as having either virologic non-response or virologic rebound:

- Virologic non-response: never achieved a $\geq 1 \log_{10}$ copies/mL decrease in plasma HIV-1 RNA through Week 24 (and still HIV-1 RNA ≥ 400 copies/mL). Confirmatory HIV-1 RNA measurement was obtained within 1 to 4 weeks.
- Virologic rebound at Week 24 or later: (1) confirmed (2 consecutive measurements at least 1 week apart) HIV-1 RNA ≥ 400 copies/mL after initial response with HIV-1 RNA <400 copies/mL OR (2) confirmed $> 1 \log_{10}$ copies/mL increase in HIV-1 RNA above nadir level (the lowest HIV-1 RNA level while on study drug)

Study P1066 consisted of 2 sequential stages, Stages 1 and 2. Stage 1 examined the PK, short-term tolerability, and safety of RAL (with background ARVs) in a limited number of subjects to permit dose selection for further study in Stage 2. Subjects enrolled in Stage 1 who remained on study after dose selection were considered to participate in the Stage 1 extension. Subjects enrolled in Stage 2 received only the Stage-1 selected dose (recommended dosage in the label). Subjects who received only the final selected dose, whether enrolled in Stage 1 or Stage 2, were considered evaluable for the primary assessment of safety and efficacy (final dose population). Subjects enrolled in the study are stratified into six cohorts based on age (one of five age groups) and formulation (one of three formulations):

- Cohort 1: ≥ 12 to <19 years of age assigned to receive adult tablets
- Cohort 2A: ≥ 6 to <12 years of age weighing at least 25 kg assigned to receive adult tablets
- Cohort 2B: ≥ 6 to <12 years of age assigned to receive chewable tablets
- Cohort 3: ≥ 2 to <6 years of age assigned to receive chewable tablets
- Cohort 4: ≥ 6 months to <2 years of age assigned to receive oral granules for suspension
- Cohort 5: ≥ 4 weeks to <6 months of age assigned to receive oral granules for suspension

These submissions include data from subjects in Cohorts 1, 2A, 2B, and 3 of the study because Cohorts 4 and 5 have not completed enrollment. A total of 126 subjects were enrolled in Cohorts 1, 2A, 2B, and 3, of which 96 were in the final dose population, and 125 of those enrolled subjects were treated with RAL (+OBT) and had at least one viral load data reported in these submissions (95 in the final dose population).

Protocol-defined virologic failure occurred in 45 subjects (35 in the final dose population) based

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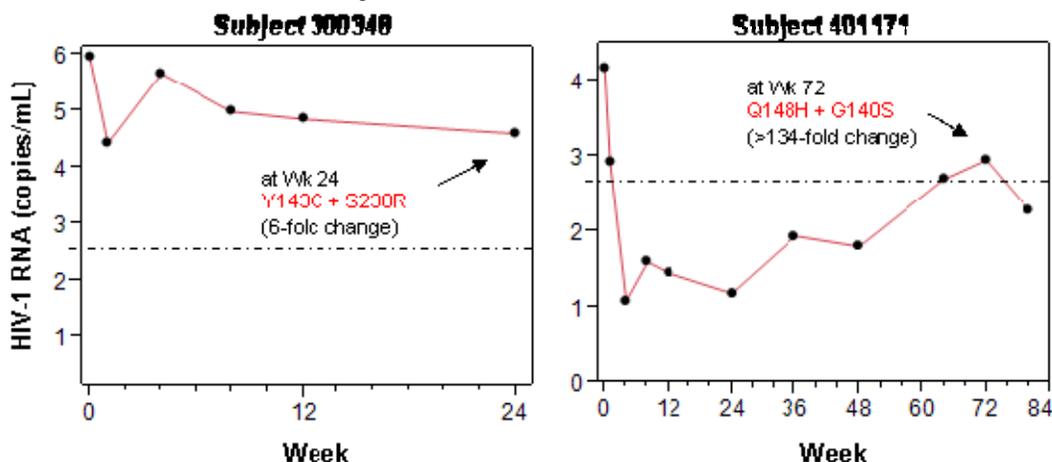
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on all available viral load data (up to Week 160): 33 non-responders and 12 rebounders (25 and 10 in the final dose population, respectively). In this resistance analysis, 7 protocol-defined non-responders (6 in the final dose population) were excluded since they eventually achieved virologic suppression (HIV-1 RNA <400 copies/mL) after Week 24 (delayed response). The Week-24 isolates from 4 of the 7 excluded subjects had no detectable RAL^R substitutions (primary and secondary) with <1.2-fold reduced susceptibility to RAL compared to wild-type reference HIV-1 (<1.1-fold change compared to their respective pre-treatment isolate). Thus, a total of 38 virologic failures were identified as resistance testing and analysis eligibles: 26 non-responders and 12 rebounders (19 and 10 in the final dose population, respectively).

As of the resistance data cut-off date (February 14, 2011) for these submissions, the applicant obtained genotypic/phenotypic data of HIV-1 IN from 29 of the 38 resistance-testing eligible RAL-treatment failures (76%): paired baseline/failure isolate data from 25 subjects and failure isolate only data from 4 subjects. In addition, the applicant included 2 more subjects' paired resistance data (Subjects 300348 and 401171; Figure 1). Both subjects who received the final selected dose of RAL were not identified as treatment failures, since Subject 300349 (Cohort 1) achieved a protocol-defined virologic response (>1 log₁₀ HIV-1 RNA copies/mL) at Week 24 (1.4 log₁₀ reduction from Baseline, and then discontinued treatment at Week 24 with HIV-1 RNA >39,000 copies/mL), and Subject 401171 (cohort 2B) experienced confirmed but transient virologic rebound at Week 64 with subsequent resuppression at Week 80 (192 copies/mL, last study-visit data in the current submission). Thus, a total of 31 subjects' IN genotypic and phenotypic data were analyzed in this review (see Appendix 2, Table A-1 for individual subjects' data).

Figure 1: HIV-1 Viral Load in Subjects 300348 and 401171



Of the 31 subjects examined, HIV-1 variants harboring at least one of the 3 primary RAL resistance-associated (RAL^R) substitutions Y143C/H/R, Q148H/K/R, or N155H in the IN protein were detected in 13 subjects' on-treatment isolates (42% [13/31]; Table 1): 7 in the final dose population (30% [7/23]) and 6 in the non-recommended dose population (75% [6/8]). As observed previously in the HIV-1-infected adult population (BENCHMRK and STARTMRK trials, NDA 22-145), the emergence of only 1 substitution at the 3 primary amino acid positions was detectable in the majority (77% [10/13]) of the 13 failure isolates (Table 2), confirming that the

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substitutions emerged independently as separate pathways to RAL resistance. Q148H/R was most frequently observed (9 of the 13 isolates; Table 2). As observed previously, the secondary RAL^R substitutions were detectable in most of those isolates with emerging primary RAL^R substitutions (77% [10/13]). It should be noted that HIV-1 variants with the primary RAL^R substitutions emerged in a significantly greater proportion of the failures who did not receive the final selected dose of RAL compared to those who received the final selected dose (75% versus 30%; Table 1, typed in red). Suboptimal dosing of RAL may contribute to the increased emergence rate of RAL^R variants during treatment in some of the failures in the non-recommended dose population: 3 of the 6 subjects received RAL 200 or 300 mg BID (the recommended dose of RAL is 400 mg BID for those 3 subjects).

Table 1: Summary¹ of Genotypic and Phenotypic Resistance Analysis by Cohort

| Cohort | Number of subjects with HIV-1 variants harboring primary RAL ^R substitutions ² | | >1.5-fold reduced susceptibility to RAL ^{3,4} | | |
|------------------------|--|------------------------------|---|--|----------------|
| | | | Isolates with primary RAL ^R substitutions ² | Isolates without primary RAL ^R substitutions ² | |
| 1 (n=18) | 3 (17%) | Final dose population (n=16) | 2 | 3 | 1 ⁶ |
| | | Others ⁵ (n=2) | 1 | | |
| 2A (n=6) | 5 (83%) | Final dose population (n=1) | 1 | 4 | 0 |
| | | Others ⁵ (n=5) | 4 | | |
| 2B (n=4) | 3 (75%) | Final dose population (n=3) | 2 | 3 | 0 |
| | | Others ⁵ (n=1) | 1 | | |
| 3 (n=3) | 2 (67%) | Final dose population (n=3) | 2 | 2 | 0 |
| | | Others ⁵ (n=0) | 0 | | |
| Total (n=31) | 13 (42%) | Final dose population (n=23) | 7 (30%) | 12 (92% [12/13]) | 1 (6% [1/18]) |
| | | Others ⁵ (n=8) | 6 (75%) | | |

¹Data Source: Individual subjects' resistance data listed in Appendix 2, Table A-1

²Primary RAL^R substitutions: Y143C/H/R, Q148H/K/R, and N155H in HIV-1 IN.

³The biological cutoff for RAL was determined to be a 1.5-fold change in EC₅₀ values using the PhenoSense HIV-1 Integrase assay (Monogram Biosciences) when 630 INSTI-naïve subjects' samples were tested (Fransen *et al.*, 2008; Abstract H-1214 at the 48th ICAAC meeting, 2008). According to the authors, reduced susceptibility (>1.5-fold) was detected in >90% of the RAL treatment failure samples with substitutions known to confer resistance to RAL.

⁴Fold-change in RAL susceptibility of virologic failure isolates, compared to baseline isolates and/or wild-type reference HIV-1.

⁵Others: subjects who did not receive the final selected dose of RAL.

⁶Subject 501124 experienced virologic rebound at Week 8 (Figure 2). The Week-24 isolate harbored 2 secondary RAL^R substitutions L74L/M and T97A in HIV-1 IN and displayed 1.6-fold reduced susceptibility to RAL, compared to wild-type reference HIV-1.

Table 2: Frequency of the Primary RAL^R Substitutions

| RAL resistance pathway | Y143C/H/R | Q148H/K/R | N155H | Q148H/R+N155H Mixture |
|---------------------------------------|-----------|-----------|----------|-----------------------|
| Final dose population (n=7) | 1 | 3 | 1 | 2 |
| Non-recommended dose population (n=6) | 1 | 3 | 1 | 1 |
| Total (n=13) | 2 | 6 | 2 | 3 |

Data Source: Individual subjects' resistance data listed in Appendix 2, Table A-1

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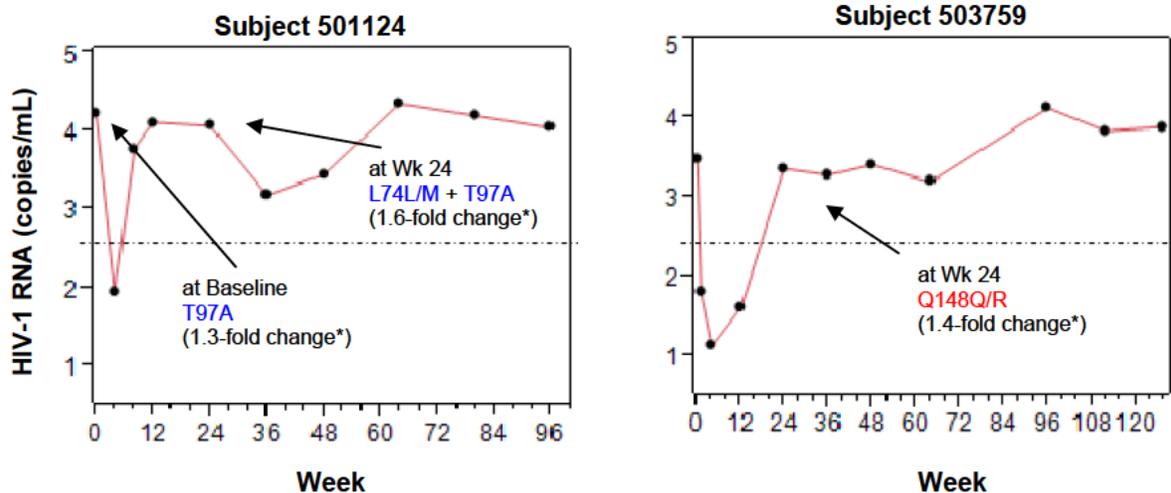
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Of the 13 isolates with the primary RAL^R substitutions, 12 isolates (92%) exhibited >5-fold reduced susceptibility to RAL (up to >180-fold) compared to the subject's pre-treatment isolate and/or wild-type reference HIV-1 (Table 1). The one isolate that showed a 1.4-fold decrease in RAL susceptibility (below the RAL biological cutoff value of 1.5 fold) compared to the baseline isolate or 1.5-fold decrease compared to wild-type reference HIV-1 was collected from a virologic rebounder at Week 24 (Subject 503759 in Cohort 2A with RAL 400 mg BID; Figure 2) and harbored the IN Q148Q/R substitution in the absence of any known secondary RAL^R substitutions. The 1.5-fold shift in susceptibility with respect to the wild type reference identified based on the biological cutoff and isolates with confirmed RAL resistance-associated substitutions establishes a maximum for the clinical cutoff, which may be lower.

Of the 18 subjects' on-treatment isolates with no detectable primary RAL^R substitutions (secondary RAL^R substitutions were detectable in one isolate from Subject 501124; Figure 2), 17 isolates with no known RAL^R substitutions showed <1.3-fold shift in RAL susceptibility (compared to their respective pre-treatment isolates or to wild-type reference HIV-1), indicating these isolates are still sensitive to RAL. The remaining one on-treatment isolate with detectable secondary RAL^R substitutions, collected from a virologic rebounder at Week 24 (Subject 501124; Figure 2), showed 1.6-fold reduced susceptibility to RAL (above the biological cutoff value for RAL resistance). Subject 501124 (Cohort 1, RAL 400 mg BID recipient) had baseline HIV-1 variants with a single secondary RAL^R substitution T97A (1.3-fold change in RAL susceptibility compared to wild-type reference HIV-1) and the failure isolate genotypic data indicated the subject acquired an additional secondary RAL^R substitution L74M while on RAL treatment. This on-treatment isolate with two known secondary RAL^R substitutions became less susceptible to RAL (1.6-fold change in RAL susceptibility compared to wild-type reference HIV-1, and 1.1-fold change compared to the baseline isolate).

Figure 2: HIV-1 Viral Load in Subjects 501124 and 503759



*Fold-change in RAL susceptibility of HIV-1 isolates compared to wild-type reference HIV-1.

*Fold-change in RAL susceptibility of HIV-1 isolates compared to the baseline isolate.

Table 3 lists all 46 amino acid residues in the HIV-1 IN protein (16% of the IN 288 residues) that were found to be substituted in those analyzed on-treatment isolates, excluding already

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established 14 RAL^R substitutions (3 primary and 11 secondary). Of the 46 additionally substituted residues, the majority (91.3% [42/46]) were observed only in one (n=37) or two (n=5) subjects, unlikely to be of any statistical significance of each of those changes for RAL resistance. The remaining 4 substitutions, three occurring at IN polymorphic amino acid positions (112, 154, and 211) and one at a conserved position (210), were observed individually in 3 subjects: only one subject developed while on RAL 2 of these, T210I+Q211K, detectable together in the tested virus population in the absence of the any known RAL^R substitutions with a 0.8-fold shift in RAL susceptibility compared to wild-type reference HIV-1. Three polymorphic-site substitutions at IN 112, 154, and 211 are not likely to be associated with RAL resistance, since not all subjects developed the same substitutions. Two of the 3 subjects harboring HIV-1 with a substitution at IN 112 developed a T112I substitution, while one subject developed an A112T substitution. Two of the 3 subjects harboring HIV-1 with a substitution at IN 154 developed an M154I substitution, while I154L emerged in the other one subject's failure isolate. Similarly, 2 of the 3 subjects harboring HIV-1 with a substitution at IN 211 developed a K211Q substitution, while one subject developed a Q211K substitution. In addition, in 5 of these subjects, the 3 polymorphic-site substitutions emerged in the absence of detectable known RAL^R substitutions, and these viruses showed no changes in RAL susceptibility compared to the pre-treatment isolates and wild-type reference HIV-1 (Appendix 2. Table A-1). All 3 pediatric subjects with the conserved-site substitution at IN T210 (T210A/I) also developed one of the 3 primary RAL^R substitutions. In previous studies in the adult population (Week-96 data from BENCHMRK and STARTMRK trials), T210A/I substitutions were observed with (2 subjects) or without (2 subjects) emerging primary RAL^R substitutions, and the viruses containing T210A/I substitutions with no evidence of primary RAL^R substitutions showed fold-changes of 0.7-0.8 in EC₅₀ values, compared to wild-type reference HIV-1, indicating no significant role of these substitutions with respect to RAL resistance.

Table 3: Frequency and Position of Individual Amino Acid Changes Found in RAL On-Treatment Isolates from 31 Subjects Included in Resistance Analysis¹

| Occurrence | Treatment-emergent substitutions at amino acid position in HIV-1 IN while on RAL (+OBT) | |
|---|--|---|
| | Polymorphic positions | Conserved positions ² |
| 1 | 7, 17, 23, 31, 45, 57, 60, 72, 101, 136, 165, 173, 208, 269, 281, 283 (n=16) | 16, 40, 42, 59, 63, 68, 78, 120, 171, 172, 176, 200, 203, 212, 228, 233, 241, 242, 253, 264, 275 (n=21) |
| 2 | 6, 14, 21 (n=3) | 82, 95 (n=2) |
| 3 | 112, 154, 211 (n=3) | 210 (n=1) |
| Observed substitutions in HIV-1 IN | (D6E, D6N), K7R, (K14R, R14K), S17G, (A21T, A21I), A23V, V31I, V45L, S57G, I60L, V72I, L101F, (A112T, T112I, T112I), K136T, (M154I, M154I, I154L), V165I, K173R, I208M, (K211Q, K211R, Q211K), I269R, V281M, S283G | H16P, C40R, K42E, G59E, I63L, L68I, H78Y, (G82R, G82R), (Q95K, Q95R), N120D, H171L, L172F, L176V, I200L, I203M, (T210A, T210I, T210I), A212E, R228G, P233S, L241F, L242F, D253N, E264K, M275T |

¹RAL resistance-associated primary and secondary substitutions are excluded.

²IN conserved residues were identified by levels of amino acid sequence variations occurring in the general population by Heckett *et al.* (2005): frequencies of <2% were considered conserved in the phylogenetic analysis of 497 HIV-1 group M isolates (76 subtype A, 81 subtype B, 70 subtype C, 43 subtype D, 15 subtype F, 10 subtype G, 1 subtype H, 48 CRF01_AE, 97 CRF02_AG, 56 MOSAIC).

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There were 2 conserved-site substitutions, G82R and Q95K/R (Table 3), each detectable separately in 2 failures isolates. Both glycine and glutamine residues at amino acid positions 82 (G82) and 95 (Q95) in HIV-1 IN, respectively, are highly conserved with no detectable variations when 1523 HIV-1 group M IN sequences in GenBank were examined (Rhee *et al.*, 2008). In 4 RAL trials (BENCHMRK, STARTMRK, SWITCHMRK, and P1066), 11 RAL-treatment failures had HIV-1 variants harboring a substitution at IN Q95 (changed to H [n=1], K [n=3], N [n=2], and R [n=5]) emerged while on RAL. All 11 isolates with the Q95H/K/N/R substitution also harbored the primary RAL^R substitutions (Table 4, written in red), indicating that this conserved-residue substitution may be selected exclusively and dependently with the primary substitutions, as observed with some of the secondary RAL^R substitutions such as E138A/K and G140A/S (Microbiology review N022145.000). Recently, Fun *et al.* (2010) also observed selection of Q95K as a secondary resistance substitution during RAL therapy failure. Furthermore, the authors showed that in the background of N155H, Q95K enhanced N155H-mediated RAL resistance in MT4 cells and improved the impaired replication of the N155H mutant virus in Supt1 cells (Figure 3). Together, it is recommended that Q95K/R be included in the list of the secondary RAL^R substitutions that may contribute to RAL resistance in the presence of the primary RAL^R substitutions. The G82R substitution has never been reported in previous studies (Week-96 data from BENCHMRK and STARTMRK trials).

Table 4: Genotypic and Phenotypic Data of RAL-Treatment Failure Isolates Harboring a Substitution at IN Q95 from 4 RAL Trials

| Study | Subject ID | Genotypic changes in HIV-1 IN developing on RAL | RAL Susceptibility (fold-change ¹) |
|------------------------|------------|--|--|
| BENCHMRK | 8212 | R14R/K, M50M/I, V72V/I, L74L/M, Q95Q/R, T97T/A, I101I/L, T112T/A/I, S119S/T, Y143C, G163G/R, V201V/I, N230N/K, | ND |
| | 8327 | Q95Q/K, N155H, E157D, G197G/R, D232D/N | ND |
| | 8381 | Q95Q/H, I135I/V, T136K, N155H, K156K/N, G163G/R, A169A/D, E170E/A | ND |
| | 16206 | Q95Q/R, N155H, G163G/R, A196A/P | 34 |
| | 16349 | C40C/W, Q95N, G140G/A/S, Q148R | 38 |
| | 16402 | Q95Q/R, G140S, Q148H, R262R/K, G272G/E | ND |
| STARTMRK | 23236 | L74L/M, E92E/Q, Q95Q/R, T97T/A, Y143Y/H | 65 |
| SWITCHMRK ² | 34953 | Q95Q/K, Y143Y/C, Q148Q/R, N155N/H, D232D/N | ND |
| | 35045 | Q95N, G140G/S, Q148Q/H/R, N155N/H | 137 |
| P1066 | 505954 | Q95K, L101L/F, E138K, Q148R, L172L/F, K173K/R, I200I/L, T210T/I, D232D/V, L241L/F, L242L/F | 79 |
| | 650976 | Q95Q/R, N155H, T210T/A, D232D/N | 24 |

ND, not determined

¹Fold-change in RAL susceptibility of virologic failure isolates, compared to the wild-type reference HIV-1

²No RAL pre-treatment genotypic data were available. Thus, known RAL^R substitutions, primary (written in red) and secondary (written in blue), detected in the virologic failure isolates are listed.

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Figure 3: RAL Resistance and Replication Capacity of HIV-1 Variant Harboring Q95K
(Source: [Fun et al., 2010](#))

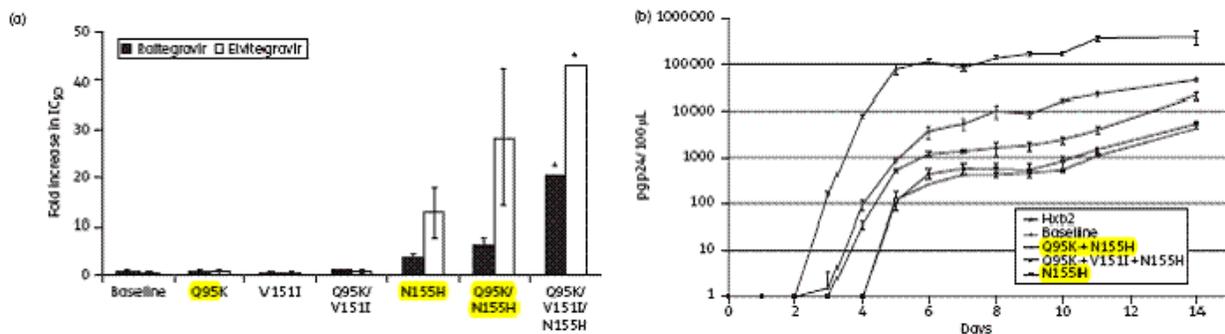


Figure 2: Drug resistance and replication capacity of viral clones. All clones are identical (complete RT-IN inserts) to the patient-derived baseline clone except for the indicated integrase mutations. (a) Raltegravir and elvitegravir susceptibilities of individual clones. Values are averages of three separate experiments. *Due to poor infectious virus titer, experiments with this clone could not be repeated. (b) Replication capacities of the different site-directed mutants were determined by monitoring p24 production in the absence of raltegravir. All viruses were tested in duplicate. Error bars indicate the SFM.

3. Administrative

3.1. Reviewer’s Signature(s)

Sung S. Rhee, Ph.D.
Microbiologist

3.2. Concurrence

Date: _____

HFD-530/MicroTL/J. O’Rear

CC:
HFD-530/NDA # 22145
HFD-530/Division File
HFD-530/PM/E. Thompson

PACKAGE INSERT UPDATES

The applicant proposed no revisions to be made to the Microbiology section of the label (Section 12.4) with respect to Study P1066.

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Genotypic resistance analysis of pooled data from multiple studies of RAL (BENCHMRK, STARTMRK, SWITCHMRK, and P1066) revealed that HIV-1 IN Q95K/R substitution was found exclusively in the same virus population harboring the primary RAL resistance-associated substitutions (see above 'Summary of Clinical Virology Assessments: Raltegravir Resistance Analysis' for details). This observation indicated that Q95K/R may be selected in the RAL-treatment failure viruses dependently with the primary substitutions and may contribute to RAL resistance. Thus, the 'Resistance' subsection under Section 12.4 labeling was revised to include Q95K/R in the list of additional substitutions associated with resistance to RAL (written in red). The package insert approved on July 01, 2010 to include Week-96 data from the ongoing BENCHMRK and STARTMRK trials in treatment-experienced and treatment-naïve HIV-1-infected adult populations, respectively, was served as the base label (written in black).

(b) (4)

APPENDICES

1. Appendix 1: Materials and Methods

1.1. Quantification of Plasma HIV-1 RNA Levels

Plasma HIV-1 RNA levels were quantified by a clinical site's local CLIA-certified (or equivalent) laboratory using the ultrasensitive processing procedure (LLOQ of 50 copies/mL) of the COBAS

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AMPLICOR HIV-1 Monitor™ Test (Roche, version 1.5) that received marketing approval from FDA (BP950005) on March 2, 1999 as an *in vitro* nucleic acid amplification test for the quantification of HIV-1 RNA in human plasma. The standard processing procedure of the assay was also used when HIV-1 RNA results from the ultrasensitive assay were beyond an acceptable upper limit (ULOQ of 750,000 copies/mL). If the local laboratory did not use this method, patient samples were tested at the (b) (4)

According to the manufacturer, the AMPLICOR HIV-1 Monitor Test yielded a specificity of >99.5%, reducing false positive results when tested in a large seronegative population of over 500 samples. It could distinguish 0.5 log₁₀ copies/mL differences. In addition, this test utilizes a primer set designed to detect non-B subtypes (HIV-1 Group M), providing reliable viral load measurement of HIV-1 subtypes A-G.

All available HIV-1 RNA results were used for the efficacy analysis, including results from the HIV-1 Monitor Test (standard and ultrasensitive) or if available, from an alternative method, (e.g., Abbott RealTime HIV-1 assay or HIV-1 RNA Quantitative bDNA test).

For all subjects, HIV-1 RNA levels were measured at screening, baseline, Weeks 1, 4, 8, 12, 24, 36, and 48, at a safety visit for Stage 1 subjects whose dose was increased to the Stage 2 dose, at the 14-day post therapy follow-up visit, and at an early discontinuation visit (for subjects who discontinued the study early). A confirmatory HIV-1 RNA test was to have been done in one week (or up to 4 weeks) later to verify viral failure/rebound. Due to the difficulty of having pediatric subjects commit and adhere to extra clinic visits, most subjects did not have the confirmatory test within 1 to 4 weeks. Therefore, the next available test for the subject, which may have been within 1 to 4 weeks or longer, was used as confirmatory test to identify virologic failures. During long-term study follow-up, for subjects who continued to receive study-provided RAL, HIV-1 RNA levels were measured every 4 months (± 6 weeks) for 5 years after initial RAL exposure (i.e., 48 weeks of RAL treatment plus 4 years follow-up), and for subjects who discontinued study-provided RAL treatment, HIV-1 RNA levels were measured every 12 months for 5 years after initial RAL exposure.

1.2. Genotypic and Phenotypic Viral Resistance Testing

Genotypic and phenotypic testing was performed to evaluate the development of viral resistance to RAL and other ARVs. Genotypic assays to detect viral resistance to PIs and RTIs were performed by the (b) (4) using TRUGENE assay* (Siemens Healthcare Diagnostics Inc.). Genotypic assays to detect resistance to RAL, and all phenotype assays to detect resistance to RAL as well as PIs and RTIs were performed by (b) (4)

For all subjects, blood samples for viral resistance assays were collected at screening, Weeks 12, 24, 36, and 48 during the study. Samples were also collected as follows:

- For subjects who met the protocol-defined virologic failure at Week 24 or later,
 - If a confirmatory blood sample, collected within 4 weeks of the visit, was available, the confirmatory or second consecutive sample with HIV-1 RNA >1,000 copies/mL was tested.

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- If a confirmatory blood sample, collected within 4 weeks of the visit, was not available, the next available HIV-1 RNA value was used to confirm viral failure. Resistance testing was performed on the earliest sample with HIV-1 RNA >1,000 copies/mL.
- For subjects who discontinued the study at or after Week 24 and were not confirmed viral failures, a blood sample with HIV-1 RNA >1,000 copies/mL at the time of discontinuation was tested.

If the samples were unavailable as described above or inadequate (e.g., insufficient volume), the samples obtained closest to the time of viral failure or discontinuation visit, as determined by the protocol team, was tested. Inadequate blood volume for resistance testing was a frequent issue in this study. During the course of the study, the protocol team, in consultation with the study virologist, made adjustments to the testing algorithm in order to ensure that adequate sample was available for resistance testing. Additionally, if limited blood volume was an issue, the testing priority was established as: 1) integrase genotype, 2) integrase phenotype, 3) PR/RT genotype, and 4) PR/RT phenotype.

*TRUGEN assay: The Division received Information Amendment on December 10, 2010 regarding the TRUGENE System (IND 77787 SDN 091). The amendment included a report entitled "Handling of HIV-1 RT Codon Insertion Mutations by the Siemens Healthcare TRUGENE System" prepared by Joseph E. Fitzgibbon, Ph.D., Microbiologist, DAIDS, NIAID. Briefly, the report described that the TRUGENE system used by one of the laboratories performing HIV drug resistance testing for DAIDS-sponsored clinical trials assigned the insertion mutation to codon 67 rather than codon 69 of the HIV-1 RT. Manual examination of the sequence indicated that the insertion might actually be a codon 69 insertion. DAIDS requested (b) (4) to examine the HIV-1 drug resistance database to see if other samples had the same or similar insertion mutations near codon 69 that were not designated as codon 69 resistance mutations. (b) (4) found 9 additional samples that had similar insertions, all using the TRUGENE system. The ten samples came from seven clinical trial subjects enrolled in three different clinical trials and were tested by four different laboratories. DAIDS is working with the clinical trial teams and the testing laboratories to try to determine whether all of these samples should have been designated as containing codon 69 resistance mutations and should have been assigned the corresponding HIV drug resistance phenotype. Laboratories are currently reviewing the sequences to see if any sequencing or editing errors were made. After reviewing the data, three of the laboratories indicated that they believe the insertions should have been placed at codon 69. The laboratories have notified Siemens and are working with technical representatives to resolve the issue. In summary, when using the TRUGENE HIV-1 drug resistance assay, results for some patients may indicate susceptibility to some anti-HIV drugs when they are actually resistant to all drugs in the NRTI class. This may cause some patients to receive sub-optimal therapy. DAIDS is working to try to determine whether these samples should be designated as resistant, whether the TRUGENE software is problematic for these samples, and whether the issue is confined to TRUGENE. DAIDS will notify the FDA of this issue.

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2. Appendix 2: Individual Subjects' Genotypic and Phenotypic Data in Study P1066

Table A-1: Thirty-One Subjects with Evaluable Genotypic and Phenotypic Data Included in RAL Resistance Analysis

| Subject ID | Cohort | Final dose population | Virus samples isolated for resistance analysis | | |
|------------|--------|-----------------------|--|---|--|
| | | | Week | Genotypic changes in HIV-1 IN emerged on RAL (n) | RAL susceptibility (fold-change ¹) |
| 300348 | I | Yes | 24 | Y143Y/C, S230S/R (2) | 6 (5) |
| 380769 | I | Yes | 24 | (0) | 0.9 (1) |
| 382147 | III | Yes | 24 | A23A/V, V45V/L, I63I/L, M154M/I (4) | 0.8 (0.9) |
| 400125 | I | Yes | 80 | S17S/G, N120N/D, M275M/T (3) | 0.9 (1) |
| 400171 | I | Yes | 36 | K7K/R, C40C/R, I60I/L, E92E/G (4) | 0.8 (0.8) |
| 400333 | I | Yes | 24 | A21A/T, H78H/Y, G82G/R, P233P/S, I269R (5) | 1 (1) |
| 401051 | IIA | No | 24 | G140G/A, Q148Q/R, N155N/H (3) | 71 (97) |
| 401171 | IIB | Yes | 72 | G140S, Q148H (2) | >134 (ND) |
| 411288 | I | Yes | 24 | (0) | 0.9 (1.2) |
| 411290 | I | Yes | 24 | No detectable RAL ^R substitutions ² | ND (1) |
| 411294 | I | Yes | 24 | V72V/I (1) | 1.3 (1.1) |
| 470159 | IIA | No | 24 (stage 1) | No detectable RAL ^R substitutions ² | ND (0.9) |
| 470289 | I | Yes | 24 | G82G/R, K211K/Q, E264K, S283S/G (4) | 0.9 (0.9) |
| 501124 | I | Yes | 24 | S57S/G, L74L/M, (A97A) ³ (2) | 1.1 (1.6) |
| 502828 | I | No | 24 | L74L/F, V151I, N155H, I208I/M, D232D/N, D253D/N (6) | >134 (ND) |
| 503759 | IIA | Yes | 24 | Q148Q/R, R228R/G (2) | 1.4 (1.5) |
| 503862 | IIB | No | 24 (stage 2) | A21A/T, G140S, Q148H, I154I/L, V165V/I (5) | >147 (ND) |
| 504261 | IIB | Yes | 24 | D6D/E, K14K/R, G59G/E, T112T/I (4) | 0.9 (0.9) |
| 505954 | IIA | No | 116 | Q95K, L101L/F, E138K, Q148R, L172L/F, K173K/R, I200I/L, T210T/I, D232D/V, L241L/F, L242L/F (11) | 69 (79) |
| 509862 | IIA | No | 28 (stage 2) | H16H/P, G140S, Q148H, V151V/L, H171H/L (5) | >137 (ND) |
| | | | 48 (stage 2) | G140S, Q148H (2) | >137 (ND) |
| 650976 | IIB | Yes | 27 | Q95Q/R, N155H, T210T/A, D232D/N (4) | 26 (24) |
| 670119 | I | No | 80 | V31V/I, M154M/I (2) | 1 (1) |
| 690747 | I | Yes | 24 | No detectable RAL ^R substitutions ² | ND (0.7) |
| 690786 | IIA | No | 24 (stage 1) | L68I, Y143R, K211K/R (3) | 108 (125) |
| | | | 32 (stage 1) | K42K/E, L68I, Y143R, I203I/M, T210T/I (5) | 114 (143) |
| 720101 | I | Yes | 44 | K136K/T (1) | 0.8 (0.6) |

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| | | | | | |
|---------|-----|-----|----|--|-----------|
| 720200 | I | Yes | 64 | T112T/I, Q211Q/K, A212A/E (3) | 0.8 (0.8) |
| 801109 | III | Yes | 24 | L74L/I, Q148Q/R, N155N/H (3) | ND (18) |
| 801522 | III | Yes | 24 | G140G/A, Q148R | 18 (20) |
| 8500049 | I | Yes | 48 | T97T/A, A112T, G140G/S, N155N/H, L176V, V281M (6) | 81 (61) |
| | | | 64 | T97T/A, A112T, G140G/S, Q148Q/H, N155N/H, L176V, V281M (7) | >181 (ND) |
| 8500345 | I | Yes | 24 | (0) | 0.9 (1) |
| 8501372 | I | Yes | 48 | D6D/N, R14R/K (2) | 1 (0.8) |

ND, not determined

¹Fold-change in RAL susceptibility of on-treatment isolates, compared to their respective pre-treatment isolate (compared to wild-type reference HIV-1)

²No RAL pre-treatment genotypic data were available. Thus, known RAL^R substitutions, primary (written in red) and secondary (written in blue), detected in the virologic failure isolates are listed: primary substitutions Y143C/H/R, Q148H/K/R, and N155H; and secondary substitutions L74M, E92Q, Q95K/R, T97A, E138A/K, G140A/S, V151I, G163R, H183P, Y226C/D/F/H, S230N/R, and D232N.

³Amino acid in parenthesis indicates that substitutions were found in samples isolated at Baseline (or Screen) and persisted during RAL treatment.

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/s/

SUNG S RHEE
12/07/2011

JULIAN J O'REAR
12/07/2011

VIROLOGY FILING CHECKLIST FOR NDA or Supplement

NDA Number: 203-045 (SDN 001) and 22-145 (SDN 230)

Stamp Date: 06/30/2011

Applicant: Merck Sharp & Dohme Corp.

Drug Name: ISENTRESS

On **initial** overview of the NDA application for filing:

| | Content Parameter | Yes | No | Comments |
|----|--|------------|-----------|---|
| 1 | Is the virology information (nonclinical and clinical) provided and described in different sections of the NDA organized in a manner to allow substantive review to begin? | X | | |
| 2 | Is the virology information (nonclinical and clinical) indexed, paginated and/or linked in a manner to allow substantive review to begin? | X | | |
| 3 | Is the virology information (nonclinical and clinical) legible so that substantive review can begin? | X | | |
| 4 | On its face, has the applicant <u>submitted</u> cell culture data in necessary quantity, using necessary clinical and non-clinical strains/isolates, and using necessary numbers of approved current divisional standard of approvability of the submitted draft labeling? | X | | |
| 5 | Has the applicant <u>submitted</u> any required animal model studies necessary for approvability of the product based on the submitted draft labeling? | | | NA |
| 6 | Has the applicant <u>submitted</u> all special/critical studies/data requested by the Division during pre-submission discussions? | X | | |
| 7 | Has the applicant <u>submitted</u> the clinical virology datasets in the appropriate format as described in the relevant guidance documents and are the datasets complete? | X | | |
| 8 | Has the applicant used standardized or nonstandardized methods for virologic outcome measures? If nonstandardized methods were used, has the applicant included complete details of the method, the name of the laboratory where actual testing was done and performance characteristics of the assay in the laboratory where the actual testing was done? | X | | |
| 9 | Has the applicant <u>submitted</u> draft labeling consistent with current regulation, divisional and Center policy, and the design of the development package? | X | | |
| 10 | Has the applicant <u>submitted</u> annotated microbiology draft labeling consistent with current divisional policy, and the design of the development package? | | | No changes were proposed in the Microbiology section of the label (12.4). |

VIROLOGY FILING CHECKLIST FOR NDA or Supplement

| | Content Parameter | Yes | No | Comments |
|----|---|-----|----|----------|
| 11 | Have all the study reports, published articles, and other references been included and cross-referenced in the annotated draft labeling or summary section of the submission? | X | | |
| 12 | Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review? | | X | |

NA, not applicable

IS THE MICROBIOLOGY SECTION OF THE APPLICATION FILEABLE? YES

If the NDA is not fileable from the microbiology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Sung Rhee 07/27/2011

 Reviewing Microbiologist Date

 Microbiology Team Leader Date

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/s/

SUNG S RHEE
07/28/2011

JULIAN J O'REAR
07/28/2011