CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205786Orig1s000

MICROBIOLOGY / VIROLOGY REVIEW(S)

DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)

VIROLOGY REVIEW

NDA: 205-786 **SDN:** 001 **DATE REVIEWED:** 10/30/13

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

Applicant Name and Address: Merck Sharp & Dohme Corp.
2015 Galloping Hill Road
Kenilworth, NJ 07033

Initial Submission Dates:
Correspondence Date: June 26, 2013
CDER Receipt Date: June 27, 2013
Reviewer Receipt Date: June 28, 2013
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Companion Efficacy Supplements:
NDA 022-145 Supplement-31 (SDN 865): June, 25, 2013
NDA 203-045 Supplement-09 (SDN 060): June, 25, 2013

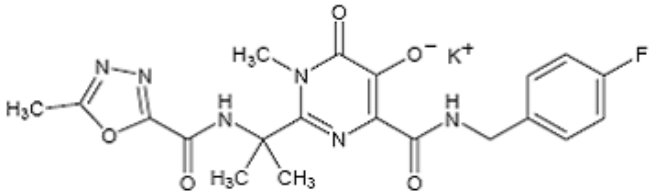
Subsequent Submission:
- **Amendments to Proposed Prescribing Information:**
  - NDA 205-786 SDN 002; NDA 022-145 SDN 877; and NDA 203-045 SDN 064: July 11, 2013
  - NDA 205-786 SDN 006; NDA 022-145 SDN 903; and NDA 203-045 SDN 070: August 19, 2013
  - NDA 205-786 SDN 017; NDA 022-145 SDN 951; and NDA 203-045 SDN 078: November 05, 2013

Related/Supporting Documents: INDs 69,928 and 77,787; NDAs 022-145 and 203-045

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-pyrimidine-carboxamide monopotassium salt

Structural Formula:



Raltegravir (RAL)

Molecular Formula: $C_{20}H_{20}FKN_6O_5$
Molecular Weight: 482.51

Dosage Form(s): Granules for suspension
- Each single-use packet contains 100 mg of granules which is suspended in 5 mL of water

giving a final concentration of 20 mg/mL.

- The suspension should be administered within 30 minutes of mixing.

Route(s) of Administration: Oral

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

Recommended Dosage: Weight-based (approximately 6 mg/kg/dose) to maximum dose 100 mg granules for suspension twice daily for children aged from 4 weeks (b) (4)

- Patients can remain on the granules for suspension formulation beyond their 2nd birthday as long as their weight is below 20 kg.

Dispensed: Rx _X_ **OTC** ___ **(Discipline relevant)**

Abbreviations: ABC, abacavir; ART, antiretroviral therapy; ARV, antiretroviral; BID, *bis in die* (twice a day); CLIA, clinical laboratory improvement amendments; EC_{50}, effective concentration inhibiting viral replication by 50%; GFS, granules for suspension; HIV-1, human immunodeficiency virus type 1; IMPAACT, the International Maternal Pediatric Adolescent AIDS Clinical Trials; IN, HIV-1 integrase; INSTI, HIV-1 integrase strand transfer inhibitor; JHU, Johns Hopkins University; LAM, lamivudine; LLOQ, lower limit of quantification; LPV/r, ritonavir-boosted lopinavir; NRTI, HIV-1 nucleos(t)ide reverse transcriptase inhibitor; NVP, nevirapine; OBR, optimized background regimen; PD, pharmacodynamic; PI, HIV-1 protease inhibitor; PK, pharmacokinetic; PMTCT, prevention of mother-to-child transmission; PR, HIV-1 protease; RAL, raltegravir; RT, reverse transcriptase; RTI, reverse transcriptase inhibitor; RT-PCR, reverse transcription-polymerase chain reaction; TAM, thymidine analogue-associated mutation; ULOQ, upper limit of quantification; UNC, University of North Carolina; ZDV, zidovudine

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VIROLOGY REVIEW

NDA: 205-786 **SDN:** 001 **DATE REVIEWED:** 10/30/13

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

EXECUTIVE SUMMARY

RAL (MK-0518, ISENTRESS®; US Prescribing Information, revised in August, 2013) is an HIV-1 integrase (IN) strand transfer inhibitor (INSTI) 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 necessary for the formation of the provirus. 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 addition, the oral tablet (400 mg) and chewable tablet (25 and 100 mg) formulations of RAL were approved for the treatment of HIV-1 infection in children and adolescents aged from 2 to <19 years old (IMPAACT P1066 study, NDAs 022-145/S-022 and 203-045, respectively) in December, 2011. Currently, 2 HIV-1 drugs in the INSTI class, ISENTRESS® (RAL) and TIVICAY® (dolutegravir), have received FDA approval for marketing to be used in combination with other approved antiretrovirals. In addition, the fixed dose tablet STRIBILD® contains the INSTI elvitegravir in combination with two FDA-approved HIV-1 NRTIs, FTC and TDF, and a pharmacokinetic enhancer cobicistat. TIVICAY® and STRIBILD® are dosed once a day.

The purpose of this original NDA is to provide data supporting the pediatric use of a new age-appropriate formulation of RAL, granules for suspension (GFS), in HIV-1-infected infants (b) (4) (b) (4) 4 weeks (b) (4) with HIV-1 infection. This submission includes safety and efficacy results from subjects (n=26) in Cohorts 4 (6 months to <2 years of age; n=14) and 5 (4 weeks to <6 months of age; n=12) of an ongoing pediatric study (IMPAACT P1066, also referred to as Merck Protocol (b) (4)) that was conducted to address the requirements of the Pediatric Written Request for RAL. In addition, this application contains a PK/PD analysis for the GFS formulation in order to demonstrate that the efficacy in these age cohorts is projected to be similar to that in older children and adolescents taking either chewable or adult tablets for the recommended dose and in adults at the 400 mg BID dose of the adult tablet.

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, 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 GFS) 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. 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

The 26 subjects enrolled in Cohorts 4 (n=14) and 5 (n=12) had a median age of 28 weeks (ranging from 4 to 100 weeks). All 14 subjects in Cohort 4 had been previously treated with 1 to 4 ARVs (median=1; mean=2.1) for a mean of 20.1 weeks (median of 6 weeks), while those in Cohort 5 were required to have failed a PMTCT prophylaxis regimen (NVP or ZDV) and were not permitted to have received prior ARV as direct treatment of HIV-1 infection. The median baseline plasma HIV-1 RNA was 5.9 $\log_{10}$ copies/mL (ranging from 3.1 to 7 $\log_{10}$ copies/mL) and 69.2% (18/26) of those had baseline HIV-1 RNA >100,000 copies/mL. RAL was administered as GFS formulation without regard to food (weight-based dosing of approximately 6 mg/kg BID) in combination with an optimized background regimen (OBR). LAM (100%), ABC (73.1%), LPV/r (65.4%), and ZDV (26.9%) were used most frequently. At Week 48, 60.8% (14/23) achieved HIV-1 RNA<400 copies/mL (3 subjects were excluded from the analysis since they had not yet reached the Week-24 study visit, as of the efficacy date cutoff date of February 07, 2013). Overall PK, safety, and efficacy results from the study support the use of the RAL GFS formulation at the age-appropriate recommended doses, given in combination with an OBT, in this HIV-infected pediatric population. Please refer to the reviews by Clinical Reviewer Brittany Goldberg, M.D. and Clinical Pharmacology Reviewer Fang Li, Ph.D. for detailed safety and efficacy analyses. Intensive PK and preliminary 24-weeks safety and efficacy data from Cohort 4 were presented at the 19^{h} Conference on Retroviruses and Opportunistic Infections by Spector *et al*. (2012).

In this Clinical Virology review, the emergence of RAL-resistant viruses was assessed in subjects who experienced virologic failure with HIV-1 RNA >1,000 copies/mL (the approximate lower limit of the resistance assay) at the end of each study year (e.g., Weeks 48 and 96) or at the last on-treatment study visit before the cutoff date for resistance data, or at the time of discontinuation for subjects who discontinued the study at any time after Week 24 with HIV-1 RNA >1,000 copies/mL.

To date, multiple independent RAL resistance pathways have been identified primarily through the emergence of Y143C/H/R, Q148H/K/R, or N155H substitutions within the HIV-1 IN protein. These IN substitutions occurring at 3 highly conserved amino acid positions were closely associated with virologic failure and virologic rebound to RAL therapy, detectable in 64% and 67% of evaluable virologic failures and rebounders, respectively, at Week 48 in the treatment-experienced BENCHMRK trials (Virology review N022145.SE7-001). The cell-based phenotypic studies demonstrated that each of these substitutions conferred significantly reduced susceptibility to RAL. Increases in EC_{50} values for failure isolates harboring an 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. Each of these primary resistance substitutions was usually accompanied by one or more of secondary substitutions at 12 amino acid positions in the HIV-1 IN protein, L74M, E92Q, Q95K/R, T97A, E138A/K, G140A/S, V151I, G163R, H183P, Y226C/D/F/H, S230R, and D232N. Of note, in long-term RAL resistance analyses, the E92Q substitution was observed occasionally in RAL-treatment failure subjects in the absence of one of the identified primary resistance substitutions (Virology review N022145.734). An additional IN substitution, F121C, was also observed in failure subjects in the absence of the primary substitutions and conferred significantly reduced susceptibility to RAL (3- to 37-fold; Virology review N022145.734). These clinical and nonclinical observations indicated that E92Q and F121C emerge independently of the primary substitutions and contribute to RAL resistance via a separate pathway.

By the resistance data cut-off date for this submission (February 07, 2013), of the 22 subjects

(14 and 8 subjects in Cohorts 4 and 5, respectively) who had completed the Week-24 visit with evaluable post-baseline viral load data, 8 subjects (n=6 in Cohort 4 and n=2 in Cohort 5) were eligible for resistance testing including one subject (Subject 8501806 in Cohort 4; Table 1) who experienced transient virologic rebound at Week 36 through Week 64 but became aviremic (HIV-1 RNA <50 copies/mL) at Week 80 through Week 112 (last study visit).

As summarized in Table 1, of those 8 RAL(+OBR)-treated subjects eligible for resistance testing in Cohorts 4 and 5, resistance data from on-treatment virus samples (± pre-treatment isolates) were available for 3 subjects (all in Cohort 4), and only one of those (Subject 8501394) developed genotypic and/or phenotypic resistance to RAL with an IN substitution N155H (6.7-fold reduction) and to at least one ARV in the OBR with an emerging RT substitution M184V (>113- and 1.4-fold reductions in susceptibilities to LAM and DDI, respectively; above the clinical cutoff used in this analysis; Monogram Biosciences, 2011). No treatment-emergent substitutions associated with resistance to RAL and ARVs in their OBR were detected in the post-baseline isolates from the remaining 2 subjects (Subjects 382192 and 8501806; IAS-USA, 2013). Subject 8501806 with transient virologic rebound had baseline HIV-1 variants harboring the M184V RT substitution associated with resistance to LAM and other NRTIs (IAS-USA, 2013), which was persistently detected in the Day-308 isolate. This post-baseline isolate with no additional treatment-emergent RT substitutions had >82-fold reduced susceptibility to LAM and 1.4-fold to DDI (both above the clinical cutoffs for LAM and DDI of 3.5- and 1.3-fold, respectively; Monogram Biosciences, 2011). In Subject 382192, baseline LAM resistance M184V substitution reverted to wild-type (M184) during LAM-containing ART (Table 1; underlined). Consequently, the subject's post-baseline isolate containing a treatment-emergent RT substitution I178M was sensitive to LAM with a 1.4-fold reduction in susceptibility and to the 2 NRTIs (DDI and ZDV) in the OBR (≤1-fold shifts in susceptibility). All 3 subjects had baseline viruses harboring PI resistance-associated substitutions (2 to 5) in the PR protein, including L10V and L63P substitutions associated with LPV/r resistance (IAS-USA, 2013), which were detectable in their post-baseline isolates. No treatment-emergent PR substitutions were observed in 2 subjects (Subjects 382192 and 8501394; Table 1), while a substitution R57K was detectable in the Day 308 isolate from Subject 8501806. All post-baseline isolates with evaluable phenotypic data were sensitive to LPV/r with <2-fold loss of susceptibility (below the clinical cutoffs for LPV and RTV of 10- and 2.5-fold, respectively; Monogram Biosciences, 2011).

Table 1: Resistance Data from 3 Subjects in Cohort 4

Subject ID	HIV-1 subtype	Concomitant ARVs[1] (OBR)	Virus samples isolated for resistance analysis Genotypic changes[2] emerged on treatment and drug susceptibility[3] (fold-change)								
			Day[4]	IN	RAL	RT	ABC	DDI	LAM	ZDV	PR	LPV/r
382192	B	DDI, LAM, ZDV, LPV/r	328	-	-	V184M	-	-	-	-	NONE (M36I, D60E, I62V, I64V, H69K)	-
			426	-	-	I178M, V184M	1.2	1	1.4	0.6	NONE (M36I, D60E, I62V, I64V, H69K)	0.6
8501394	F1	ABC, LAM, ZDV, LPV/r	197	-	-	I142V, M184V	-	-	-	-	NONE (L10V, M36I, L89M)	-
			281	H155[5]	6.7	I142V, R174R/K, M184V	2.8	1.4	>113	0.3	NONE (L10V, M36I, L89M)	1

8501806	B	ABC, DDI, LAM, ZDV, LPV/r	308	NONE[5]	0.9	NONE (M184V)	2.7	1.4	>82	0.3	R57K (D60E, L63P)	1.6

'-', not determined; NONE, no amino acid substitutions detectable emerged while on treatment.

Note 1: Amino acid substitutions underlined indicate that the substitution is associated with drug resistance (IAS-USA, 2013), and was present at Baseline or Screening but became undetectable in samples isolated at on-treatment time points, possibly due to the outgrowth of or reversion to wild-type virus.

Note 2: Amino acid substitutions in parenthesis indicate that the substitution is associated with drug resistance (IAS-USA, 2013), and was present at Baseline or Screening and persistently detectable in on-treatment samples.

[1] Including any ARVs that subject received with RAL.

[2] Amino acid substitutions in the HIV-1 integrase (IN; complete sequence encompassing amino acid 1-288), reverse transcriptase (RT; partial sequence encompassing amino acid 1-305), and protease (PR; complete sequence encompassing amino acid 1-99) proteins emerged in the virus population within samples collected during the on-treatment periods.

- IN substitutions associated with RAL resistance (written in red; Virology reviews N022145.SE7-001 and N022145.734):
  - Primary substitutions: E92Q, F121C, Y143C/H/R, Q148H/K/R, or N155H.
  - Secondary substitutions: L74M, E92Q, Q95K/R, T97A, E138A/K, G140A/S, V151I, G163R, H183P, Y226C/D/F/H, S230R, and D232N.
- RT substitutions associated with resistance to any NRTIs (written in blue; IAS-USA, 2013): M41L, K65R, D67N, K70E/R, L74V, Y115F, M184I/V, L210W, T215F/Y, K219E/Q, TAMs (M41L, D67N, K70R, L210W, T215F/Y, K219E/Q), Q151M complex (Q151M with A62V, V75I, F77L, and F116Y), and T69 insertion complex (a substitution at codon 69 + an insertion of 2 or more amino acids + ≥1 TAMs).
- PR substitutions associated with resistance to LPV/r (written in green) or other PIs (IAS-USA, 2013): L10F/I/R/V/C, V11I, G16E, K20M/R/I/T/V, L24I, D30N, V32I, L33F/I/V, E34Q, M36I/L/V, K43T, M46I/L, I47A/V, G48V, I50V/L, F53L/Y, I54A/L/M/S/T/V, Q58E, D60E, I62V, L63P, I64L/M/V, H69K/R, A71T/V/I/L, G73S/A/C/T, T74P, L76V, V77I, V82A/F/S/T/I/L, N83D, I84V, I85V, N88D/S, L89I/M/V, L90M, and I93L/M (underlined substitutions are associated with LPV/r resistance).

[3] Fold-change in drug susceptibility of on-treatment isolates, compared to wild-type reference HIV-1. The fold-change value above the clinical or biological cutoff for each tested drug (Monogram Biosciences, 2011) is highlighted in green.

[4] Day resistance sample was collected relative to the start of study therapy.

[5] IN genotypic data were obtained only from post-baseline isolates. IN substitutions known to be associated with RAL resistance (see Footnote 2) are listed.

In this submission the applicant also included long-term follow-up data from Cohorts 1 to 3 (2 through 18 years of age, receiving either the chewable or adult tablet formulation). Previously, the applicant submitted resistant data from 31 subjects who had been receiving RAL (+ background ARVs) for up to 160 weeks in these 3 cohorts and were eligible for resistance-testing (Virology review N203045.001). Of these 31 subjects with evaluable data, 14 subjects (45.2%, 14/31) developed genotypic resistance to RAL: 13 subjects had on-treatment HIV-1 variants harboring ≥1 primary RAL resistance-associated substitutions and one subject had those harboring 2 secondary RAL resistance-associated substitutions (in the absence of primary substitutions). Q148H/R was most frequently observed (9 of the 14 subjects). As observed previously, the secondary RAL resistance substitutions were detectable in most of those isolates with emerging primary substitutions (77% [10/13]). All 14 variants were phenotypically resistant to RAL with 1.5- to >169-fold reduced susceptibility (above the biological cutoff for RAL; Fransen *et al.*, 2008). The remaining 17 subjects' on-treatment isolates where RAL resistance-associated IN substitutions were not detectable showed ≤1.2-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.

By the February 7, 2013 data cut-off date for this present submission (up to 240 weeks of treatment), according to the applicant, all subjects (n=126) in these 3 cohorts completed the Week-144 study visit, or, for subjects who discontinued prior to Week 144, had the potential to complete the Week 144 visit. Resistance data were obtained cumulatively from a total of 49 resistance-testing eligible subjects including the 31 subjects previously analyzed. Appendix Table A2-1 lists all 49 subjects and their available genotypic and phenotypic resistance (new data reported only in this submission are shaded green). Overall, 49% (24/49) of those developed RAL resistance (Table 2). As observed in the previous analysis, Q148H/R was most frequently observed (12 [50%] of the 24 subjects), followed by N155H (10 [41.7%] of the 24

subjects). On-treatment HIV-1 isolates from these 24 subjects who developed genotypic resistance to RAL exhibited phenotypical resistance to RAL with 1.5- to >169-fold reduced susceptibility (Table 2; above the biological cutoff for RAL; Fransen *et al*., 2008). Of note, on-treatment isolates collected from subjects (n=25) where RAL resistance-associated IN substitutions were not detectable appeared to remain sensitive to RAL with ≤1.2-fold shift in RAL susceptibility (compared to wild-type reference HIV-1; Table 2).

Table 2: Summary[1] of Long-Term RAL Resistance Analysis of Cohorts 1 to 3

RAL resistance pathway	Number of subjects					RAL susceptibility[3] (fold-change[1])
	Cohort 1	Cohort 2A	Cohort 2B	Cohort 3	Total	
Number of subjects evaluated	28	8	4	9	49	0.6 - >169
• Detectable RAL resistance-associated IN substitutions[2]	8 (28.6%)	5 (62.5%)	3 (75%)	8 (88.9%)	24 (49%)	1.5 - >169
- Primary substitutions						
E92Q	0	0	0	1	1	162
Y143C/H/R	1	1	0	1	3	5.2 - 143
Q148H/R	1	3	2	1	7	1.5 - >169
N155H	1	0	1	2	4	14 - >150
E92Q + N155H mixture	1	0	0	0	1	66
Q148H/R + N155H mixture	2	1	0	1	4	18 - >146
E92Q + Q148 R + N155H mixture	0	0	0	1	1	31
- Secondary substitutions only	2	0	0	1	3	1.6 - 3
• No detectable RAL resistance-associated IN substitutions	20 (71.4%)	3 (37.5%)	1 (25%)	1 (11.1%)	25 (51%)	0.6 - 1.2

[1] Data Source: Individual subjects' resistance data listed in Appendix 2. Table A2-1.
[2] Amino acid substitutions in the HIV-1 integrase (IN; complete sequence encompassing amino acid 1-288) proteins emerged in the virus population within samples collected during the on-treatment periods Virology reviews N022145.SE7-001 and N022145.734):
- Primary substitutions (written in red): E92Q, F121C, Y143C/H/R, Q148H/K/R, or N155H.
- Secondary substitutions (written in blue): L74M, E92Q, Q95K/R, T97A, E138A/K, G140A/S, V151I, G163R, H183P, Y226C/D/F/H, S230R, and D232N.

[3] Fold-change in RAL susceptibility of on-treatment isolates, compared to wild-type reference HIV-1.

The applicant proposed no revisions to be made to the Microbiology section of the label (Section 12.4) with respect to Study P1066. Overall RAL resistance patterns observed in this HIV-1-infected pediatric population are consistent with those observed in the adult population (BENCHMRK and STARTMRK trials; Virology reviews N022145.000 and N022145.735).

1. Recommendations

1.1. Recommendation and Conclusion on Approvability: Approval of this pediatric new drug application for the ISENTRESS® granules for suspension formulation (100 mg/ single-use packet) is recommended with respect to Clinical Virology for the treatment of HIV-1 infection in combination with other antiretroviral agents in children aged from 4

weeks (b) (4).

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

2. Administrative

2.1. Reviewer's Signature(s)

_____

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

2.2. Concurrence

_____

HFD-530/MicroTL/J. O'Rear

CC:
HFD-530/NDA # 205786
HFD-530/Division File
HFD-530/PM/K. Schumann

APPENDICES

Appendix 1: Virological Assays in Clinical Virology

A1.1. Quantification of Plasma HIV-1 RNA Levels

At the beginning of the study plasma HIV-1 RNA levels were quantified by a local CLIA-certified (or equivalent) laboratory using the ultrasensitive processing procedure (LLOQ of 50 copies/mL) of the Roche COBAS AMPLICOR HIV-1 MONITOR™ Test (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. If the local laboratory did not use this method, subject plasma samples was then tested at the (b) (4) In some instances, the (b) (4) internal protocol required reflex testing using the standard processing procedure of the assay, when HIV-1 RNA results using the ultrasensitive assay were beyond an acceptable upper limit (ULOQ of 750,000 copies/mL).

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 $\log_{10}$ 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.

Starting in June, 2010, a plan was instituted through a protocol letter of amendment (Amendment 16, dated June 21, 2010, submitted to IND 77,787) to transition HIV-1 RNA testing to the Abbott RealTime™ HIV-1 assay from the Roche MONITOR Test at a specific study visit. The Abbott RealTime HIV-1 assay received marketing approval from FDA (BP060002) on May 11, 2007 as an *in vitro* RT-PCR assay for the quantification of HIV-1 on the automated m2000™ automated instrument system in human plasma from HIV-1 infected individuals over the range of 40 to 10,000,000 copies/mL.

At the transition visit, two HIV-1 RNA samples were collected, one was to be analyzed by each method. The transition visit was to occur for each cohort at the following time points:

- Cohorts 1 and 2A: Transition at the Week 144 visit
- Cohorts 2B and 3: Transition at the Week 96 visit
- Cohorts 4 and 5: All samples were processed using the Abbott RealTime HIV-1 assay, starting at the screening visit.

An assay sensitivity analysis which includes all subjects in Cohorts 1 to 3 with two different assay test results for the sample collected

at the same time was performed to assess the effect of different assay on the efficacy endpoints (Table A1-1). Overall, the applicant observed a similar number of samples that were measured as below the LLOQ using the Roche MONITOR Test ultrasensitive assay (LLOQ of 50 copies/mL; 51.4% [37/72]) and the Abbott RealTime assay (LLOQ of 40 copies/mL, 55.6% [40/72]). However, the proportion of subjects with HIV-1 RNA <50 copies/mL (efficacy endpoint of the study) was determined, the Abbott RealTime assay yielded a numerically higher rate with 3 additional subjects whose viral loads were measured as between 40 and 50 copies/mL, 59.7% (43/72) versus 51.4% (37/72). However, this observed numeric difference was not statistically significant with a p-value of 0.324 (based on Chi-Square test).

Table A1-1: Assay Sensitivity Analysis of HIV-1 RNA Levels at Transition Visits for Subjects in Cohorts 1 to 3

Parameter	n/N	% (95% CI)
Proportion of samples with HIV RNA <50 copies/mL (Ultra Sensitivity Assay)	37/72	51.4 (39.3, 63.3)
Proportion of samples with HIV RNA <40 copies/mL (Abbott Real Time Assay)	40/72	55.6 (43.4, 67.3)
Proportion of samples with HIV RNA <50 copies/mL (Abbott Real Time Assay)	43/72	59.7 (47.5, 71.1)

n/N = (Number of responders)/(Number of samples).

For all subjects in this study, 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). 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. 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. All available HIV-1 RNA results (excluding those collected after subjects went off study treatment) were used for the efficacy analysis.

A1.2. HIV-1 Resistance Testing

Genotypic and phenotypic testing was performed in this study 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 ((b) (4) while 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.
  - 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 virologic 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 virologic 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.

Appendix 2: Results from Clinical Virology Analyses in Study P1066

Table A2-1: Updated Long-Term Resistance Data for Subjects in Cohorts 1 to 3 Included in RAL Resistance Analysis

Subject ID	Cohort	Final dose population	Virus samples isolated for resistance analysis		
			DAY[1]	Genotypic changes in HIV-1 IN emerged on RAL[2]	RAL susceptibility[3] (fold-change[1])
300348	1	Yes	176	Y143Y/C, S230S/R	5.2 (6)
360799	1	Yes	1025	S90S/P, N155H	nd
			1130	S90S/P, G140G/S, Q148Q/H, N155N/H, I208I/M	88 (99.9)

361701	1	Yes	1150	S206S/T, V260V/I	0.7 (1.2)
380769	1	Yes	160	NONE	1 (0.9)
382147	3	Yes	193	A23A/V[4], V45V/L[4], I63I/L[4], M154M/I[4]	0.9 (0.8)
			868	I60L, **T97A**, I113V	3 (4.1)
400125	1	Yes	565	S17S/G, N120N/D, M275M/T	1 (0.9)
400171	1	Yes	254	K7K/R, C40C/R, I60I/L, E92E/G	0.8 (0.8)
400214	1	Yes	1000	E48E/D, Y/C143Y, R188R/K, I208I/V	1 (0.9)
400333	1	Yes	171	I269R	0.8 (0.9)
			177	A21A/T, H78H/Y, G82G/R, P233P/S, I269R	1 (1)
401051	2A	No	172	**G140G/A**, **Q148Q/R**, **N155N/H**	97 (71.2)
401171	2B	Yes	501	**G140S**, **Q148H**	>169 (>133)
			698	L68L/V, **G140S**, **Q148H**	>142 (>133)
411288	1	Yes	169	NONE	1.2 (0.9)
411290	1	Yes	176	NONE[5]	1 (nd)
411294	1	Yes	176	V72V/I	1.1 (1.3)
470159	2A	No	179 (stage 1)	NONE[5]	0.9 (nd)
470289	1	Yes	174	G82G/R, K211K/Q, E264K, S283S/G	0.9 (0.9)
501124	1	Yes	171	S57S/G, **L74L/M**, (T97A)	1.6 (1.1)
502828	1	No	196	L74L/F, **V151V/I**, **N155H**, I208I/M, **D232D/N**, D253D/N	>150 (>133)
502968	1	Yes	799	I31V, **E92Q**, T112T/K, **N155H**	66 (86.6)
503013	2A	Yes	169	NONE[5]	1 (nd)
503045	1	Yes	291	NONE	0.9 (1.2)
503257	1	Yes	1123	**L74L/M**, K127K/R, **G140G/A/S/T**, **Q148R**	>117 (>184)

503759	2A	Yes	175	Q148Q/R, R228R/G	1.5 (1.4)
503862	2B	No	286 (stage 2)	A21A/T, G140S, Q148H, I154I/L, V165V/I	>145 (>147)
504261	2B	Yes	175	D6D/E[4], K14K/R[4], G59G/E[4], T112T/I[4]	0.9 (0.9)
			644	NONE	0.9 (1.2)
505954	2A	No	813	Q95K, L101L/F, E138K, Q148R, L172L/F, K173K/R, I200I/L, T210T/I, D232D/V, L241L/F, L242L/F	79 (69)
509229	1	Yes	798	S206T	0.8 (0.9)
509862	2A	No	367 (stage 2)	H16H/P[4], G140S, Q148H, V151V/L[4], H171H/L[4]	>145 (>136)
			505 (stage 2)	G140S, Q148H	>135 (>136)
509917	3	Yes	1233	P95S, N155H, E157Q, V265A	34 (80.1)
650061	1	Yes	1464	NONE[5]	0.9 (nd)
650976	2B	Yes	280	Q95Q/R, N155H, T210T/A, D232D/N	24 (25.9)
670119	1	No	561	V31V/I, M154M/I	1 (1)
690747	1	Yes	204	NONE[5]	0.7 (nd)
690786	2A	No	160 (stage 1)	L68I, Y143R, K211K/R[4]	125 (108.3)
			218 (stage 1)	K42K/E, L68I, Y143R, I203I/M, T210T/I	143 (114.3)
720101	1	Yes	310	K136K/T	0.6 (0.8)
720200	1	Yes	477	T112T/I, Q211Q/K, A212A/E	0.8 (0.8)
730158	2A	No	716 (stage 2)	NONE	0.8 (0.9)
801109	3	Yes	169	Q148Q/R[5], N155N/H[5]	18 (nd)
801287	3	Yes	673	NONE	0.8 (1)
801522	3	Yes	169	G140G/A, Q148R	20 (18.2)
			265	E92E/Q, A105A/V, G140G/A, Q148Q/R, N155N/H, G247G/E	31 (35.8)
1220166	3	Yes	776	Y143H	nd

1270500	1	Yes	167	I84I/M[4], D167D/E[4]	0.8 (1.1)
			926	V75V/I, **T97T/A**, E152E/K, **G163G/R**	1.9 (3.1)
8500049	1	Yes	358	**T97T/A**, A112T, **G140G/S**, **N155N/H**, L176V, V281M	61 (81)
			443	**T97T/A**, A112T, **G140G/S**, **Q148Q/H**, **N155N/H**, L176V, V281M	>146 (>180)
8500345	1	Yes	190	NONE	1 (0.9)
8501372	1	Yes	336	D6D/N, R14R/K	0.8 (1)
8501553	1	Yes	917	T125A, V201V/I	0.9 (0.9)
8503076	3	Yes	589	**G140S**, **Q148H**, (V151I), V259V/I	>117 (>158)
8503088	3	Yes	267	**N155H**[5]	14 (nd)
8503090	3	Yes	178	**E92E/Q**[5], **T97A**[5], **V151I**[5], **N155N/H**[4,5]	44 (nd)
			693	**E92Q**[5], **T97A**[5], **V151I**[5]	162 (nd)

nd, not determined; NONE, no amino acid substitutions detectable emerged while on treatment.

Note 1: Amino acid substitutions underlined indicate that the substitution is associated with RAL resistance (listed in Footnote 2), and was present at Baseline (or Screening) but became undetectable in samples isolated at on-treatment time points, poss bly due to the outgrowth of or reversion to wild-type virus.

Note 2: Amino acid substitutions in parenthesis indicate that the substitution is associated with RAL resistance (listed in Footnote 2), and was found in samples isolated at Baseline (or Screening) and persisted during RAL treatment.

[1] Day resistance sample was collected relative to the start of study therapy.

[2] Amino acid substitutions in the HIV-1 integrase (IN; complete sequence encompassing amino acid 1-288) proteins emerged in the virus population within samples collected during the on-treatment periods Virology reviews N022145.SE7-001 and N022145.734):

- Primary substitutions (written in red): E92Q, F121C, Y143C/H/R, Q148H/K/R, or N155H.
- Secondary substitutions (written in blue): L74M, E92Q, Q95K/R, T97A, E138A/K, G140A/S, V151I, G163R, H183P, Y226C/D/F/H, S230R, and D232N.

[3] Fold-change in RAL susceptibility of on-treatment isolates, compared to wild-type reference HIV-1 (compared to their respective pre-treatment isolate). The fold-change values above the biological cutoff for RAL (Fransen *et al*., 2008) are written in purple.

[4] Amino acid substitutions were found in on-treatment samples isolated at earlier time points but became undetectable.

[5] IN genotypic data were obtained only from post-baseline isolates. IN substitutions known to be associated with RAL resistance (see Footnote 2) are listed.

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/s/

SUNG S RHEE
11/07/2013

JULIAN J O REAR
11/07/2013

VIROLOGY FILING CHECKLIST FOR NDA or Supplement

NDA Number: 205-786, SDN 001 **NDA Type:** Original **Stamp Date:** 06/27/2013

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 submitted 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 submitted any required animal model studies necessary for approvability of the product based on the submitted draft labeling?			NA
6	Has the applicant submitted all special/critical studies/data requested by the Division during pre-submission discussions?			NA
7	Has the applicant submitted 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 submitted draft labeling consistent with current regulation, divisional and Center policy, and the design of the development package?	X		
10	Has the applicant submitted 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 07/17/2013

Reviewing Microbiologist Date

Microbiology Team Leader Date

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/s/

SUNG S RHEE
08/02/2013

JULIAN J O REAR
08/02/2013

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 19 July 2013

TO: NDA 205786

FROM: Bryan S. Riley, Ph.D.
Team Leader (Acting)
OPS/New Drug Microbiology Staff

THROUGH: Stephen E. Langille, Ph.D.
Senior Review Microbiologist
OPS/New Drug Microbiology Staff

cc: Katherine Schumann, M.S.
Regulatory Project Manager
OND/DAVP

SUBJECT: Product Quality Microbiology assessment of Microbial Limits for ISENTRESS® [Submission Date: 27 June 2013]

The Microbial Limits specification for ISENTRESS® is acceptable from a Product Quality Microbiology perspective. Therefore, this submission is recommended for approval from the standpoint of product quality microbiology.

ISENTRESS® granules are for suspension and oral administration.

The drug product is tested for Microbial Limits at release using a method consistent with USP Chapter <61> (Microbiological Examination of Non-sterile Products: Microbial Enumeration Tests) and <62> (Microbiological Examination of Non-sterile Products: Tests for Specified Microorganisms). The Microbial Limits acceptance criteria are consistent with USP Chapter <1111> (Microbiological Examination of Non-sterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use).

M E M O R A N D U M

Table 1 –Microbial Limits Specifications

Test	Acceptance Criteria	Test Method
Total Aerobic Microbial Count	NMT (b) (4)	USP <61>
Total Combined Yeast and Mold Count	NMT	USP <61>
E. coli	Absent in (b) (4)	USP <62>

The Microbial Limits test methods were verified to be appropriate for use with the drug product following procedures consistent with those in USP Chapter <61> and <62>.

The drug product will not be tested for Microbial Limits as part of the post-approval stability protocol. The (b) (4) finished drug product is (b) (4), therefore, the drug product is unlikely to support microbial growth during storage.

The drug product is suspended in water and administered orally within 30 minutes.

ADEQUATE

Reviewer Comments – The microbiological quality of the drug product is controlled via a suitable testing protocol. The lack of microbial limit testing on stability is acceptable (b) (4) . Since the drug product is administered immediately after suspension in water, there are no product quality microbiology concerns related to dosage and administration.

END

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/s/

BRYAN S RILEY
07/22/2013

STEPHEN E LANGILLE
07/22/2013