

Canadian Agency for
Drugs and Technologies
in Health



Agence canadienne
des médicaments et des
technologies de la santé

OVERVIEW OF CDR CLINICAL AND PHARMACOECONOMIC REPORTS

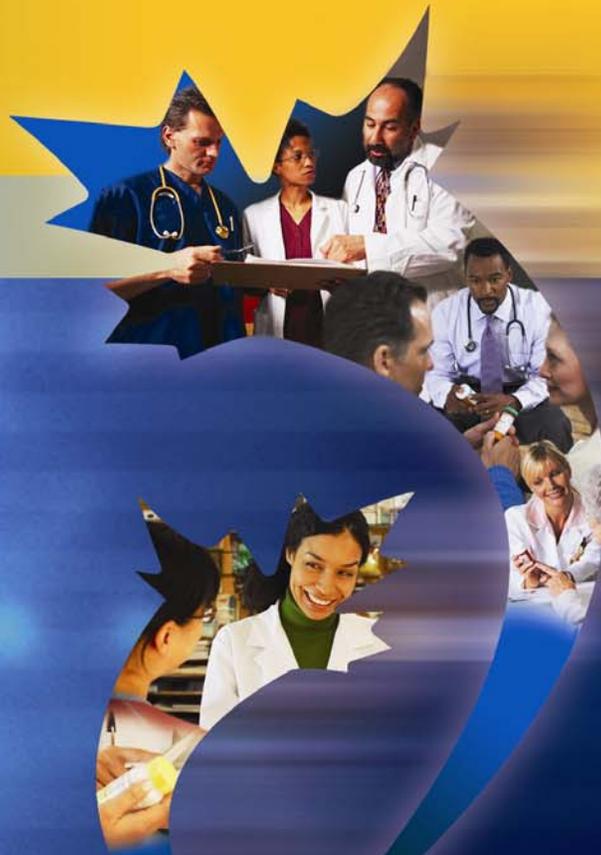
CDR

July 2008

Raltegravir

Isentress™ – Merck Frosst Canada Ltd.

Indication – HIV Infection



Supporting Informed Decisions

À l'appui des décisions éclairées

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Canadian Agency for
Drugs and Technologies
in Health

COMMON DRUG REVIEW

Overview of CDR Clinical and Pharmacoeconomic Reports

Raltegravir

Isentress™ – Merck Frosst Canada Ltd.

Indication – HIV Infection

July 2008

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LIST OF ABBREVIATIONS

AIDS	Acquired Immunodeficiency Syndrome
ADC	AIDS-defining conditions
ART	antiretroviral therapy
DNA	deoxyribonucleic acid
HIV	human immunodeficiency virus
NNT	number needed to treat
OBT	optimized background therapy
QALY	quality-adjusted life year

REVIEW IN BRIEF

Raltegravir (Isentress™) was submitted by the manufacturer to the Common Drug Review (CDR) for consideration for formulary listing by participating public drug plans. This summary is based on the best available clinical and pharmacoeconomic evidence identified and reviewed by CDR, including information submitted by the manufacturer.

CEDAC Recommendation

The Canadian Expert Drug Advisory Committee (CEDAC) recommended that raltegravir be listed for the treatment of HIV infections in patients who are antiretroviral experienced and have virologic failure due to resistance to at least one agent from each of the three major classes of antiretroviral agents, nucleoside/tide reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors and protease inhibitors.

Reasons for the Recommendation

- Raltegravir has been shown to improve virologic and immunologic outcomes in patients who have experienced virologic failure with other antiretroviral therapy.
- Raltegravir is similar or lower in cost compared to other antiretroviral agents currently listed by drug plans for treatment of patients who had experienced virologic failure with other antiretroviral therapy.

Drug

- Raltegravir in combination with other antiretroviral agents is approved by Health Canada for the treatment of HIV-1 infection in treatment-experienced adult patients who have evidence of viral replication and HIV-1 strains resistant to multiple antiretroviral agents.
- Raltegravir has been issued a Notice of Compliance with Conditions (NOC/c) by Health Canada, pending the results of studies to verify its clinical benefit.
- Raltegravir inhibits the catalytic activity of HIV integrase, an HIV-encoded enzyme that is required for viral replication.

Condition

HIV infection is caused by the Human Immunodeficiency Virus (HIV), a retrovirus, and can lead to Acquired Immunodeficiency Syndrome (AIDS).

Clinical Review

- A systematic review (SR) included three double-blind, randomized controlled trials (RCTs) comparing raltegravir with placebo in patients on optimized background therapy (OBT) who had experienced virologic failure with other antiretroviral therapy, and with resistance to at least one drug from each major antiretroviral drug class.
- Two of the three trials were identically designed, 48-week studies in a total of 699 patients, comparing raltegravir plus OBT with placebo plus OBT.
- The third trial in the systematic review was a small phase II trial.

Results

Pooled analysis from the two identically-designed trials reported the following statistically significant differences in favour of raltegravir plus OBT over placebo plus OBT at 16 weeks (treatment effect was maintained at 48 weeks):

- Number of patients with HIV-1 RNA levels <400 copies/mL [number needed to treat (NNT) = 3]
- Number of patients with HIV-1 RNA levels <50 copies/mL (NNT = 4)
- Mean increase in CD4 cell count

Adverse Events

There were no statistically significant differences in the incidence of serious adverse events, withdrawals due to adverse events or drug-related adverse events; however, the extent of exposure to raltegravir is limited to the clinical trial exposure with less than 3 years of follow-up.

Pharmacoeconomic Review

The pharmacoeconomic analysis submitted by the manufacturer was assessed and critiqued.

Highlights

- Raltegravir costs \$27 per day, which is similar to or less than the cost for other antiretroviral agents approved for use in treatment-experienced patients who are not responding to therapy:
 - \$31 per day for darunavir boosted with ritonavir
 - \$40 per day for tipranavir boosted with ritonavir
 - \$81 per day for enfuvirtide.
- The manufacturer's base case analysis, based on a cost utility analysis comparing raltegravir in addition to OBT versus OBT alone in patients with triple class failure with HIV, reported that raltegravir plus OBT is associated with a cost per quality-adjusted life year (QALY) of \$35,800.
- It was felt that the manufacturer's base case analysis did not address the most likely use of raltegravir in clinical practice – i.e., that

raltegravir will likely replace or be used in place of other similar drugs. The manufacturer's secondary analysis, in which raltegravir was substituted for another agent (tenofovir), was considered a more realistic estimate. The manufacturer reported an incremental cost-effectiveness ratio of \$6443 per QALY for raltegravir when replacing tenofovir in a treatment regimen.

What is the CDR?

The CDR conducts objective, rigorous reviews of the clinical and cost-effectiveness of drugs, and provides formulary listing recommendations to the publicly funded drug plans in Canada (except Québec).

OVERVIEW

Context

This document is an overview of two Common Drug Review (CDR) reports: the CDR Clinical Review Report (a systematic review of the clinical evidence) and the CDR Pharmacoeconomic Review Report (a critique of the submitted pharmacoeconomic evaluation). These reports were prepared by the CDR Directorate to support the Canadian Expert Drug Advisory Committee (CEDAC) in making a formulary listing recommendation to participating publicly funded drug plans. The reviews are an assessment of the best available evidence that the CDR Directorate has identified and compiled, including that submitted by the manufacturer.

This Overview Report is based on the Raltegravir CDR Clinical Review Report, 52 pages in length with 24 references, and the Raltegravir CDR Pharmacoeconomic Review Report, 17 pages with 10 references. The manufacturer had the opportunity to provide feedback on each of the full reports and on this Overview Report. The CDR Directorate has considered the feedback in preparing the final versions of all of these reports. The manufacturer's confidential information, as defined in the [CDR Confidentiality Guidelines](#), may have been used in the preparation of these documents and, thus, considered by CEDAC in making its recommendation. The manufacturer has reviewed this document and has not requested the deletion of any confidential information.

Introduction

Raltegravir in combination with other antiretroviral agents is approved by Health Canada for the treatment of HIV-1 infection in treatment-experienced adult patients who have evidence of viral replication and HIV-1 strains resistant to multiple antiretroviral agents. It has been issued a Notice of Compliance with Conditions, pending the results of studies to verify its clinical benefit. The recommended dose for raltegravir is 400 mg orally twice daily, without regard to food.

Raltegravir is the first agent in the integrase inhibitor class of antiretrovirals to receive approval in Canada. It inhibits the catalytic activity of HIV integrase and thus blocks the integration of HIV DNA into host DNA during the early phase of infection, thus preventing HIV replication.

The current standard of care for HIV management is to treat with a combination of antiretroviral agents with the primary goal of achieving and maintaining maximal suppression of viral load (HIV DNA <50 copies/mL), leading to restoration and preservation of immunologic function, and reduction of HIV-related morbidity and mortality.

Currently, available antiretroviral therapy (ART) drugs include: nucleoside/nucleotide reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, protease inhibitors, fusion inhibitors, integrase inhibitors, and CCR5 inhibitors.

Studies of treatment-experienced patients have demonstrated better virologic responses to be associated with lower HIV viral load at the time of treatment change, the use of ritonavir-boosted protease inhibitors in protease inhibitor-experienced patients, and the use of a new class of drugs. In addition to raltegravir, several licensed antiretrovirals are indicated for the treatment of antiretroviral-experienced patients, including tipranavir (Aptivus[®]), darunavir (Prezista[™]), enfuvirtide (Fuzeon[®]), maraviroc (Celsentri[®]), and etravirine (Intelence).

Clinical Review

Objective

To assess the therapeutic advantage of raltegravir (given in combination with other antiretroviral agents) over optimized background therapy (OBT) for the management of HIV-1 infection in treatment-experienced patients with evidence of viral replication and HIV-1 strains resistant to multiple antiretroviral agents.

Methods

For information about the methodology employed in the full CDR Clinical Review of raltegravir, refer to Appendix I.

Selection Criteria

Studies were chosen for inclusion in the review based on the criteria listed in Table 1.

Table 1: Selection Criteria				
Clinical Trial Design	Patient Population	Intervention	Appropriate Comparator*	Outcomes
Published or unpublished DB RCT	Treatment-experienced HIV-1 patients in whom viral replication continues despite ongoing ART	Raltegravir 400 mg twice a day in combination with OBT [†]	OBT [†] with placebo OBT [†] without placebo	<ul style="list-style-type: none"> • Mortality • HIV/AIDS-related mortality and morbidity (ADC, malignancy) • Treatment failure • Time to treatment failure • Emergence of viral resistance • Change in plasma HIV-1 RNA levels • HIV-1 RNA levels <400 copies/mL • HIV-1 RNA levels below level of detection (<50 copies/mL) • Change in CD4 cell counts • Health resource utilization (hospitalizations, ER visits, physician visits, home care requirements) • QoL using any validated scale • SAEs • WDAEs • WDs • AEs (e.g., hypersensitivity reactions, metabolic changes, biochemical changes, other malignancies) • Adherence/Compliance

ADC=AIDS-defining conditions; AEs=adverse events; ART=antiretroviral therapy; DB RCT=double-blind randomized controlled trial; ER=emergency room; OBT=optimized background therapy; QoL=quality of life; SAEs=serious adverse events; WDs=withdrawals; WDAEs=withdrawals due to adverse events.

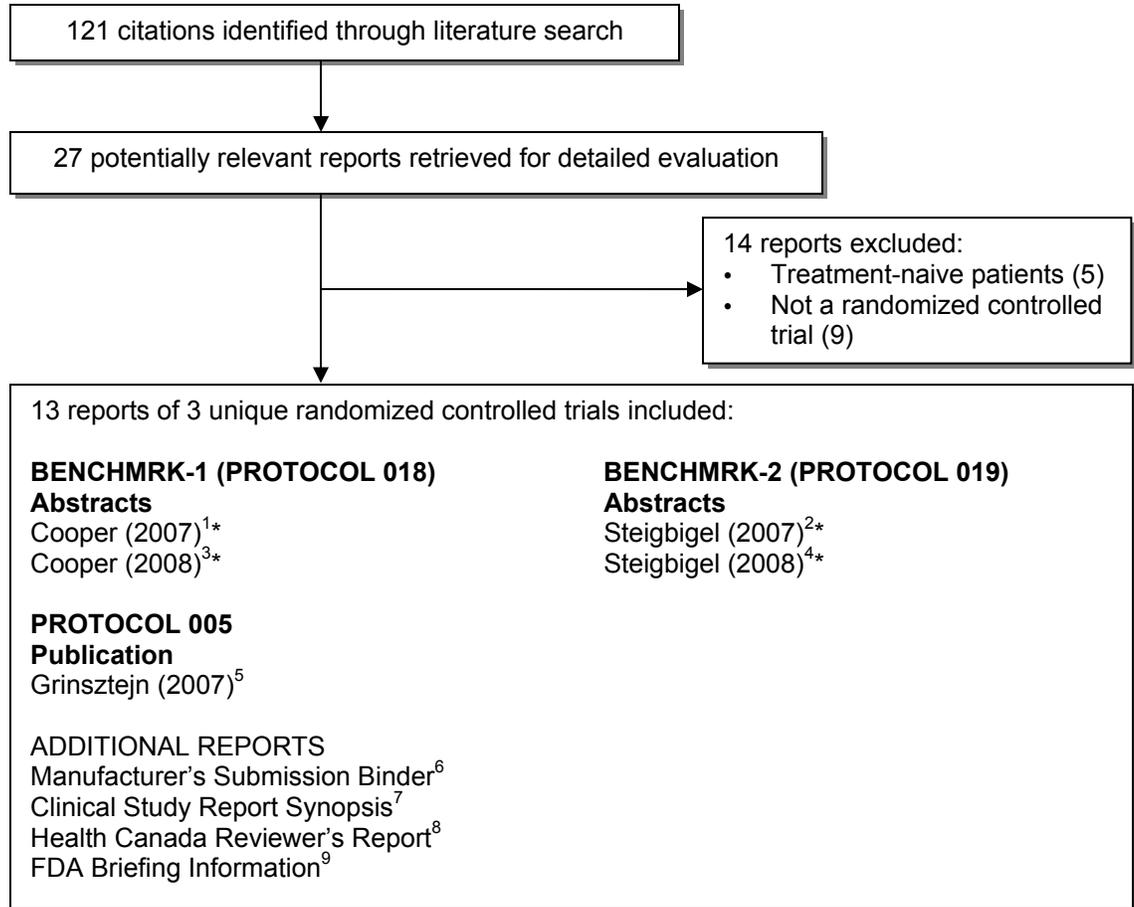
*Standard therapies available in Canada (may include drug- and non-drug interventions).

[†] Multiple ARTs from at least two classes, but preferentially including nucleoside reverse transcriptase inhibitors (NRTIs), protease inhibitors (PIs), and non-nucleoside reverse transcriptase inhibitors (NNRTIs)

Results

Findings from the Literature

Figure 1: QUOROM Flowchart Detailing Flow of Studies



* Additional information provided by manufacturer upon request from CDR.

Summary of Evidence

Included Studies and Trial Characteristics

- Three randomized double-blind trials of raltegravir plus OBT versus placebo plus OBT (Protocol 005, BENCHMRK-1, and BENCHMRK-2) met the inclusion criteria for this systematic review. Data up to 48 weeks was available at the time of this review. Patients included in the trials were those who experienced viral progression despite ongoing optimized ART with at least one drug from each of the three main antiretroviral drug classes.
- In BENCHMRK 1 and 2, enfuvirtide was used in OBT in about 38% of patients, darunavir in about 40% and tipranavir in about 20% of patients; however, these agents were not permitted in Protocol 005.
- Patients were highly treatment-experienced with an average of 10 years of ART history and with prior use of a mean of 12 different ARTs. There were 20% to 25% of patients who had no active drugs in their OBT at baseline.
- Patients were randomized to raltegravir 400 mg twice daily plus OBT (n=462 in BENCHMRK-1 and 2) or placebo plus OBT (n=237 in BENCHMRK-1 and 2).
- Since Protocol 005 was a small phase II, dose finding trial, it was considered as supportive information. The BENCHMRK trials were the focus for this review.

Summary of Results

See Table 2 for a summary of trial outcomes.

Raltegravir 400mg twice daily, when added to OBT, statistically significantly reduced viral load and improved immunologic response in treatment-experienced patients with triple-class failure when compared with placebo plus OBT.

- For BENCHMRK and Protocol 005 trials, at week 16, approximately 77% to 78% of patients receiving raltegravir achieved HIV ribonucleic acid (RNA) suppression below 400 copies/mL compared with 18% to 42% of patients receiving placebo. The NNT was 2 to 3 for achieving HIV RNA <400 copies/mL at weeks 16, 24, and 48.
- By week 16, about 61% to 64% of patients receiving raltegravir achieved HIV RNA levels below detectable limits (<50 copies/mL) compared with 13% to 35% of placebo-treated patients. The NNT was 2 to 4 to achieve HIV RNA levels <50 copies/mL at weeks 16, 24, and 48.
- Virologic failure [defined as non-responders who did not achieve >1.0 log₁₀ reduction in HIV RNA or <400 copies/mL HIV RNA or viral rebound, which was defined as: (a) HIV RNA >400 copies/mL on two consecutive measurements after initial response with HIV RNA <400 copies/mL, or (b) >1.0 log₁₀ increase in HIV RNA above nadir on two consecutive measurements], was less likely to occur in patients treated with raltegravir versus placebo [absolute risk reduction (ARR) 35.4%, NNT= 3 at weeks 16 and 24].
- Change from baseline in HIV RNA levels with raltegravir was approximately 1 to 1.5 log₁₀ copies/mL more than placebo within 16 weeks, and was sustained to 48 weeks.
- By week 16, improvement in CD4 count over baseline was 48 to 80 cells/mm³ greater with raltegravir than with placebo. CD4 counts were also improved at 48 weeks (58 to 93 cells/mm³ greater).
- Death and AIDS-defining conditions (ADC) were not reduced.
- Health resource utilization (hospitalizations, emergency room visits, physician visits, and home care requirements) were not reported in any of the randomized trials.
- Resistance secondary to integrase gene mutations developed in most patients who experienced virologic failure while on raltegravir.

- There were no statistically significant differences between raltegravir and placebo in patients experiencing serious adverse events, adverse events, drug-related adverse events, or withdrawals due to adverse events.
- Most serious adverse events were thought to be related to the underlying disease and did not require discontinuation. Considered individually, the types of serious adverse events did not appear to suggest clinically-significant differences between groups, with the exception of malignancies which were more common in the raltegravir group in early analyses. Ongoing surveillance is planned to monitor the incidence of malignancy with raltegravir versus other ARTs.
- Laboratory adverse events were slightly more common in the raltegravir group, and the most common laboratory adverse events were AST and ALT elevations. However, discontinuations due to laboratory adverse events were rare (0.2% vs 0% for raltegravir versus placebo). Of note, cholesterol and triglycerides were not elevated in the raltegravir group.

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Table 2: Summary of Trial Outcomes

Study Reference	Design	RAL Dose (n)	Week	HIV RNA <400 %	HIV RNA <50 %	Virologic Response [†] %	Δ CD4, cells/mm ³ (from baseline)	Δ RNA 1.0 log ₁₀ (from baseline)	ADC	Death n/N (%)
BENCHMRK-1 and BENCHMRK-2 Pooled[§] (not published) n=699	RCT, DB, PC Phase III 16 weeks (1 [†]) 24 weeks (2 [†]) Ongoing, with extension to 156 weeks (NR)	400 mg b.i.d. (462) + OBT	Week 16 (primary analysis)	RAL 76.8 PBO 41.8 NNT=3*	RAL 61.3 PBO 34.6 NNT=4*	RAL 83.8 PBO 46.0 NNT=3*	RAL 83.9 PBO 35.6 Mean Δ= +48.3*	RAL -1.88 PBO -0.92 Mean Δ= -0.96*	RAL 2.4 PBO 2.1 p=NS	RAL 6/462 (1.3) PBO 3/237 (1.3) p=NS
			Week 24	RAL 75.1 PBO 40.1 NNT=3*	RAL 62.6 PBO 33.8 NNT= 4*	RAL 80.3 PBO 44.3 NNT=3*	RAL 83.7 PBO 36.5 Mean Δ=+47.2*	RAL -1.82 PBO -0.87 Mean Δ= -0.95*	RAL 3.5 PBO 2.5 p=NS	RAL 7/462 (1.5) PBO 3/237 (1.3) p=NS
			Week 48 [§]	RAL 72.3 PBO 37.1 NNT=3*	RAL 62.1 PBO 32.9 NNT=4*	NR	RAL 98 ^{B2} , 120 ^{B1} PBO 40 ^{B2} , 49 ^{B1} Mean Δ= +58 to 71*	RAL -1.7 ^{B1} , -1.8 ^{B2} PBO -0.7 ^{B1} , -0.9 ^{B2} Mean Δ= ~ -1.0*	NR	RAL 10/462 (2.2) PBO 6/237 (2.5) p=NS
Protocol 005[‡] n=178	RCT, DB, PC Phase II 16 weeks, 24 weeks (1 [†]) with extension for an additional 96 weeks (NR)	200 mg b.i.d. (45) 400 mg b.i.d. (45) 600 mg b.i.d. (45) +OBT Note: Only the 400 mg b.i.d. arm is included in the efficacy analysis for this review.	Week 16	RAL 77.8 PBO 17.8 NNT=2*	RAL 64.4 PBO 13.3 NNT=2*	RAL 88.9 PBO 24.4 NNT=2*	RAL 110.3 PBO 29.7 Mean Δ= +80.6*	RAL -2.06 PBO -0.56 Mean Δ= -1.49*	NR	RAL 0 PBO 0
			Week 24 (primary analysis)	RAL 71.1 PBO 15.6 NNT= 2*	RAL 55.6 PBO 13.3 NNT=3*	RAL 80.0 PBO 17.8 NNT=2*	RAL 112.8 PBO 5.4 Mean Δ= +107.4*	RAL -1.87 PBO -0.35 Mean Δ= -1.52*	NR	RAL 0 PBO 0
			Week 48	RAL 64 PBO 13 NNT=2*	RAL 46 PBO 9 NNT=3*	RAL 66 PBO 13 NNT=2*	RAL 110 PBO 17 Mean Δ= +93*	RAL -1.55 PBO -0.28 Mean Δ= -1.27*	NR	NR

(1[†])=primary analysis; (2[†])=secondary analysis; ADC=AIDS-defining conditions; B1=BENCHMRK-1; B2=BENCHMRK-2; b.i.d.=twice daily; DB=double-blind; NNT=number needed to treat; NR=not reported; NS=not significant; OBT=optimized background therapy; PBO=placebo; PC=placebo controlled; RAL=raltegravir; RCT=randomized controlled trial; RNA=ribonucleic acid.

[‡]Patients with >1 log₁₀ drop in HIV RNA or HIV RNA <400 copies/mL; *p<0.001; [§] Week 48 data was obtained from conference abstracts; [†]Since the double-blind period of the study ended after Week 24, the Week 48 data for Protocol 005 includes a combination of double-blind, open label post-virologic failure (for patients who reached the definition of virologic failure during the study), and open-label patients.

Discussion

Quality of Evidence

- Methods of randomization and double-blinding were not described in the included studies. All patients were accounted for, discontinuations were low, and patients were analyzed by intention to treat.
- BENCHMRK-1 and BENCHMRK-2 have not been published, and data for this systematic review came solely from the manufacturer's submission for week 16 to 24 data and from conference abstracts for week 48 data.
- The patients included in the trials appear representative of patients likely to be eligible for raltegravir in Canada: male, Caucasian, middle-aged, with triple-class failure, and many without a single active agent in their ART regimen.
- Background therapy was optimized at the discretion of the physician and was not specifically predetermined by the study protocol. In the BENCHMRK studies, patients were allowed to use newer agents such as tipranavir, darunavir, and enfuvirtide.
- Outcomes were based on primarily surrogate outcomes, such as viral load reduction and immunologic response.
- The relatively small number of patients and relatively short duration of follow-up precludes adequate power to detect significant differences in outcomes that are less common or delayed, including ADCs and death. Conclusions regarding comparative safety are also premature, since detection of uncommon adverse events or events that require prolonged exposure to manifest are not possible until extensive experience with raltegravir has accrued.

Efficacy

Outcomes from Randomized Controlled Trials

- Statistically significant and sustained virologic and immunologic response was found for raltegravir versus placebo in treatment-experienced patients with triple-class failure for whom few alternatives exist.
- Death and ADC were not reduced. However, the trials were not adequately powered to show differences in these endpoints. Furthermore, the allowance for crossover to open-label raltegravir after virologic failure reduced the likelihood that patients would develop ADC before they were switched to open-label raltegravir.
- Quality of life was not reported, and this is a notable omission as quality of life may be adversely affected by pill burden and ART side effects.

Surrogate Outcomes and Clinical Outcomes

- While the evidence of efficacy for raltegravir is based on surrogate outcomes of virologic response, the assumption that improvements in viral load and CD4 counts provided by ART will translate into reduced risk of ADC and improved survival over the long term is widely accepted. However, the extent of proven validity for the surrogates is not without controversy.
- Observational trials have shown that death and ADC have been significantly reduced since the introduction of ART in the 1990s,¹⁰ and this has been supported by meta-analysis of randomized trials that demonstrates significant reduction in death and ADC when ART monotherapy is compared with no therapy and when dual or triple ART is compared to monotherapy¹¹. What remains unclear, is whether further recent advances in highly-active ART result in continued incremental improvements in survival and ADC beyond the original benefit afforded by the initial introduction of ART.¹²

- A recent updated cohort analysis of >20,000 patients showed that, while survival and ADC have been improved in the post-ART era compared to the pre-ART era,¹⁰ further improvements in virologic response with newer agents has not resulted in corresponding further reductions in the rate of ADC or death.¹³

Development of Resistance

- Resistance secondary to integrase gene mutations developed in most patients who experienced virologic failure while on raltegravir. The clinical relevance of these mutations over the short and long term remains to be defined.

Harm

- Initial concern about increased malignancy with raltegravir has been mitigated by appropriate adjustment for time at risk and by continued observation during open-label extensions, which suggest that the rate is not significantly increased over placebo and is not increasing over time. (Appendix II)
- Three cases of Immune Reconstitution Syndrome have been reported to date for raltegravir. Immune Reconstitution Syndrome, which has been associated with a number of ARTs, is thought to be related to rapid viral load reduction and improved CD4 counts. It is a paradoxical deterioration in clinical status (fever, lymphadenopathy/lymphadenitis, other symptoms consistent with infection) that ranges from mild to life-threatening and is thought to be due to improved immune function allowing for an inflammatory response against resident infectious pathogens (mycobacteria, tuberculosis, cytomegalovirus, herpes simplex virus, hepatitis virus, progressive multifocal leukoencephalopathy, and others).
- There are no known clinically relevant drug interactions with raltegravir, and no dosage adjustment is required for hepatic or renal insufficiency.

Issues for Consideration

- There is inadequate clinical trial experience to draw conclusions from subgroup analyses, which precludes identification of patients who will benefit most from raltegravir.
- The optimal sequencing of raltegravir with respect to other newer antiretrovirals remains unclear.
- It is unclear whether raltegravir will replace other agents within current regimens or simply be added to current regimens when patients fail OBT.
- The BENCHMRK-1 and BENCHMRK-2 trials are ongoing, with data from 156 weeks expected in 2010.
- To satisfy the conditions for NOC/c approval, the manufacturer has committed to submit to Health Canada updated safety and efficacy results at 48 weeks for BENCHMRK-1 and BENCHMRK-2 by the 3rd quarter of 2008 and to submit Periodic Safety Update Reports semi-annually. (Appendix III)

Pharmacoeconomic Review

Context

The CDR assesses and critiques the economic evaluation, submitted by the manufacturer, with respect to its quality and validity, including the appropriateness of the methods, assumptions and inputs, and results. The CDR may provide additional information on the cost-effectiveness of the submitted drug, where relevant, from other sources or by using the economic model to consider other scenarios.

Objective of the Manufacturer's Economic Evaluation

The purpose of this study is to describe the cost-effectiveness of using raltegravir in treatment-experienced HIV patients.

Summary of the Pharmacoeconomic Submission

The manufacturer has submitted a cost utility study to evaluate the cost-effectiveness of raltegravir in addition to OBT versus OBT alone in patients with HIV-1 infection who are treatment-experienced. The model is based on the BENCHMRK trials through 24 weeks, after which published data sources are used to derive transition matrices to model the longer term. The model is driven by changes in both viral load and CD4 count, which affects the need for HIV care and patient quality of life. Costs associated with HIV were obtained from the BC Centre of Excellence in HIV/AIDS, and utility values were obtained from the literature. The model is run over the patient's lifetime (50 years), where the costs and clinical benefits are discounted at 3% per annum.

Cost Comparison Tables

The CDR has produced Table 3 and Table 4 to provide a comparison of the cost of treatment of the submitted drug with comparator treatments deemed appropriate by clinical experts. Comparators may reflect recommended or actual practice. Comparators are not restricted to drugs — they may include devices or procedures where appropriate. Costs are manufacturer list prices, unless otherwise specified.

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Table 3: Cost Comparison of Raltegravir versus Non-nucleoside Reverse Transcriptase Inhibitors, Nucleoside Reverse Transcriptase Inhibitors, Combination Drugs, and Other Agents

Drug/Comparator	Strength	Dosage Form	Price (\$)	Average Daily Use	Average Daily Drug Cost (\$)	Frequency of use (per day)	Number of pills (per day)
Raltegravir (Isentress)*	400 mg	Tablet	13.5000	400 mg twice daily	27.00	2	2
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)							
Efavirenz (Sustiva)	50 mg 100 mg 200 mg 600 mg	Capsule Capsule Capsule Tablet	1.1717 2.3430 4.6861 14.0583	200 mg 3 times daily	14.06	3	3
Delavirdine mesylate (Rescriptor)	100 mg	Tablet	0.7178	400 mg 3 times daily	8.61	3	12
Nevirapine (Viramune)	200 mg	Tablet	4.9383	200 mg daily x 14 days, then 200 mg twice daily	4.94, then 9.88	1, then 2	1, then 2
Nucleoside reverse transcriptase inhibitors (NRTIs)							
Emtricitabine and tenofovir (Truvada)	200 mg and 300 mg	Tablet	25.0500	1 tablet daily	25.05	1	1
Abacavir sulfate (Ziagen)	300 mg	Tablet	6.5472	300 mg twice daily	13.09	2	2
Lamivudine (3TC)	150 mg 300 mg	Tablet Tablet	4.6090 9.2181	150 mg twice daily 300 mg once daily	9.22 9.22	2 1	2 1
Zidovudine (AZT) (generic)	100 mg	Capsule	1.3020	200 mg 3 times daily or 300 mg twice daily	7.81	2 or 3	6
Lamivudine and zidovudine (Combivir)	150 mg and 300 mg	Tablet	9.9516	1 tablet twice daily	19.90	2	2
Abacavir and lamivudine (Kivexa)	600 mg and 300 mg	Tablet	21.7260	1 tablet daily	21.73	1	1
abacavir and lamivudine and zidovudine (Trizivir)	300 mg and 150 mg and 300 mg	Tablet	16.4987	1 tablet twice daily	33.00	2	2
Stavudine (Zerit, d4T)	15 mg 20 mg 30 mg 40 mg	Capsule	3.9985 4.1572 4.3370 4.4957	20 mg to 40 mg twice daily	8.00 to 8.99	2	2
Didanosine EC (Videx EC, ddl)	125 mg 200 mg 250 mg 400 mg	EC cap	3.2793 5.2467 6.5583 10.5147	400 mg once daily (or for patients < 60 kg: 250 mg once daily)	10.50 6.56	1	1
Other agents							
Tenofovir (Viread)	300 mg	Tablet	16.2500	1 tablet daily	16.25	1	1
Enfuvirtide (Fuzeon) [†]	108 mg/vial	Injection	40.2600	90 mg s/c twice daily	80.52	2	2

EC cap=enteric coated capsule; s/c=subcutaneous.

Source: Ontario Drug Benefit (February 2008)

*Manufacturer (Merck-Frosst Canada Ltd.) submission binder.

†Saskatchewan Drug Formulary (February 2008).

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Table 4: Cost Comparison of Raltegravir versus Protease Inhibitors

Drug/Comparator	Strength	Dosage Form	Price (\$)	Average Daily Use	Average Daily Drug Cost (\$)	Frequency of use (per day)	Number of pills (per day)
Raltegravir (Isentress)*	400 mg	Tablet	13.5000	400 mg twice daily	27.00	2	2
Protease inhibitors							
Tipranavir (Aptivus) plus ritonavir	250 mg / 100 mg	Capsule Capsule	8.5000 1.4353	500 mg twice daily +200 mg twice daily ritonavir	34.00 39.74**	2	4 8
Darunavir (Prezista) plus ritonavir	300 mg / 100 mg	Tablet Capsule	6.9600 1.4353	600 mg twice daily +100 mg twice daily ritonavir	27.84 30.71**	2	4 6
Fosamprenavir (Telzir) plus ritonavir	700 mg / +100 mg	Tablet Capsule	7.9200 1.4353	700 mg twice daily /1,400 mg daily +ritonavir (200 mg/day)	15.84 18.71**	1 or 2	2 4
Nelfinavir (Viracept)	625 mg 250 mg	Tablet Tablet	4.5500 1.8200	1,250 mg twice daily 750 mg 3 times daily	16.38 to 18.20	2 3	4 9
Atazanavir sulfate (Reyataz) plus ritonavir	200 mg 150 mg +100 mg	Capsule Capsule Capsule	10.1970 10.1623 1.4353	400 mg daily or 300 mg daily +100 mg daily ritonavir	20.39 21.76**	1	2 3
Amprenavir (Agenerase) plus ritonavir	50 mg 150 mg 15 mg/mL +100 mg	Capsule Capsule Oral liquid Capsule	0.6528 1.9584 0.1958 1.4353	1,200 mg twice daily or 600 mg twice daily +100 mg twice daily ritonavir	31.33 18.54**	2	16 10
Lopinavir and ritonavir (Kaletra)	133.3 mg and 33.3 mg 200 mg and 50 mg 80 mg/mL and 20 mg/mL	Capsule Tablet	3.4954 5.2431 2.0973	 400 mg/100 mg twice daily	 20.97	 2	6 4
Ritonavir (Norvir)	80 mg/mL 100 mg	 Capsule	1.1446 1.4353	300 mg twice daily x3 days 400 mg twice daily x4 days 500 mg twice daily x5 days then 600 mg twice daily	 17.22	 2	 12
Saquinavir (Fortovase)	200 mg	Capsule	1.0557	1200 mg 3 times daily	19.00	3	18
Saquinavir (Invirase)	200 mg 500 mg	Capsule Tablet	1.8200 4.2000	600 mg 3 times daily	16.38	3	9
Indinavir (Crixivan)	200 mg 400 mg	Capsule	1.3467 2.6933	800 mg every 8 hours	16.16	3	6 12

Source: Ontario Drug Benefit (February 2008).

*Manufacturer's (Merck-Frosst Canada Ltd.) submission binder.

** combined daily cost of protease inhibitor plus ritonavir

Common Drug Review

Results (as submitted by the manufacturer)

The manufacturer reports that raltegravir plus OBT is associated with an incremental cost per quality-adjusted life year (QALY) of \$35,796 when compared with OBT alone (Table 5).

Table 5: Manufacturer's Base Case Analysis (Canadian\$, 2007)				
Strategy	Undiscounted Months of Life Gained	Quality-Adjusted Life Months (discounted)	Total Cost, \$ (discounted)	Incremental Cost per QALY
Raltegravir+OBT	362.569	209.01	\$899,123	
OBT alone	287.883	167.106	\$774,911	
DIFFERENCE	74.686 months (~6 years)	41.904 months (~3.5 QALY)	\$124,212	\$35,796

OBT=optimized background therapy; QALY=quality-adjusted life year.
Source: Manufacturer's (Merck-Frosst Canada Ltd) submission binder

In the manufacturer secondary analysis, where raltegravir specifically replaces tenofovir, the same clinical benefits were observed at a lower incremental cost for the raltegravir-treated individuals (given that OBT no longer includes the higher treatment costs associated with tenofovir) at \$22,499 for a cost per QALY estimate of \$6,443 (Table 6).

Table 6: Manufacturer's Secondary Analysis Base Case Analysis (Canadian\$, 2007)				
Strategy	Undiscounted months of life gained	Quality adjusted life months (discounted)	Total cost, \$ (discounted)	Incremental cost per QALY
Raltegravir + OBT (excluding patients taking tenofovir/Truvada)	362.569	209.01	\$797,410	
OBT alone	287.883	167.106	\$774,911	
DIFFERENCE	74.868 months (~6 years)	41.904 months (~3.5 QALY)	\$22,499	\$6,443

OBT=optimized background therapy; QALY=quality-adjusted life year.
Source: Manufacturer's (Merck-Frosst Canada Ltd.) submission binder

Pharmacoeconomic Analysis Discussion Points

In reviewing the manufacturer's submission, the reviewers noted the following:

- Length of clinical trials.** The BENCHMRK-1 and BENCHMRK-2 trials form the basis of efficacy estimates used to populate this model. These studies were of short duration, 24 weeks, at the time of model development. Data on 24 weeks is unlikely long enough to discern whether certain patients could develop raltegravir-resistant virus within the first year of treatment; although, based on the CDR clinical review, it appears that the effects on viral load and CD4 counts remain stable through week 48. This, however, remains a theoretical possibility in the absence of longer-term data. It is conceivable that with longer-term and broader use of this drug, a higher failure rate could be experienced. The authors have partially addressed this concern with a sensitivity analysis for drug failure rate up to 16% per year; however, as this is a new class of medication, a potential for a higher failure rate should be considered. More

importantly, efficacy estimates based on two trials are not challenged with sensitivity analysis, which is a major weakness.

- *Modeling beyond 24 weeks.* The manufacturer used the published literature to inform the longer-term model (beyond 24 weeks).¹⁴⁻¹⁶ It is unclear whether the patients in these studies are reflective of the patients in the BENCHMRK trials, as a lower proportion of patients in these studies have a diagnosis of AIDS (compared with 90% of patients in the BENCHMRK trials). Basing the longer-term model on patients with better prognosis may lead to results that are not reflective of the true use of raltegravir – patients will remain in better health states and on treatment medication for a longer period of time.
- *Model validation.* The manufacturer has indicated that the model was validated based on consultation with experts (face validity of assumptions) and by comparing the results of the analyses to other studies and trials (predictive validity). Of note, the studies considered for predictive validity are of 24 and 48 weeks; thus, the long-term predictive ability of the model has not been assessed. The model predicts an incremental benefit of six years of survival (undiscounted) and about 3.5 QALYs (discounted) over a patient's lifetime, based on 24-week data from the BENCHMRK trials. While these benefits may be realized in actual practice, the benefits are greater than reported by other published economic evaluations where treatments are associated with similar improvement in viral load and CD4 counts at 48 weeks. Had virologic failure been considered in the model, greater improvements in survival and QALYs may have been expected based on the results of the BENCHMRK trials. Longer-term data would be required to confirm these purported benefits.
- *OBT used in clinical trials.* OBT is changing constantly with the approval of new ARTs. As no head-to-head randomized controlled trials are available with these novel drugs (e.g., tipranavir, darunavir, maraviroc), and current trials are often performed under different conditions and in heterogeneous patient populations and are typically of a short duration, it becomes increasingly difficult to draw conclusions as to which is the most effective or cost-effective of the new agents.
- *Manufacturer's secondary analysis.* In a secondary analysis conducted by the manufacturer, a scenario is considered in which raltegravir is substituted for tenofovir in OBT. This leads to a cost per QALY of \$6,443. In the highly treatment-experienced patient cohort of the BENCHMRK trial, patients with triple-class failure had virus inactive to tenofovir about 80% of the time. It is possible, but not routine in clinical practice, to withdraw medications from a treatment regimen in this fashion. Consequently, the applicability of this analysis in actual practice may be limited.

Summary of the Clinical and Pharmacoeconomic Reviews

- Highly treatment-experienced HIV patients with triple-class failure receiving raltegravir plus optimized background therapy were significantly more likely to achieve virologic response (NNT=2 to 3 for viral load <50 copies/mL), and were significantly less likely to progress to virologic failure (NNT=2 to 3) than placebo plus OBT at 16 weeks, and this treatment effect was maintained at 48 weeks. In addition, mean change in HIV RNA levels and CD4 cell counts were significantly improved over baseline. Trials were not designed to detect reductions in ADC and all-cause mortality with raltegravir.
- The evidence for the clinical benefit of raltegravir is limited to three randomized trials in 507 raltegravir-treated patients, with outcomes reported up to 48 weeks. The BENCHMRK trials

are ongoing, and 156-week data is anticipated within a few years. Whether the significant virologic and immunologic response provided by raltegravir will translate into measurable impact on risk of ADC or survival is unknown.

- The manufacturer reports that based on their cost utility analysis comparing raltegravir in addition to OBT versus OBT alone in patients with triple-class failure with HIV, raltegravir plus OBT is associated with an incremental cost per QALY of \$35,800. The efficacy estimates used to populate this economic model are limited by the short study duration of the BENCHMRK-1 and BENCHMRK-2 trials. As a result, the model should be revisited once longer-term randomized controlled trial data becomes available.

CEDAC Final Recommendation — Issued May 14, 2008

Following careful consideration and deliberation of the information contained within the CDR Clinical and Pharmacoeconomic Review Reports, CEDAC recommended that raltegravir be listed for the treatment of HIV infections in patients who are antiretroviral experienced and have virologic failure due to resistance to at least one agent from each of the three major classes of antiretroviral agents, nucleoside/tide reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors and protease inhibitors.

APPENDIX I: METHODOLOGY FOR THE FULL CDR CLINICAL REVIEW

Methods

Reviewer Information

- Systematic Review of Clinical Trials and Executive Summary were prepared by two CDR clinical reviewers in consultation with an external clinical expert specializing in infectious diseases, who treats patients with HIV.
- Additional Safety Information was prepared by two CDR clinical reviewers.
- The Supplemental Issues section was prepared by one CDR reviewer.
- Background Information on the Condition was prepared by an external clinical expert specializing in infectious diseases.

Systematic Review Methods

Review Protocol

- The review protocol was developed jointly by the two CDR clinical reviewers and the external clinical expert in consultation with the internal and external pharmacoeconomic reviewers. Members of CEDAC also provided input and comments.

Literature Search Methods

- The literature search was performed by an internal CDR information specialist using a standardized search strategy.
- Published literature was identified by searching the following bibliographic databases: BIOSIS Previews, EMBASE and MEDLINE via Ovid, and The Cochrane Library (2007, Issue 3) via Wiley InterScience.
- Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. The initial search was peer-reviewed by a CADTH information specialist and completed in January 2008. Regular alerts were established to update the search until CEDAC's April 2008 meeting.
- Grey literature was obtained by searching the web sites of regulatory agencies, health technology assessment agencies, near-technology assessment agencies, and clinical trial registries. Google and other Internet search engines were used to search for a variety of web-based information including conference abstracts.
- In addition, the manufacturer of the drug was contacted for information regarding unpublished studies and updates with longer duration of follow-up for identified trials.

Selection of Studies

- Each CDR clinical reviewer independently selected studies for inclusion according to the predetermined selection criteria. All articles considered potentially relevant by at least one reviewer were acquired from library sources. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion.

Selection Criteria

- Studies were chosen for inclusion in the review based on the criteria listed in Table 1, located in the body of this report.

Quality Assessment

- Study bias was critically assessed independently by the two CDR clinical reviewers.

Data Analysis Methods

- Pooled analysis of BENCHMRK-1 and BENCHMRK-2 was preferred over individual analysis of each trial, since these trials were identical in design and did not show heterogeneity in results. Pooled analysis was provided by the manufacturer for most outcomes, and it was unnecessary for CADTH reviewers to perform pooled analyses de novo except in the case of a few outcomes reported only in abstract form for longer-term follow-up (48-week data from a Conference on Retroviruses and Opportunistic Infections presentation).^{3,4}
- CDR reviewers calculated the NNT for discrete outcomes that reached statistical significance. GraphPad was used to calculate NNT and 95% confidence interval.

Methods for Supplemental Issues

In addition to the systematic review, a number of supplemental issues were extensively considered and reported within an 11-page supplemental issue section.

Issues included:

- Special populations: sub-analyses by prognostic factors and demographics
- Supplemental trial information: treatment-naive patients
- Additional harms information
- Drug interactions
- Virologic failures and resistance
- Further research commitments.

APPENDIX II: ADDITIONAL HARMS INFORMATION

Malignancy

Malignancy Cases during Double Blind Phase

For a comprehensive assessment of malignancy, the manufacturer's submission included an analysis of all double blind data from Phase II and III studies (Protocol 004, Protocol 005, BENCHMRK-1 and 2), as shown in Table 7. There were 13 cases in the raltegravir group versus 1 case in the control group. However, when the incidence was adjusted for time at risk, the rate was higher in the raltegravir group, but did not reach statistical significance (2.09/100 PYR versus 0.49 cases/100 PYR for raltegravir versus control, respectively; RR = 4.26, 95%CI 0.64-180).

Table 7: Cancer-Related Events throughout Double-Blind Period in all Clinical Trials ⁶							
	Raltegravir			Placebo or Efavirenz			Relative Risk [95%CI]
	N	Cases/PYR	Rate	N	Cases/PYR	Rate	
Protocol 004	163	1/228	0.44	41	1/53	1.88	4.26 (0.64, 180)
Protocol 005	133	0/100	0	45	0/23	0	
BENCHMRK-1	232	6/150	4.00	118	0/63	0	
BENCHMRK-2	230	6/145	4.15	119	0/64	0	
Total	758	13/623	2.09	323	1/204	0.490	

CI=confidence interval; N=number; PYR=patient-years at risk; Rate=events per 100 person-years at risk

Malignancy Cases during Cumulative Follow-Up

When all of the data is considered from the cumulative follow-up period provided in the manufacturer's submission (including the open-label follow-up after completion of the double-blind phase), there were 20 malignancies reported in 19 patients treated with raltegravir, and 1 patient with 1 malignancy in the efavirenz group of Protocol 004. No cancers occurred in the placebo group. The 20 malignancies included: 3 Kaposi's sarcoma, 6 lymphomas (2 Hodgkins' disease, 4 non-Hodgkin's lymphoma), 4 squamous cell carcinoma (cutaneous), 3 squamous cell carcinoma in situ (anorectal), 1 anal cancer (unspecified), 1 basal cell carcinoma, 1 hepatocellular carcinoma, and 1 rectal adenocarcinoma. The overall rate of malignancy during this extended follow-up period was 2.12 cases/100 patient-years, which is similar to the overall rate found during the double-blind phase of the studies.

None of the neoplasms was considered to be drug-related as most of them were detected within three months of enrolment and were common to the HIV/AIDS population (lymphoma, Kaposi's sarcoma, anal cancer related to human papillomavirus) or had other likely etiologies (chronic hepatitis B and hepatic neoplasm; tobacco history and squamous cell carcinoma of the vocal cord), and 7 were recurrent cancers.

Lipidemia, Lipodystrophy, Lipoatrophy

Data from Protocol 005 and BENCHMRK 1 and 2 over a period of 48 weeks of raltegravir compared with placebo⁶ showed a low frequency of lipodystrophy or lipoatrophy (<1%) in both treatment groups during the double-blind phase of the studies, and 1.4% (7/507 patients) during the cumulative period of follow-up including the open-label phase of the studies.

Hyperglycemia

Data from Protocol 005 and BENCHMRK 1 and 2 reported hyperglycemia in 0.2% of patients during the double-blind phase and in 0.4% (2/507) of patients treated with raltegravir during the cumulative period of double-blind and open-label follow-up. Diabetes mellitus was reported in 1.0% of patients (5/507) during the cumulative period of double-blind and open-label follow-up.⁶

Immune Reactions

Occurrence of rash was slightly higher in the raltegravir group compared with placebo, but most rashes were mild to moderate in intensity and none were serious or led to discontinuation. Coadministration of darunavir did not increase the frequency of rash. Hypersensitivity reactions were rare, and similarly distributed between raltegravir and placebo groups.

During the cumulative period of follow-up, there have been 3 reported cases of Immune Reconstitution Syndrome (IRS) with raltegravir.⁶ Immune Reconstitution Syndrome is an adverse consequence of restoration of pathogen specific immune responses, and is thought to be related to more rapid reduction in viral replication and increases in CD4 cells due to more potent ARTs.¹⁷

APPENDIX III: FURTHER RESEARCH COMMITMENTS^{6,9}

At least nine trials are ongoing or planned by the manufacturer, as outlined in Table 8.

Table 8: Planned/Ongoing Studies of Raltegravir				
Protocol	Type	Population	Raltegravir Exposure	Description
005, BENCHMRK-1 and 2 (ongoing)	C	Adult, treatment-experienced	1,382 person-years	Ongoing double-blind phase of original randomized trials of raltegravir plus OBT versus placebo plus OBT, or open-label extension with raltegravir treatment for all patients who have completed the double-blind phase or were switched to open-label RAL after experiencing virologic failure
023 (ongoing)	NC	Adult, treatment-experienced	>2,000 patients	Early access study of raltegravir plus OBT in highly treatment-experienced patients with few options
004, 021 (ongoing) 032, 033 (planned)	C	Adult, treatment naive Adult, treatment experienced	1,210 person-years	004 and 021 are double-blind ongoing trials (96-144 weeks) 032 and 033 are planned randomized, double-blind trials to evaluate the safety and efficacy of raltegravir versus Kaletra in HIV-infected patients switched from a stable Kaletra-based regimen for 48 weeks
022	NC	Pediatric, treatment-experienced	120 person-years	Planned trial of raltegravir added to initial stable background therapy in treatment-experienced children

C=comparative; NC=non-comparative; OBT=optimized background therapy.

In addition, pharmacovigilance activities are planned, including routine Periodic Safety Updates during the postmarket experience, and a large, active post-licensure observational prospective cohort safety surveillance database is planned by the manufacturer to monitor malignancies and other safety issues with the following objectives:

- Assess incidence of medical outcomes of interest in HIV-infected patients treated with raltegravir in routine post-licensure use;
- For comparison, describe background incidence rates of these medical outcomes in two control cohorts: (a) a pre-licensure historical control cohort of treatment-experience HIV-infected patients who would have been eligible to receive raltegravir had it been available, (b) a post-licensure concurrent control cohort of treatment-experienced HIV-infected patients not treated with raltegravir.

The manufacturer is currently exploring the feasibility of such active observational surveillance in large medical insurance databases and cohorts in order to establish a study population of treatment-experienced patients who can be followed after raltegravir licensure. Active surveillance is proposed for three years post-licensure and until >100 person-years of raltegravir exposure to allow for adequate power to detect clinically relevant medical outcomes, such as ADC.

The manufacturer will also participate in the Antiretroviral Pregnancy Registry, which is an international collaborative project to monitor reported exposures to ARTs during pregnancy and association with birth defects and pregnancy outcomes.

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