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# 48-Week Results from BENCHMRK-1, a Phase III Study of Raltegravir (RAL) in Patients Failing Antiretroviral Therapy (ART) with Triple-Class Resistant HIV-1

D.A. Cooper[1], J. Gatell[2], J. Rockstroh[3], C. Katlama[4], P. Yeni[5], A. Lazzarin[6], X. Xu[7], R. Isaacs[7], H. Teppler[7], B-Y. Nguyen[7] for the BENCHMRK-1 Study Group

[1]University of New South Wales, Sydney, Australia; [2]University of Barcelona, Spain; [3]University of Bonn, Germany; [4]Hospital Pitié Salpêtrière, Paris, France; [5]Hospital Bichat-Claude Bernard, Paris, France; [6]San Raffaele Scientific Institute, Milan, Italy; [7]Merck Research Laboratories, PA, USA

David A. Cooper, MD, D.Sc.
National Center for HIV Epidemiology and Clinical Research
University of New South Wales
Sydney NSW 2010, Australia
d.cooper@nchecr.unsw.edu.au
phone: +61 2 9385 0900
fax: +61 2 9385 0930

## Abstract

**Background:** In 3 studies of HIV-infected patients (pts) with limited treatment options, RAL with optimized background therapy (OBT) was generally well tolerated and provided superior viral suppression for ≥24 weeks compared to OBT alone. These are the follow-up 48-week results from BENCHMRK-1 (Protocol 018), an ongoing multi-center, double-blind Phase III study conducted in Europe, Asia/Pacific, and Peru.

**Methods:** Pts failing ART with triple-class resistant HIV-1 were randomized 2:1 to oral BID raltegravir (RAL) 400 mg or placebo (PBO), both in combination with OBT. Pre-specified efficacy endpoints included % of pts with vRNA levels <400 and <50 copies/mL, and the mean change from baseline in CD4 cell counts.

**Results:** Of 352 pts randomized, 350 received ≥ 1 dose of study drug. Baseline characteristics were comparable between the RAL and PBO groups. At baseline, median CD4 counts were 140 and 105 cells/$mm^3$, and geometric mean viral loads were 4.6 and 4.5 $log_{10}$ copies/mL in the RAL and PBO groups, respectively. OBT contained < 1 active drug (genotypic sensitivity score of 0) in 30% and 29% of pts in the RAL and PBO groups, respectively. Pre-planned 48-week efficacy analyses are shown below, along with the 24-week results:

| | % pts (95% CI) with HIV RNA <400 copies/mL‡ | | % pts (95% CI) with HIV RNA <50 copies/mL‡ | | Change from baseline in CD4 count¶ (cells/mm³) | |
|---|---|---|---|---|---|---|
| | Week 24 | Week 48 | Week 24 | Week 48 | Week 24 | Week 48 |
| RAL§ (N=232) | 75 (69, 81) | 74 (67, 79) | 60 (54, 67) | 65 (58, 71) | 87 (74, 99) | 120 (102, 138) |
| PBO§ (N=118) | 39 (30, 48) | 36 (28, 46) | 33 (25, 42) | 31 (23, 41) | 35 (23, 48) | 49 (30, 69) |
| RAL - PBO† | 36 (26, 46)* | 37 (26, 47)* | 27 (16, 37)* | 33 (22, 43)* | 52 (34, 69)* | 71 (45, 97)* |

§RAL and PBO were given with OBT
† Difference between RAL and PBO; a positive value favors RAL over PBO
‡ Non-Completer=Failure
¶ Baseline values carried forward for virologic failures
*Nominal P<0.001

RAL was generally well tolerated over 48 weeks.

**Conclusions:** In this pivotal study of pts failing ART with triple-class resistant HIV, RAL plus OBT demonstrated superior antiretroviral and immunological responses compared to OBT alone, that were sustained out to 48 weeks.

## Background

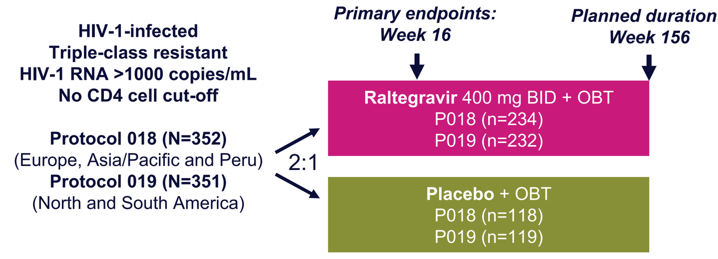
Raltegravir (MK-0518, ISENTRESS™) is an HIV-1 integrase strand-transfer inhibitor (InSTI) with

- Potent *in vitro* activity:
  - $IC_{95}$ = 31 nM ± 20 nM (50% human serum)
  - Active against multi-drug resistant HIV-1, CCR5 and CXCR4 tropic HIV-1
  - HIV resistant to raltegravir remains sensitive to other ARTs
  - Additive/synergistic with NRTIs, NNRTIs, PIs, and enfuvirtide
- Clinical efficacy when used in combination with OBT:
  - in ART-naive patients, 83 – 88% had HIV RNA < 50 copies/mL at Week 48 (Markowitz et al, JAIDS 2007; 46:125-33)
  - In patients failing therapy with triple class resistant virus:
    - 56 – 67% had HIV RNA < 50 copies/mL at Week 24 in the phase II dose-ranging study (Grinsztejn et al, LANCET 2007; 369:1261–69)
    - 63% had HIV RNA < 50 copies/mL at Week 24 in the phase III BENCHMRK-1 and 2 studies combined (Kumar et al, EACS Oct 2007)

## Methods

### BENCHMRK-1 and -2 Study Design

- Randomized, double-blind, placebo-controlled with Data and Safety Monitoring Board
- Primary analysis at Week 16; secondary analysis at Week 48




- OBT selected by investigator based on baseline resistance testing and prior treatment history. Selected investigational antiretrovirals, darunavir and tipranavir, were permitted.

### Statistical Analysis

- The durability of antiretroviral and immunological activity was assessed by the following predefined endpoints measured at Week 48: HIV RNA <50 copies/mL, HIV RNA <400 copies/mL, change from baseline in plasma HIV RNA ($log_{10}$ copies/mL), and change from baseline in CD4 cell count (cells/$mm^3$).
- For binary endpoints (proportions) over time analysis, Non-Completer = Failure (NC=F) is applied for missing data approach.
- For change from baseline in $log_{10}$ HIV RNA and change from baseline in CD4 cell counts, Observed Failure (OF) approach assumes baseline value was carried forward for virologic failures.
- Data from BENCHMRK-1 & 2 were combined for additional analyses:
  - Efficacy by subgroups — OF approach (virologic failure carried forward) used for missing data.
  - Cancer events — time adjusted analysis based on all treated patients as they were originally randomized.

## Results

### Table 1. Patient Disposition

| | Raltegravir + OBT N | (%) | Placebo + OBT N | (%) |
|---|---|---|---|---|
| Randomized | 234 | | 118 | |
| Treated | 232 | (99) | 118 | (100) |
| Continuing in Double-Blind phase | 193 | (83) | 50 | (42) |
| Entered Open-Label post VF* phase | 33 | (14) | 60 | (51) |
| Discontinued study | 6 | (3) | 8 | (7) |
| Discontinued due to adverse event | 4 | (2) | 4 | (3) |

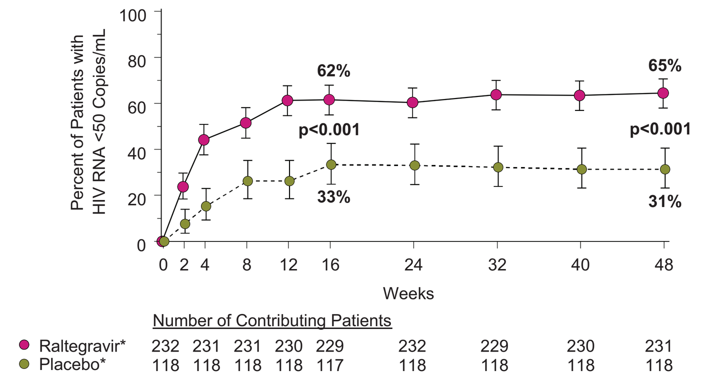
* Definition of virologic failure:
1) <1 $log_{10}$ ↓ HIV RNA from baseline and HIV RNA >400 copies/mL at wk 16, OR
2) virologic relapse: >1 $log_{10}$ ↑ HIV RNA above nadir or >400 copies/mL from nadir after response <400 copies/mL (on 2 consecutive measurements at least 1 week apart).

### Table 2. Patient Characteristics

| | Raltegravir + OBT N = 232 | Placebo + OBT N = 118 |
|---|---|---|
| Mean Age, yrs (SD) | 46 (9) | 44 (8) |
| % Male | 84 | 87 |
| % Caucasian | 75 | 81 |
| Median CD4 Count, cells/mm³ | 140 | 105 |
| GM Viral Load, copies/mL ($log_{10}$ HIV RNA) | 40519 (4.6) | 31828 (4.5) |
| % with AIDS | 94 | 89 |
| Median yrs of prior ARTs (Mean # ART) | 11 (12) | 10 (12) |
| % Hepatitis B+ / % Hepatitis C+ / both | 6 / 13 / 2 | 3 / 19 / 2 |
| % GSS† 0 / 1 | 30 / 33 | 29 / 41 |
| % PSS† 0 / 1 | 19 / 29 | 18 / 33 |
| % new enfuvirtide in OBT | 21 | 20 |
| % new darunavir in OBT | 27 | 25 |

† GSS/PSS = total ART in OBT to which patient's virus showed geno/phenotypic sensitivity by Phenosense GT assay. Enfuvirtide and darunavir use in naïve patients were each counted at +1 active agent and added to GSS/PSS.

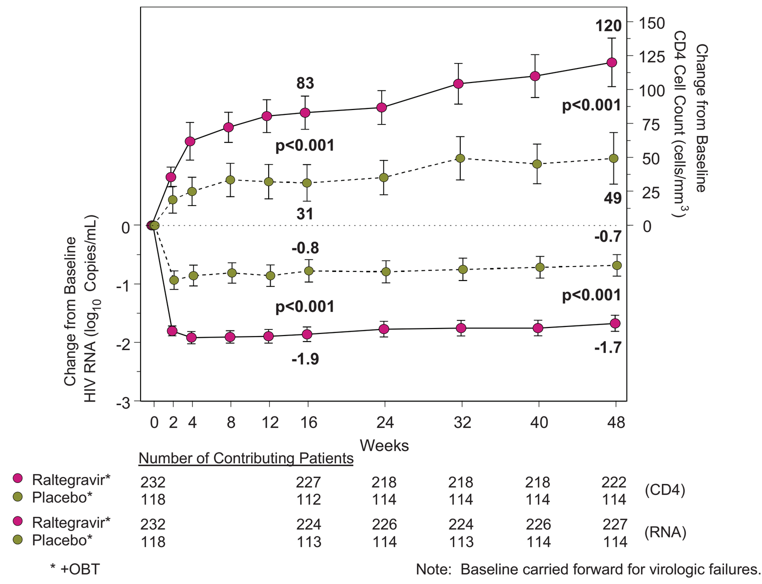
### Figure 1. Percent of Patients Achieving HIV RNA <50 Copies/mL (95% CI) (BENCHMRK-1, Non-Completer=Failure Approach)




* + OBT; p-value derived from logistic regression model adjusted for baseline HIV RNA level ($log_{10}$), first enfuvirtide use in OBT, first darunavir use in OBT, and active PI in OBT.

At week 48, HIV RNA <400 copies/mL was achieved in 74% of the raltegravir group vs 36% of the placebo group (p<0.001).

### Figure 2. Change From Baseline in CD4 Cell Count (cells/mm³) and $Log_{10}$ HIV RNA (BENCHMRK-1, Observed Failure Approach)




For change from baseline in CD4 cell counts, p-value was derived from a mixed-effects model adjusted for baseline CD4 cell count, stratum, treatment, visit, interactions between visit and previous variables. For change from baseline in $log_{10}$ HIV RNA level, p-value was derived from a parametric regression model adjusted for baseline HIV RNA level($log_{10}$), first enfuvirtide use in OBT, first darunavir use in OBT and active PI in OBT.

### Table 3. Number (%) of Patients Treated with Raltegravir with Virologic Failure† by Week 48 with HIV Integrase Mutations at Amino Acids 148 and/or 155 (BENCHMRK-1)

| | Virologic Failure§ (n=50) Patients with Baseline and Follow-up sequence¥ (n=49) |
|---|---|
| With Mutation at Amino Acid 148 or 155 | 28 (57) |
| With Mutation at Amino Acid 148 | 13 (27) |
| With Mutation Q148H | 9 (18) |
| With Mutation Q148K | 3 (6) |
| With Mutation Q148R | 6 (12) |
| With Mutation at Amino Acid 155 | 19 (39) |
| With No Mutation at either 148 or 155 | 21 (43) |
| With Other Known RAL Resistance Mutations‡ | 5 (10) |
| With Changes from Baseline, Unknown Phenotype†† | 7 (14) |
| With No Significant AA Changes from Baseline‡‡ | 9 (18) |

Virologic failure is generally associated with mutations at one of two primary residues, Q148 or N155, in combination with at least one other mutation.

† Virologic failure with integrase tests.
§ Includes only patients with virologic failure (as defined in Table 1) for whom integrase genotypic data were available.
¥ 1 patient with only baseline sequence available
‡ Included 4 patients with Y143C/R/H + a secondary mutation, 1 patient with E92E/Q, I203M, and one patient with L74M, E92Q
†† Included 3 patients with a single amino acid change of I203M, 3 patients with a single polymorphic change from baseline at S230N, and 1 patient with multiple changes (S24N, M50I, L68E, G70D, L234I).
‡‡ Included 3 patients with a polymorphic change from baseline (S230N) that does not confer resistance.

### Table 4. Summary of Clinical Adverse Events (AEs) in BENCHMRK-1

| | Raltegravir + OBT (N=232) | Placebo + OBT (N=118) | Difference from Placebo† % (95% CI) | p-Value |
|---|---|---|---|---|
| Mean follow-up (weeks) | 54.5 | 38.6 | | |
| % patients with: | | | | |
| Any AE | 90.9 | 84.7 | 6.20 (-0.7, 14.4) | 0.105 |
| Drug-related‡ AE | 48.7 | 54.2 | -5.53 (-16.4, 5.6) | 0.366 |
| Serious AE | 19.8 | 17.8 | 2.03 (-7.1, 10.2) | 0.774 |
| Serious drug-related AE | 3.0 | 0.8 | 2.17 (-1.8, 5.4) | 0.275 |
| Death | 1.3 | 2.5 | -1.25 (-6.0, 1.7) | 0.409 |
| Discontinued due to AE | 1.7 | 3.4 | -1.67 (-6.8, 1.6) | nps§ |

† Tests of significance were performed on the percentage of patients with at least one adverse event in the category. The 95% CIs were calculated using Miettinen and Nurminen's method. p-Values were generated using the Fisher exact test.
‡ Determined by the investigator to be possibly, probably, or definitely drug related.
§ nps=not pre-specified for statistical analysis.

### Table 5. Percent of Patients with Drug Related‡ Clinical Adverse Events (≥ 2%, any intensity, BENCHMRK-1)

| | Raltegravir + OBT (N = 232) | Placebo + OBT (N = 118) |
|---|---|---|
| Mean follow-up (weeks) | 54.5 | 38.6 |
| % patients with: | | |
| Abdominal Distension | 0.4 | 3.4 |
| Abdominal Pain | 1.3 | 3.4 |
| Diarrhea | 6.9 | 14.4 |
| Nausea | 3.9 | 6.8 |
| Vomiting | 2.6 | 7.6 |
| Fatigue | 2.2 | 0 |
| Injection Site Nodule | 0.4 | 2.5 |
| Injection Site Pain | 2.6 | 1.7 |
| Injection Site Reaction | 7.3 | 11.9 |
| Arthralgia | 2.2 | 0 |
| Headache | 3.0 | 6.8 |
| Insomnia | 1.7 | 3.4 |
| Lipodystrophy Acquired | 1.7 | 3.4 |
| Pruritus | 2.2 | 0 |
| Subcutaneous Nodule | 1.7 | 2.5 |

‡ Determined by the investigator to be possibly, probably, or definitely related to any drug in the treatment regimen.

### Table 6. Percent of Patients with Grade 3 or 4 Laboratory Abnormalities (BENCHMRK-1)

| Laboratory Test (Unit) | Toxicity Criteria* | | Raltegravir (N=232) | Placebo (N=118) |
|---|---|---|---|---|
| ANC (10³/µL) | Grade 3 | 0.50 - 0.749 | 2.6 | 2.5 |
| | Grade 4 | <0.50 | 0.9 | 0 |
| Hemoglobin (gm/dL) | Grade 3 | 6.5 - 7.4 | 1.3 | 0.8 |
| | Grade 4 | < 6.5 | 0.4 | 0 |
| Platelet count (10³/µL) | Grade 3 | 25 - 49.999 | 0.9 | 0.8 |
| | Grade 4 | <25 | 1.7 | 0.8 |
| Fasting LDL-C (mg/dL) | Grade 3 | ≥190 | 7.8 | 6.4 |
| Fasting cholesterol (mg/dL) | Grade 3 | >300 | 11.6 | 4.2 |
| Fasting triglyceride (mg/dL) | Grade 3 | 751 - 1200 | 4.3 | 1.7 |
| | Grade 4 | >1200 | 3.0 | 0.8 |
| Fasting glucose (mg/dL) | Grade 3 | 251 - 500 | 1.7 | 1.7 |
| | Grade 4 | >500 | 0 | 0 |
| Total bilirubin (mg/dL) | Grade 3 | 2.6 - 5.0 x ULN | 2.6 | 0.8 |
| | Grade 4 | >5.0 x ULN | 1.7 | 0 |
| Serum creatinine (mg/dL) | Grade 3 | 1.9 - 3.4 x ULN | 0 | 0 |
| | Grade 4 | ≥3.5 x ULN | 0 | 0 |
| AST (IU/L) | Grade 3 | 5.1 - 10.0 x ULN | 2.6 | 2.5 |
| | Grade 4 | >10.0 x ULN | 0.4 | 0.8 |
| ALT (IU/L) | Grade 3 | 5.1 - 10.0 x ULN | 5.2 | 2.5 |
| | Grade 4 | >10.0 x ULN | 1.3 | 1.7 |
| Alkaline phosphatase (IU/L) | Grade 3 | 5.1 - 10.0 x ULN | 0.4 | 1.7 |
| | Grade 4 | >10.0 x ULN | 1.3 | 0.8 |
| Pancreatic amylase (IU/L)§ | Grade 3 | 2.1 - 5.0 x ULN | 3.9 | 2.5 |
| | Grade 4 | >5.0 x ULN | 0 | 0 |
| Lipase (IU/L) | Grade 3 | 3.1 - 5.0 x ULN | 1.7 | 0.8 |
| | Grade 4 | >5.0 x ULN | 0 | 0 |
| Creatine kinase (IU/L) | Grade 3 | 10.0 - 19.9 x ULN | 3.4 | 2.5 |
| | Grade 4 | ≥20.0 x ULN | 1.3 | 0 |

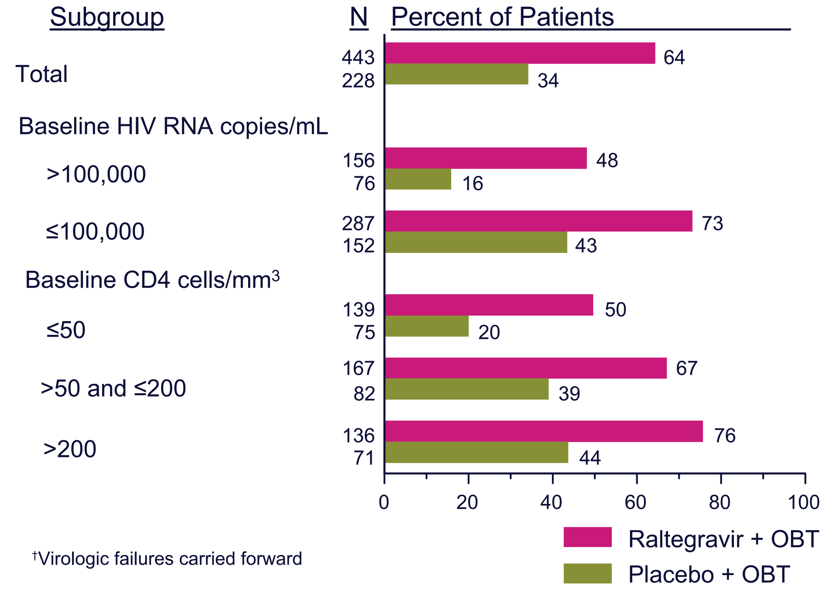
*Grades 3 and 4 per DAIDS toxicity criteria.
§ Defined as (number of patients meeting the specific serum pancreatic amylase criteria) / (number of patients with serum amylase test result).

## Combined Analyses

- Data from BENCHMRK-1 & -2 combined
- Also displayed in poster #789 (BENCHMRK-2)

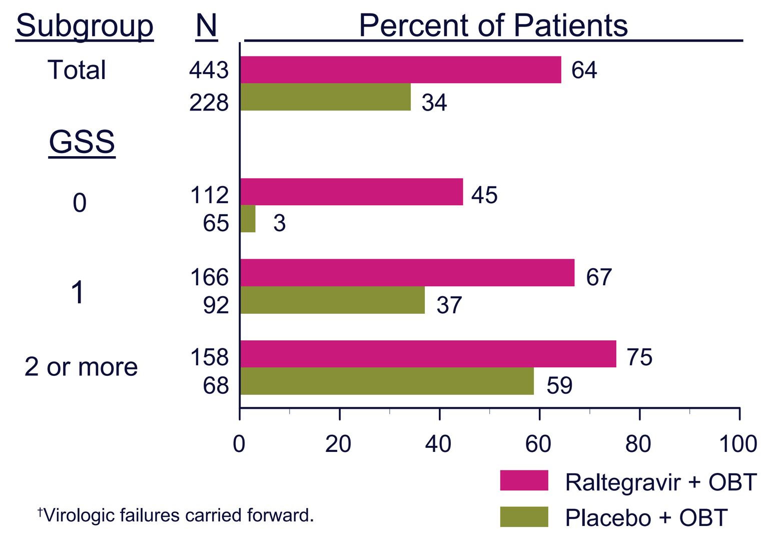
### Efficacy by Subgroups

### Figure 3. BENCHMRK-1 & -2 Combined Efficacy† Percent of Patients with HIV RNA <50 copies/mL at Week 48 by Baseline HIV RNA and CD4 Cell Count




†Virologic failures carried forward

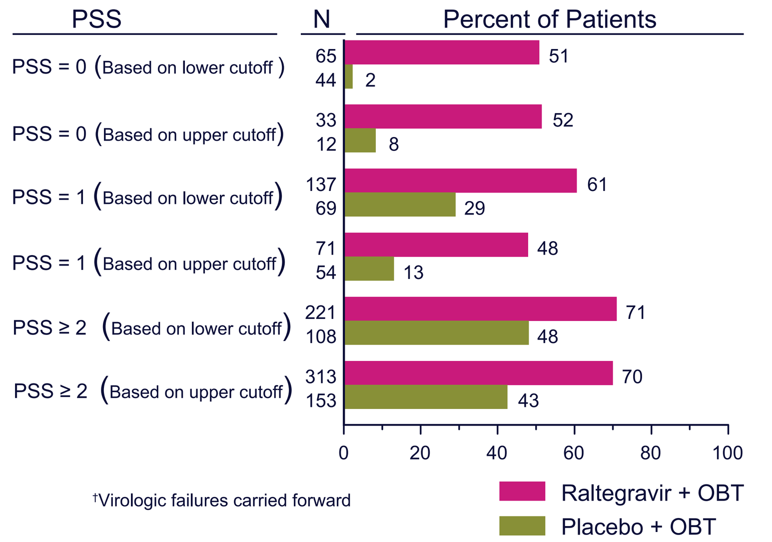
### Figure 4. BENCHMRK-1 & -2 Combined Efficacy† Percent of Patients With HIV RNA <50 copies/mL at Week 48 by Genotypic Sensitivity Score (GSS)




†Virologic failures carried forward.

For patients with GSS=1, 4 ART agents represented at least 80% of the active agents in OBT: darunavir (52%, 52% in raltegravir and placebo groups, respectively), enfuvirtide (8%, 16%), tenofovir (12%, 6%), and tipranavir (11%, 11%).

### Figure 5. BENCHMRK-1 & -2 Combined Efficacy† Percent of Patients with HIV RNA <50 copies/mL at Week 48 by PSS Based on Upper and Lower cutoffs

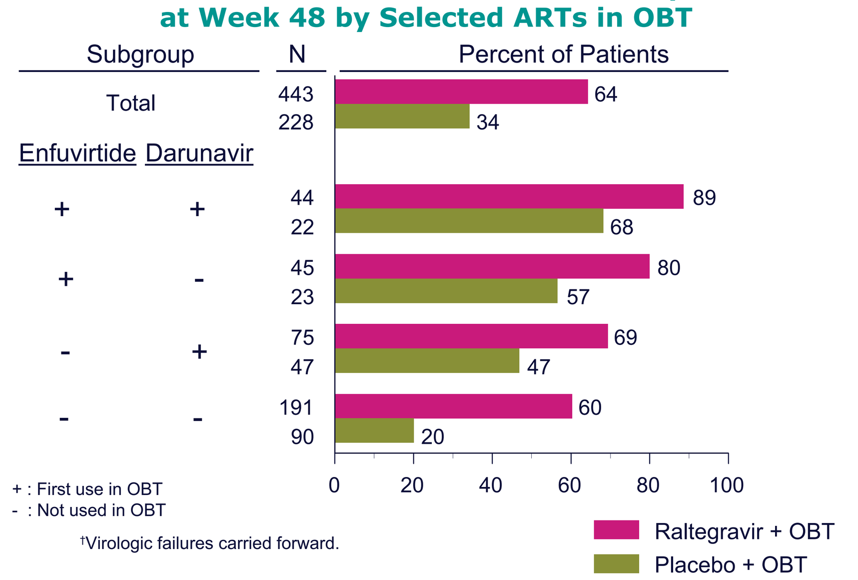



†Virologic failures carried forward

- The analysis by PSS score has been reanalyzed using the upper cutoff to better account for the impact of partial ART activity.
- Isolates with fold-change $IC_{50}$ above the lower but below the upper cutoff are now reported as "partially sensitive". The upper cutoff was developed because the lower cutoff may underestimate partial ART activity in a regimen.
- At the time the BENCHMRK studies were initiated, only the lower cutoff was reported. The efficacy by PSS has been reanalyzed using the upper cutoffs, where available, to better account for the impact of partial ART activity.

**Conclusion:** At all levels of PSS, the results using the upper and lower cutoffs are similar, confirming the contribution of raltegravir in the treatment regimen.

### Figure 6. BENCHMRK-1 & -2 Combined Efficacy† Percent of Patients With HIV RNA <50 copies/mL at Week 48 by Selected ARTs in OBT




†Virologic failures carried forward.

### Table 7. Cancer Events – Relative Risk and Associated 95% CI (BENCHMRK-1 and -2)

| | Raltegravir Group | | Control Group | | Relative Risk |
|---|---|---|---|---|---|
| | N | Cases/PYR† (Rate‡) | N | Cases/PYR† (Rate‡) | (95% CI) |
| Total | 462 | 16/460 (3.5) | 237 | 4/178 (2.3) | 1.5 (0.5, 6.3) |
| BENCHMRK-1 | 232 | 8/237 (3.4) | 118 | 1/87 (1.2) | |
| BENCHMRK-2 | 230 | 8/224 (3.6) | 119 | 3/91 (3.3) | |

† Patients-years at risk.
‡ Per 100 person-years (PYR).

For a comprehensive assessment of risk, a similar analysis was done including all double blind data from Phase II and Phase III studies (Protocols 004, 005, and BENCHMRK-1 and -2), which provides a malignancy rate of 2.2/100 PYR for raltegravir and 1.8/100 PYR for the comparator group, resulting in a relative risk (95% CI) of 1.2 (0.4, 4.1).

## Conclusions

In HIV-infected, treatment-experienced patients failing antiretroviral therapy with triple-class resistant HIV:

- Raltegravir 400 mg b.i.d. plus OBT has potent and superior antiretroviral and immunological efficacy compared to placebo plus OBT, which is sustained through Week 48.
  - In patients receiving new, active antiretroviral therapies in OBT, up to 89% achieved HIV RNA < 50 copies/mL at Week 48.
- Virologic failure is generally associated with mutations at one of two primary residues, Q148 or N155, in combination with at least one other mutation.
- Raltegravir 400 mg b.i.d. plus OBT is generally well tolerated, as compared to placebo in combination with OBT.
  - Few adverse events leading to discontinuation.
  - Risk of developing malignancy is comparable between raltegravir and comparator groups, whether only the Phase III data are examined, or all Phase II and Phase III data are included.

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