All Wales Medicines Strategy Group

Grŵp Strategaeth Meddyginiaethau Cymru Gyfan

Final Appraisal Report:

Raltegravir (Isentress®▼) in combination with other antiretroviral medicinal products for the treatment of human immunodeficiency virus (HIV-1) infection in treatment-experienced adult patients with evidence of HIV-1 replication despite ongoing antiretroviral therapy.

Merck Sharp & Dohme Limited

Advice No: 1808 – October 2008

Recommendation of AWMSG

Raltegravir (Isentress®▼) is recommended as an option for use within NHS Wales for the treatment of HIV-1 infection in treatment-experienced adults in accordance with British HIV Association (BHIVA) guidance.

Raltegravir (Isentress®▼) is not suitable for shared care within NHS Wales.

This report should be cited as:

1.0 RECOMMENDATION OF AWMSG:

The AWMSG recommendation is based on: the Preliminary Appraisal Report, the Company Response to this, medical expert opinion, lay perspective and discussions at the AWMSG meeting.

Date: Wednesday, 15th October 2008

The recommendation of AWMSG is:

Raltegravir (Isentress®▼) is recommended as an option for use within NHS Wales for the treatment of HIV-1 infection in treatment-experienced adults in accordance with British HIV Association (BHIVA) guidance.

Raltegravir (Isentress®▼) is not suitable for shared care within NHS Wales.

Additional note:

- Raltegravir (Isentress®▼) should be used in combination with at least one other active agent to enhance benefit and to reduce the risk of virologic failure and development of resistance to raltegravir (Isentress®▼).

2.0 PRODUCT DETAILS

2.1 Licensed indication

Raltegravir (Isentress®▼) is indicated in combination with other antiretroviral medicinal products for the treatment of human immunodeficiency virus (HIV-1) infection in treatment-experienced adult patients with evidence of HIV-1 replication despite ongoing antiretroviral therapy[1].

This indication is based on safety and efficacy data from two double-blind, placebo-controlled trials of 24 weeks duration in treatment-experienced patients[1].

2.2 Dosing

Raltegravir should be initiated by a physician experienced in the management of HIV infection. The recommended dosage of raltegravir is 400mg administered orally twice daily with or without food[1].

Raltegravir should be used in combination with at least one other active agent to enhance benefit and to reduce the risk of virologic failure and development of resistance to raltegravir[1].

2.3 Market authorisation date

EU marketing authorisation was granted 20 December 2007[2]. This was a conditional approval subject to the marketing authorisation holder providing comprehensive clinical data up to 48 weeks to further assess important issues including long-term viral suppression, the safety profile and resistance patterns. It was considered that further monitoring of resistance to raltegravir and the risk for malignancies is required[3].

2.4 UK Launch date

07 January 2008[2].

3.0 DECISION CONTEXT

Most people infected with HIV-1 who start highly active antiretroviral therapy (HAART) will experience good virological responses to treatment. However, due to a range of factors, including pre-existing or newly developed antiretroviral resistance, responses may fail over time and subsequent regimens may be progressively less likely to produce a durable virological response. Highly pre-treated patients may not achieve the goals of undetectable and durable HIV plasma viral load suppression and immunological improvement[4].

The British HIV Association (BHIVA) guidelines emphasise that, in highly pre-treated HIV-1 infected patients, therapy has to be tailored based on a range of factors, including their individual prior antiretroviral treatment histories and resistance profiles[4]. There is, therefore, a need for new antiretroviral agents that are active against HIV-1 where other agents are no longer active.

Raltegravir is the first drug of a new class of antiretroviral agents, called integrase strand transfer inhibitors, to be licensed. It inhibits the catalytic activity of integrase, an HIV-encoded enzyme that is required for viral replication, thus inhibiting integration of the HIV genome into the host cell genome and preventing propagation of the viral infection[1]. The company submission considers that the greatest need for raltegravir is amongst patients who have documented resistance to at least one therapy in each of the three major antiretroviral classes, and estimates that there will be around 35 patients eligible for treatment in Wales in 2008[2].

4.0 EXECUTIVE SUMMARY

4.1 Review of the evidence on clinical effectiveness

BENCHMRK 1 and 2 are ongoing phase III trials that provide the main efficacy data. Patients with HIV-1 who were highly treatment-experienced and triple-class resistant were randomised to receive double-blind raltegravir 400mg twice daily or placebo in addition to optimised background therapy (OBT) selected by investigators. The 16-week results indicate that raltegravir significantly improved viral load, including those achieving less than 50 copies/ml, and CD4 cell counts compared with placebo. Pre-specified analyses confirm that the results were consistent and sustained through 48 weeks of treatment in each of the studies, with 64% of raltegravir recipients achieving viral loads less than 50 copies/ml compared with 34% of placebo recipients. As would be expected, the proportion of patients achieving viral loads less than 50 copies/ml in both the raltegravir and the placebo groups was numerically greater in those who had lower HIV ribonucleic acid (RNA) levels and higher CD4 cell counts at baseline, and those who had a higher number of agents in their OBT to which their virus was sensitive. There were no significant differences between raltegravir and placebo in the incidence of all adverse events, drug-related adverse events, serious adverse events, or discontinuations due to adverse events or deaths.

4.2 Review of the evidence on cost-effectiveness

The company submission describes a primary cost utility analysis of raltegravir plus OBT as compared to OBT alone in highly treatment-experienced, triple-class resistant HIV-1 patients. A secondary cost utility analysis considers raltegravir as compared to darunavir and a further simple cost analysis considers raltegravir as compared to enfuvirtide.

The cost utility analyses are based on a cohort state-transition model in which patients move between health states defined by HIV RNA levels, CD4 cell count, and opportunistic infection states. The 48 week virological and immunological failure rates observed in the BENCHMRK studies are assumed to remain constant and are extrapolated to five years, which would appear to be a source of uncertainty. There are no data directly comparing raltegravir with darunavir or enfuvirtide, and so *post hoc* sub-group analyses of the BENCHMRK data have been conducted. Due to the small numbers of patients in the sub-groups, these data have not been adjusted for important baseline characteristics, which appear to favour raltegravir and would potentially introduce some uncertainty into the cost utility analyses.

For the primary analysis, the incremental cost per quality adjusted life year (QALY) gained for raltegravir plus OBT as compared to placebo plus OBT was estimated as £16,470. For the secondary analysis, the incremental cost per QALY gained for raltegravir as compared to darunavir was £2,038. However, this figure could not be verified, and is substantially lower than the £33,142 per QALY gained reported in the submission to the Scottish Medicines Consortium. On the basis that raltegravir is less expensive than enfuvirtide and is assumed to be no less effective, the company submission considers that raltegravir dominates enfuvirtide and a formal cost utility analysis has not been conducted.

5.0 LIMITATIONS OF DECISION CONTEXT

- The safety and efficacy of raltegravir has not been established in patients with severe liver disorders[1]. Only 10-20% of patients in the BENCHMRK studies were co-infected with the hepatitis B and/or C virus.

6.0 CLINICAL EVIDENCE

The company submission provides details of two ongoing, randomised, placebo-controlled, phase III trials of raltegravir in treatment-experienced patients (BENCHMRK 1 and 2)[5,6]. Brief details of a placebo-controlled, dose-finding study conducted in treatment-experienced patients (PN005)[7] and an active-controlled, dose-finding study conducted in treatment-naive patients (PN004)[8] are also provided. The BENCHMRK studies are discussed below, and further details of these and PN005 are included in Table 1A in Appendix 1. As PN004 was not conducted in the licensed population, efficacy data from this study are not included here.

6.1 Clinical efficacy

The BENCHMRK 1[5] and 2[6] studies were conducted in heavily pre-treated patients who were predominantly white, middle-aged males. Median baseline HIV RNA levels in both studies were around 50,000 copies/ml and CD4 cell counts were 130 cells/mm^3 and 111 cells/mm^3 in BENCHMRK 1 and 2, respectively. Over 90% of patients had prior AIDS diagnoses, and around 10-20% were co-infected with hepatitis B or C. All had documented resistance to at least one drug from each of the three main classes of antiretroviral agents (nucleoside and non-nucleoside reverse transcriptase inhibitors, and protease inhibitors [PIs]). Patients received OBT selected by investigators on the basis of treatment history and genotypic/phenotypic resistance testing[3,5,6], which could only be changed during the double-blind phase of the study for toxicity management or confirmed virological failure. Around 65% of patients in both studies were sensitive to less than two of the agents in their OBT (and around 20-30% were not sensitive to any agents) based on genotypic sensitivity scores[5,6] (see Table 1A in Appendix 1).

Patients were randomised to raltegravir 400mg twice a day or placebo, which was added to their OBT. The primary end point was the percentage of patients with HIV RNA levels less than 400 copies/ml at 16 weeks, which the scientific discussion of the European Public Assessment Report (EPAR) suggests may be criticised, as the optimal outcome would be to achieve viral loads less than 50 copies/ml^3. The week 16 results indicate that raltegravir significantly improved viral load (including those achieving viral loads less than 50 copies/ml) and CD4 cell counts compared with placebo (see Table 1A in Appendix 1).

Forty-eight-week data from the BENCHMRK studies have recently been presented at conference[5,6]. Pre-defined analyses indicate that the significant improvements in viral load and CD4 cell counts with raltegravir were consistent and sustained through 48 weeks of treatment (see Table 1). These data provide an indication of those factors that potentially influence response to treatment (see Table 1B in Appendix 1), although it should be noted that patients were not stratified at randomisation for all of these factors. As would be expected, the proportion of patients achieving HIV RNA less than 50 copies/ml in both the raltegravir and the placebo groups was numerically greater in those who had lower HIV RNA levels and higher CD4 cell counts at baseline, and those who had a higher number of agents in their OBT to which their virus was sensitive (as assessed by genotypic or phenotypic sensitivity scores).

Table 1. 48 week data from BENCKMRK 1 and 2[5,6]

	BENCHMRK 1		BENCHMRK 2	
	Raltegravir (n=232)	Placebo (n=118)	Raltegravir (n=230)	Placebo (n=119)
HIV RNA <400 copies/ml	74%	36%	71%	38%
HIV RNA <50 copies/ml*‡	65%	31%	60%	34%
HIV RNA change from baseline (log_{10} copies/ml) †¶	-1.7	-0.7	-1.8	-0.9
Mean CD4 count change (cells/mm^3) †#	+120	+49	+98	+40

p<0.001 for all comparisons of raltegravir versus placebo (adjusted for baseline values)
*Analysis assumes non-completers are failures
†Analysis based on observed failures with baseline values carried forward for virological failures
‡ No. raltegravir and placebo contributing patients 231 and 118 in BENCHMRK1 and 228 and 119 in BENCHMRK2, respectively
¶ No. raltegravir and placebo contributing patients 227 and 114 in BENCHMRK1 and 216 and 114 in BENCHMRK2, respectively
# No. raltegravir and placebo contributing patients 222 and 114 in BENCHMRK1 and 217 and 114 in BENCHMRK2, respectively

A higher proportion of patients in the raltegravir and the placebo groups who received enfuvirtide and/or darunavir for the first time as part of the OBT also achieved HIV RNA levels less than 50 copies/ml compared with those who had neither agent in their OBT. In each analysis, raltegravir was numerically superior to placebo, but the statistical significance is not reported for the 48 week data. Both 16 week and 24 week data indicate that raltegravir was significantly superior to placebo in achieving HIV RNA levels less than 400 copies/ml and 50 copies/ml overall in each of these sub-groups, but not in those patients who had darunavir in their OBT and were darunavir-experienced[3]. However, darunavir-experienced patients made up only a small proportion of patients and hence this result in darunavir-experienced patients is not reliable based on these data.

Around 39% of all patients had one agent in their OBT to which their virus was sensitive (based on genotypic sensitivity scores), and four agents represented at least 80% of these active agents: darunavir (52% and 52% in raltegravir and placebo groups, respectively), enfuvirtide (8% and 16%), tenofovir (12% and 6%), and tipranavir (11% and 11%)[5,6]. The placebo response in these studies was high, possibly due to the inclusion of these agents in the OBT.

Points to note

- The BENCHMRK studies were conducted in different regions (BENCHMRK 1 in Europe, Asia/Pacific and Peru; BENCHMRK 2 in North and South America), but had identical designs and no evidence of heterogeneity was found in treatment effect across the protocols[3]. Therefore, combining the results is appropriate.
- The EPAR notes that, while the response rates were higher in the raltegravir group, the relative effects of including enfuvirtide and darunavir in the OBT in naive patients were greater in the placebo group. While darunavir and enfuvirtide made some contribution to overall response rates in the raltegravir group, these two agents probably accounted for much of the response seen in the placebo group[3].

- In the dose-ranging study PN005, darunavir and tipranavir were not permitted, but patients were stratified by the inclusion of atazanavir in their OBT on the basis of earlier interaction studies that indicated atazanavir (boosted with ritonavir) may increase exposure to raltegravir. The observed benefit of raltegravir over placebo was not significantly different between those who did or did not receive atazanavir in study PN005. However, the data showed some possible numerical advantages for the proportions achieving HIV RNA less than 400 and less than 50 copies/ml and for the change in CD4 cell counts when raltegravir was co-administered with atazanavir[3] (see Table 1A in Appendix 1).

6.2 Safety

Based on pooled data from the double-blind phases of the BENCHMRK 1 and 2 and PN005 studies (median follow-up 35 weeks and total follow-up 332.2 patient-years in the raltegravir 400mg twice daily group, and median follow-up 27 weeks and total follow-up 150.2 patient-years in the placebo group)[3], the most commonly reported adverse reactions, of all intensities and regardless of causality were: diarrhoea (16.6% and 19.5%), nausea (9.9% and 14.2%), headache (9.7% and 11.7%), pyrexia (4.9% and 10.3%) in patients receiving raltegravir 400mg twice daily raltegravir and placebo, respectively[1,3]. The rates of discontinuation of therapy due to adverse reactions were 2.0% in patients receiving raltegravir plus OBT and 1.4% in patients receiving placebo plus OBT[1].

The recently available 48 week BENCHMRK 1 and 2 data indicate there were no significant differences between raltegravir (mean follow-up in excess of 50 weeks) and placebo (mean follow-up in excess of 38 weeks) in the incidence of all adverse events, drug-related adverse events, serious adverse events, discontinuations due to adverse events or deaths[5,6]. The EPAR noted a numerically higher incidence of malignancies in the raltegravir group compared to the placebo group in the phase II and III studies (relative risk 1.2, 95% confidence interval [CI] 0.4 to 4.1)[3], though this was not found to be statistically significant. Combined 48 week data from the BENCHMRK studies are consistent with this finding (3.5 cases per 100 patient-years at risk with raltegravir versus 2.3 cases per 100 patient-years with placebo; relative risk 1.5, 95% CI 0.5 to 6.3)[5,6].

The incidence of grade 3 or 4 abnormalities (elevations) in fasting low density lipoprotein (LDL)-cholesterol, total cholesterol and triglycerides were also numerically, (though not statistically significant), higher with raltegravir compared with placebo in the BENCHMRK studies[2,5,6]. In the dose-ranging PN004 study in treatment-naive patients there was no significant elevation of triglycerides, total cholesterol or LDL-cholesterol in the raltegravir groups compared with the efavirenz group[3]. In pooled data in treatment-experienced patients with 400 mg twice daily, the frequency of grade 3 or 4 lipid abnormalities and the mean change from baseline in fasting lipids were generally similar between raltegravir and placebo groups. However, it should be noted that hyperlipidaemia was commonly present at baseline in the different studies and lipid lowering agents were commonly used along with antiretroviral agents associated with lipid disorders[3].

Myopathy and rhabdomyolysis have occurred in ongoing studies and, although the relationship to raltegravir is not clear, the SPC recommends that raltegravir is used with caution in those with a history of, or predisposing factors for, these events[1]. Raltegravir is not a substrate or inhibitor of cytochrome P450 enzymes, and no dose adjustment of raltegravir is required with other antiretroviral agents (see SPC for further details)[1]. However, the incidence of diarrhoea and nausea, elevations in aminotransferases, and the incidence of rash appear higher when raltegravir is co-administered with certain other antiviral agents[3]. In patients with hepatitis B and/or C virus co-infection, the

safety profile of raltegravir was similar to that in patients without co-infection. Grade 2 or higher laboratory abnormalities that represent a worsening from baseline of aspartate aminotransferase (AST), alanine aminotransferase (ALT) or total bilirubin occurred in 26%, 27% and 12%, respectively, of raltegravir-treated co-infected subjects as compared to 9%, 8% and 7% of all other raltegravir-treated subjects[1].

7.0 SUMMARY OF CLINICAL EFFECTIVENESS ISSUES

7.1 Comparator medications

No other integrase strand transfer inhibitors are currently licensed. Competitor therapies are most likely to be other therapies licensed for treatment-experienced patients, and in the economic analysis enfuvirtide and darunavir, have been considered as comparators in sub-analyses (see Section 8.3). However, raltegravir is added to background therapy and in many situations it would be used in addition to, rather than for replacement of, other therapies.

7.2 Comparative effectiveness

Raltegravir has a different mode of action to other classes of antiretroviral agents and the company submission asserts that there is no natural primary resistance to this agent[2]. Raltegravir may, therefore, be expected to reduce viral loads in cases that are resistant to other agents. However, virological failure on raltegravir has been observed in clinical trials. Most viruses isolated from patients failing raltegravir had high-level raltegravir resistance resulting from the appearance of two or more mutations[1]. Viruses with mutations have emerged from about weeks 2-4 onwards, which suggests that there is potentially a low genetic barrier to the selection of raltegravir-resistant mutants[3]. Having a low CD4 cell count (≤50 cells/mm^3 versus >200 cells/mm^3) or a genotypic/phenotypic sensitivity score of zero (i.e. no agents in the OBT to which the virus was sensitive) increased the likelihood of developing these mutations. Factors that decreased the likelihood included lower viral load, the use of darunavir in the OBT, and having genotypic and phenotypic sensitivity scores greater than zero[1,3]. Therefore, the SPC states that raltegravir should be used in combination with at least one other active agent to enhance benefit and to reduce the risk of virologic failure and development of resistance to raltegravir[1].

Preliminary data indicate that there is potential for at least some degree of cross-resistance to occur between raltegravir and other integrase inhibitors[1] (and it should be noted that, although raltegravir is currently the only integrase inhibitor that is licensed, other integrase inhibitors are in development[4]).

Raltegravir is mainly metabolised by glucuronidation and no dose adjustment of raltegravir is required when administered with other antiretroviral agents[1]. In contrast to PIs (e.g. atazanavir[9], darunavir[10] and tipranavir[11]), ritonavir boosting is not required with raltegravir. However, in many cases raltegravir will be administered in addition to, rather than instead of, one of these agents. Enfuvirtide, a fusion inhibitor licensed in triple-class resistant patients, requires subcutaneous injection[12], and if raltegravir is considered a direct comparator its oral route of administration may be preferred.

There were no statistically significant elevations in lipid parameters with raltegravir compared with placebo[5,6] or efavirenz[8] in the clinical studies conducted. However, many patients in the trials had hyperlipidaemia and were taking lipid-lowering agents at baseline[3], so interpretation of these findings is difficult. Again, raltegravir will often be administered in addition to, rather than instead of, agents that have been associated with the development of abnormal lipid profiles.

The BENCHMRK studies are ongoing, with a planned follow up of 156 weeks. This follow up data may become available in early 2010. Raltegravir was granted conditional approval by the European Medicines Agency (EMEA)[3], as was darunavir when it was licensed[13].

8.0 SUMMARY OF HEALTH ECONOMIC EVIDENCE

8.1 Overview of the key economic issues for AWMSG to consider

The key economic issues for AWMSG to consider are whether any additional benefits offered by raltegravir over the relevant comparator(s) justify any additional costs and, if so, whether the total budgetary impact of supporting the use of raltegravir is acceptable.

8.2 Review of published evidence on cost-effectiveness

Standard literature searches conducted by WMP have not identified any published evidence on the cost-effectiveness of raltegravir.

8.3 Review of company submission on cost-effectiveness

8.3.1 Description and critique of the company's submission

The company submission describes a primary cost utility analysis of raltegravir plus OBT as compared to OBT alone in highly treatment-experienced, triple-class resistant HIV-1 patients. A secondary cost utility analysis compares raltegravir to darunavir and a further simple cost analysis compares raltegravir to enfuvirtide.

The cost utility analyses are based on a cohort state-transition model in which patients move between health states defined by seven HIV RNA levels, six CD4 cell count, seven acute opportunistic infection (OI) states and OI History state. Patients enter the model with a given HIV-1 viral load and CD4 cell count and move to a higher or lower viral load and CD4 cell count state, an OI state or non-HIV-related death. Patients who develop an OI event can either die, or recover and move to a health state of OI History. Each cycle of the model is one month[2].

The main source of raltegravir and OBT efficacy data is the BENCHMRK studies. It is assumed that the virological and immunological failure rates observed at 48 weeks remain constant up to a total of five years, after which patients are assumed to stop receiving raltegravir and have the same transition probabilities as the OBT arm[2]. This extrapolation of 48 week data to five years would appear to be a source of uncertainty. There are also some uncertainties in the utility values used in the base case analysis. Probabilistic sensitivity analysis has not been conducted to explore the combined effects of parameter uncertainty due to the large number of variables involved.

No direct comparative data exists for raltegravir versus darunavir or versus enfuvirtide, and so *post hoc* sub-group analyses of the BENCHMRK data have been conducted. Due to the small numbers of patients in the sub-groups, these data have not been adjusted for important baseline characteristics, which appear to favour raltegravir and would potentially introduce some bias into the analysis. On the basis of the *post hoc* sub-group analysis, and other non-comparative data, it is assumed that raltegraivir is at least as effective as enfuvirtide. As raltegravir is less expensive than enfuvirtide, it is concluded that raltegravir would dominate enfuvirtide, and so no formal cost utility analysis of these treatments has been conducted.

The model has been provided by the company and it is reported that three UK clinicians have validated various assumptions and parameter inputs. However, it

appears that only the base case analysis is included in the model, and so verification of the model outputs for the darunavir comparison is not possible.

8.3.2 Population

The patient cohort that has been modelled reflects the patient population of the BENCHMRK trials[2]. These were highly treatment-experienced patients who in the main were middle-aged, white, and male. Over 90% had a history of AIDS and around 10-20% had hepatitis B or C (see Table 1A of Appendix 1)[5,6].

8.3.3 Perspective and time horizon

The model considers the cost effectiveness of raltegravir from the perspective of NHS Wales. A 30 year time horizon has been assumed on the basis that it would be a suitable approximation of life expectancy of patients entering the model (median age approximately 45 years)[2].

8.3.4 Comparator

The primary analysis compares raltegravir plus OBT against OBT alone[2]. Secondary analyses have been conducted against darunavir and enfuvirtide, reportedly on the basis of expert opinion from a UK advisory panel[2]. No comparisons are made against ritonavir boosted tipranavir.

8.3.5 Clinical inputs

8.3.5.1 Efficacy data

8.3.5.1.1 Viral load

The main source of raltegravir and OBT efficacy data is the BENCHMRK studies. The efficacy of raltegravir relative to OBT is measured over time according to the extent that viral load is suppressed. As the viral load drops relatively quickly in the first four weeks of treatment and the trend generally tapers off later on, the pattern of transitions is considered different in the two periods. Therefore, the model was fitted separately and intensity matrices were estimated separately for baseline to week four and week four to week 48 periods[2].

It is assumed that the virological failure rates would remain constant between week 48 and five years. The company submission states that the suitability of this assumption for raltegravir was confirmed by three UK clinicians involved in an advisory panel. Extrapolation of 48 week data to five years would appear to be a source of uncertainty and the extent to which this may or may not bias the model is unclear.

For the secondary analysis there are no data directly comparing raltegravir and darunavir. Therefore, sub-group analysis of the BENCHMRK data has been undertaken, but these data remain confidential[2].

An indirect, non-quantitative comparison is also made between the BENCHMRK studies of raltegravir and the TORO trials of enfuvirtide[15-17]. The company submission notes that the difference between the active and placebo arms in terms of the percentage of patients achieving a viral load less than 50 copies/ml at 24 weeks was 29% in the raltegravir trials and 10% in the enfuvirtide trials. This is interpreted to demonstrate that raltegravir is more effective than enfuvirtide. However, it should be noted that the median viral load was somewhat lower (4.6 $\log_{10}$ copies/ml versus 5.2 $\log_{10}$ copies/ml) and the CD4 count may be somewhat higher (mean of 151 copies/ml versus a median of 88 copies/ml) in the raltegravir trials than in the enfuvirtide trials.

8.3.5.1.2 CD4 cell counts

The CD4 cell count is used in the model as a surrogate marker of disease progression. The rate at which CD4 cell count changes in any individual patient per month is determined by the patient's current HIV RNA level according to equations derived from a joint analysis of 13 HIV cohorts involving patients with triple-class virological failure (the PLATO Collaboration)[18]. It was assumed that all patients in a CD4 cell count category are at the mean values for that category. The monthly relative change in CD4 cell count was computed and equated to the total transition rate out of that category. This was distributed across the remaining CD4 cell count categories according to the difference between mean CD4 cell count of the original category and the boundary of each of the other categories. Two time periods were considered for CD4 transition rates (baseline to week four and week four to five years), which differs from the modelled approach to the viral load above.

8.3.5.1.3 Opportunistic infections

The monthly incidence of OIs is based on rates used in a previous published cost effectiveness analysis of genotypic resistance testing[19]. As these rates were derived prior to the use of combination therapy, the rates have been adjusted by the relative hazards of events derived from two studies that compared the changes over time in the risks of specific AIDS-defining diseases following the introduction of HAARTs[20,21].

8.3.5.1.4 Mortality

The probabilities of death in the model are related to mortality rates due to current OI, a history of OI or non-HIV-related deaths[2]. Death rates in patients without a history of OI are derived from Welsh life tables. Patients with a history of OI have had an adjustment made to their baseline Welsh life table-derived death rate such that their relative risk of death is 1.5 times that of patients without OI history. This adjustment factor is referenced to two studies that use EuroSIDA data, which relates to the development of new AIDS-defining illnesses or deaths in the late HAART era[2].

Estimates of the duration and monthly probability of death in the presence of specific acute OIs is derived from a range of sources, including an observational study published in 1996 that followed 1246 HIV patients for a mean of 441 days[22]. Although the monthly risk of other OIs (taken to be lymphoma) is considered by CD4 stratum, the monthly risk of death due to other OIs has not been incorporated due to the diverse nature of this OI. According to the observational study published in 1996, Non-Hodgkins lymphoma is associated with the greatest risk of death over one year (0.94)[22]. The model appears to allow only one OI event to occur in each patient at any one time, which may underestimate the interactive effects of OIs.

8.3.5.2 Adverse events

Adverse events have not been considered in the model. The recently available 48 week BENCHMRK 1 and 2 data indicate there were no significant differences between raltegravir (mean follow-up >50 weeks) and placebo (mean follow-up >38 weeks) in the incidence of all adverse events, drug-related adverse events, serious adverse events, discontinuations due to adverse events or deaths[5,6] (see Section 6.2).

8.3.5.3 Utility weights

In the base case analysis, utility weights from a previous cost-effectiveness study of first line treatments[23] have been used[2]. The utility weights in that study were derived from EQ-5D data obtained from around 21,000 clinical trial participants, the majority of who were receiving ritonavir. The utility values were therefore adjusted using regression techniques to remove the influence of ritonavir side effects on the health state[23]. The company submission considers that these utility weights may not be adequately reflective of the highly treatment-experienced patients modelled currently,

due to the fact that the lowest utility value is 0.781, which seems high for a highly pre-treated patient group. The company speculates that this might bias the model against raltegravir, as fewer patients taking raltegravir would be in the worst health states[2]. Sensitivity analyses have been conducted on the utility weights, but the values used for the sensitivity analyses are also considered to have several limitations, including not being stratified by CD4 cell count and viral load, and being out dated[2]. Therefore, there would appear to be some uncertainty with the utility values assumed in the model.

8.3.6 Healthcare resource utilisation and cost

8.3.6.1 Drug costs

For the primary analysis, the composition of the OBT drugs was assumed to be the same for the raltegravir and the placebo arms. The costs of the OBT assumed in the model were based on the weighted costs of the various agents making up the OBT regimens in the BENCHMRK trials, with individual drug prices obtained from the Monthly Index of Medical Specialities (MIMS) for the recommended daily dose being applied[2]. Patients in each group are assumed to receive the same OBT until death and the company submission acknowledges that the OBT costs assumed in the model must be considered as a best estimate[2].

For the secondary analyses, the OBT for the darunavir arm and the raltegravir arm differed (see Section 8.3.5.1.1). The daily cost of the OBT for the raltegravir group in the secondary analysis is reported to be £30.77. The daily cost of the OBT for the darunavir group (including darunavir) is reported to be £35.82[2].

For the secondary analysis of raltegravir as compared to enfuvirtide, raltegravir drug costs are based on the recommended dose of 400mg twice daily, which is £21.58 per day. Enfuvirtide at a dose of 90mg twice daily costs £38.27 per day. As enfuvirtide is more expensive than raltegravir but is assumed to be no more effective (see Section 8.3.5.1.1), a full cost effectiveness analysis was not conducted[2]. Therefore, OBT costs for this analysis have not been calculated.

8.3.6.2 Adverse event costs

Adverse events have not been considered in the analyses.

8.3.6.3 Other resource use and costs

OI prophylaxis has been considered in the model and is reported to have been validated by a UK advisory board. This involves prophylaxis against pneumocystis jirovecii pneumonia (co-trimoxazole given as a 30 day course to patients with CD4 cell counts less than 200) and mycobacterium avium complex (azithromycin given to patients with CD4 cell count less than 50). Drug costs are based on MIMS prices[2].

The costs of treatment of OI are not specifically modelled, as this was considered too complex due to a range of possible 'co-morbidities'. Instead, resource utilisation associated with specific CD4 cell counts and viral load levels have been incorporated, reportedly based on data from a HIV database of the British Columbia Centre for Excellence in HIV that tracked resource utilisation of 2,700 patients between 1995 and 2001. As this was Canadian data, the UK advisory panel was used in order to adjust the data to better reflect resource use in the UK[2]. The number of hospitalisations, GP and specialist visits, accident and emergency visits, CD4 and viral load tests, and genotypic tests for each category of CD4 cell count and viral load has been estimated and costed using unit costs derived from standard published sources and UK expert opinion[2]. The costs of the last 30 days before death are also considered.

8.3.7 Discounting
Costs and outcomes are discounted at 3.5% per annum[2], which is the preferred discount rate.

8.3.8 Results
8.3.8.1 Primary base case analysis – raltegravir plus OBT compared to placebo plus OBT
The incremental cost per QALY gained for raltegravir plus OBT as compared to placebo plus OBT was £16,470. This was based on a raltegravir treatment duration of five years, resulting in a discounted incremental cost of £35,841 and a discounted gain of 2.18 QALYs over the 30 year time horizon[2].

8.3.8.2 Secondary analysis – raltegravir plus OBT compared to darunavir plus OBT
The incremental cost per QALY gained for raltegravir plus OBT as compared to darunavir plus OBT was £2,038. This figure could not be verified, and is substantially lower than the £33,142 per QALY gained reported in the submission to the Scottish Medicines Consortium.

8.3.8.3 Secondary analysis – raltegravir compared to enfuvirtide
On the basis that raltegravir is less expensive than enfuvirtide and is assumed to be no less effective, a formal cost utility analysis has not been conducted. The company submission considers that by cost minimisation, raltegravir dominates enfuvirtide treatment[2].

8.3.9 Sensitivity analysis
8.3.9.1 One way sensitivity analyses
A range of one-way sensitivity analyses have been conducted around the base case analysis. These indicate that the model is most sensitive to the assumptions around raltegravir treatment duration (at three years the incremental cost effectiveness ratio [ICER] is estimated as £10,560 per QALY gained, (at 10 years it is £26,532) and the cost of the OBT (varying the OBT cost by $\pm$50% the ICER ranges £9,722 to £23,218 per QALY gained). Further increasing the time horizon had little impact on the model outputs. Varying the assumed utility values by $\pm$25% also had little impact.

8.3.9.2 Probabilistic sensitivity analysis
Probabilistic sensitivity analysis has not been performed. The reason stated was the complexity of the large number of health states involved.

8.4 Review of evidence on budget impact
8.4.1 Description and critique of the company's submission
The budget impact analysis uses Welsh prevalence data to estimate the number of diagnosed HIV-1 patients and the proportion receiving antiretroviral treatment. Market research data is used to estimate the number of patients likely to be requiring a new line of therapy due to treatment failure. Assumptions on the proportion of these patients that are likely to receive raltegravir are then used. The resultant budget impact estimates may be subject to some uncertainty.

8.4.2 Perspective and time horizon
The budget impact analysis is conducted from the perspective of NHS Wales and considers a time horizon of five years.

8.4.3 Data sources

8.4.3.1 Incident and prevalent cases

Data from the Health Protection Agency has been used to estimate the number of patients with HIV diagnosed in Wales in 2006 as 884[24]. The average annual increase in the HIV population between the years 2000 and 2006 was 18% and this is assumed to remain constant over the next five years. This data also indicates that 72% of patients in Wales are receiving antiretroviral therapy[24].

8.4.3.2 Rates of adoption

Not all patients who are eligible for raltegravir will necessarily receive raltegravir. Therefore, the company submission assumes that 20% of patients who are eligible will receive raltegravir. It is also assumed that patients who start on raltegravir treatment remain on raltegravir for five years (as in the economic model).

Based on the above assumptions, cumulative patient numbers in Wales are therefore estimated to be seven in 2008, rising to 50 in 2012.

8.4.3.3 Costs and resource use

The list cost of raltegravir and selected other agents are included in Table 2 and have been used in the budget impact analysis.

Table 2. Selected comparator costs

Product	Recommended daily dose	Yearly cost*
Raltegravir	400mg bd orally	£7,876.70
Darunavir plus ritonavir	600mg/100mg bd orally	£6,252.80
Enfuvirtide	90mg bd by sc injection	£13,964.90
Doses and costs are for general comparison and do not imply therapeutic equivalence All costs obtained/calculated from British National Formulary No. 55, 2008[26] bd = twice daily; sc = subcutaneous		

For simplicity, costs have been calculated by assuming that each patient is on therapy for a full year[2].

8.4.4 Results

Assuming that raltegravir is added to existing OBT, rather than replacing any agents, the company submission estimates the budget impact of introducing raltegravir would be £55,804 in 2008, rising to £396,423 in 2012[2].

A supplementary analysis has been conducted to estimate the impact of using raltegravir as a replacement for enfuvirtide or darunavir. In this analysis it is assumed that patients eligible for raltegravir treatment would be equally eligible for darunavir or enfuvirtide treatment as add on treatment to OBT (i.e. each has a 33% weighting). In this analysis, the estimated impact of raltegravir would be £8,046 in 2008, rising to £57,156 in 2012. This reduced budget impact reflects cost savings from reduction in enfuvirtide use[2]. However, the likelihood of this scenario in practice is unclear and these results should be interpreted with caution.

8.4.5 Sensitivity analysis

No sensitivity analysis was conducted.

9.0 ADDITIONAL INFORMATION

9.1 Guidance and audit requirements

- BHIVA issued updated guidelines on antiretroviral treatment of HIV-1 in adults online in May 2008[4]. These indicate that in treatment-experienced patients with therapy options, the physician should construct a new HIV treatment that includes at least two (or preferably three) active agents guided by HIV resistance testing and by the patient's previous antiretroviral drug history. The use of an agent from a new drug class is likely to be more effective. Raltegravir is discussed as a new drug[4]..
- The London New Drugs Group, on behalf of the HIV Drugs and Treatment sub-group of the London HIV Consortium, issued a review raltegravir in April 2008[27]. This recommended that raltegravir may be considered for emergency use in individuals who are at risk of clinical progression[27].
- The Health Protection Agency, in collaboration with National Public Health Survey for Wales, conduct an annual survey (SOPHID) of all patients seen for HIV-related treatment or care[24].
- As raltegravir is intended for patients who are highly pre-treated and may have few therapeutic options available to them[1,2], it should be initiated by specialists and would not currently be deemed suitable for shared care within NHS Wales.

9.2 Previous AWMSG advice

- Enfuvirtide (Fuzeon®) –recommended for use for the treatment of patients with HIV-1, with restrictions; May 2004[28].
- Emtricitabine (Emtriva®) – recommended for use within NHS Wales as an option for the treatment of HIV-1 infected adults in combination with other antiretroviral agents for use in treatment-naive patients in line with current BHIVA guidelines; June 2007[29].
- Emtricitabine/tenofovir DF (Truvada®) – recommended for use within NHS Wales as an option for the treatment of HIV-1 infected adults who are treatment-naive and in line with current BHIVA guidelines; June 2007[30].
- Darunavir (Prezista®) – recommended for the treatment of HIV-1 infection in highly pre-treated adults who have failed more than one regimen containing a PI, and where resistance profiling suggests it is appropriate; August 2007[31].
- Tipranavir (Aptivus®) – recommended for the treatment of HIV-1 infection, only for the treatment of highly pre-treated adult patients who have failed multiple PIs, and where resistance profiling suggests it is appropriate; August 2007[32].

9.3 Ongoing studies

The two BENCHMRK studies are ongoing studies in HIV patients with documented resistance to at least one drug in each of 3 classes of licensed oral ART. They will provide longer data on the efficacy and safety of raltegravir compared to placebo for a planned period of 156 weeks[2].

PN004 is also an ongoing study which will provide additional safety and efficacy data of raltegravir in ART naïve, HIV-infected patients. This study will run for a minimum of 156 weeks[2].

9.4 Patient organisation information

A patient organisation submission by The Terrence Higgins Trust was provided to AWMSG members.

REFERENCES

1. Summary of Product Characteristics. Isentress®. Merck Sharp & Dohme Limited; January 2008. Available at: http://emc.medicines.org.uk/ (accessed May 2008).
2. Form B: Detailed appraisal information. Merck Sharp & Dohme Limited; May 2008.
3. European Medicines Agency. European Public Assessment Report – Scientific discussion. Isentress®; December 2007. Available at: http://www.emea.europa.eu/humandocs/PDFs/EPAR/isentress/H-860-en6.pdf (accessed 25 May 2008).
4. Gazzard BG on behalf of the BHIVA Treatment Guidelines Writing Group. British HIV Association guidelines for the treatment of HIV-infected adults with antiretroviral therapy 2008. *In Press*. Available at: http://www.bhiva.org/files/file1030835.pdf (accessed 26 August 2008).
5. Cooper DA, Gatell J, Rockstroh J et al. 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. Poster #788. 15th Conference on Retroviruses and Opportunistic Infections. Boston, Mass. February 3rd-6th, 2008. Available at: http://www.retroconference.org/2008/PDFs/788.pdf (accessed 27 May 2008).
6. Steigbigel R, Kumar P, Eron J et al. 48-week results from BENCHMRK-2, a phase III study of raltegravir (RAL) in patients failing antiretroviral therapy (ART) with triple-class resistant HIV-1. Poster #789. 15th Conference on Retroviruses and Opportunistic Infections. Boston, Mass. February 3rd-6th, 2008. Available at: http://www.retroconference.org/2008/PDFs/789.pdf (accessed 27 May 2008).
7. Grinsztejn B, Nguyen BY, Katlama C et al. Safety and efficacy of the HIV-1 integrase inhibitor raltegravir (MK-0518) in treatment-experienced patients with multidrug-resistant virus: a phase II randomised controlled trial. Lancet 2007; 369: 1261-9.
8. Markowitz et al. Rapid and Durable Antiretroviral Effect of the HIV-1 Integrase Inhibitor Raltegravir as Part of Combination Therapy in Treatment-Naive Patients with HIV-1 Infection. Results of a 48-Week Controlled Study. J Acquir Immun Defic Syndr 2007; 46(2): 125-33.
9. Summary of Product Characteristics. Reyataz®. Bristol-Myers Squibb Pharmaceuticals Ltd; May 2008. Available at: http://emc.medicines.org.uk/ (accessed May 2008).
10. Summary of Product Characteristics. Prezista®. Janssen-Cilag Ltd; January 2008. Available at: http://emc.medicines.org.uk/ (accessed May 2008).
11. Summary of Product Characteristics. Aptivus®. Boehringer Ingelheim Ltd; February 2008. Available at: http://emc.medicines.org.uk/ (accessed May 2008).
12. Summary of Product Characteristics. Fuzeon®. Roche Products Ltd; November 2007. Available at: http://emc.medicines.org.uk/ (accessed May 2008).
13. European Medicines Agency. European Public Assessment Report – Scientific discussion. Prezista®; February 2007. Available at: http://www.emea.europa.eu/humandocs/Humans/EPAR/prezista/prezista.htm (accessed 25 May 2008).
14. Commercial/academic in confidence reference.

15. Lalezari JP, Henry K, O'Hearn M, et al. Enfuvirtide, an HIV-1 fusion inhibitor, for drug-resistant HIV infection in North and South America. N Engl J Med 2003; 348: 2175-85.
16. Lazzarin A, Clotet B, Cooper D, et al. Efficacy of enfuvirtide in patients infected with drug-resistant HIV-1 in Europe and Australia. N Engl J Med 2003; 348: 2186-95.
17. Nelson M, Arasteh K, Clotet B, et al. Durable efficacy of enfuvirtide over 48 weeks in heavily treatment-experienced HIV-1-infected patients in the T-20 versus optimized background regimen only 1 and 2 clinical trials. J Acquir Immune Defic Syndr 2005; 40: 404-12.
18. Ledergerber B, Lundgren JD, Walker AS, et al. Predictors of trend in CD4-positive T-cell count and mortality among HIV-1-infected individuals with virological failure to all three antiretroviral-drug classes. Lancet 2004; 364: 51-62.
19. Weinstein MC, Goldie SJ, Losina E, et al. Use of genotypic resistance testing to guide HIV therapy: clinical impact and cost-effectiveness. Ann Intern Med 2001; 134: 440-50.
20. Babiker A, Darbyshire J, Pezzotti P, et al. Changes over calendar time in the risk of specific first AIDS-defining events following HIV seroconversion, adjusting for competing risks. Int J Epidemiol 2002; 31: 951-8.
21. Kirk O, Gatell JM, Mocroft A, et al. Infections with Mycobacterium tuberculosis and Mycobacterium avium among HIV-infected patients after the introduction of highly active antiretroviral therapy. EuroSIDA Study Group JD. Am J Respir Crit Care Med 2000; 162: 865-72.
22. Moore RD, Chaisson RE. Natural history of opportunistic disease in an HIV-infected urban clinical cohort. Ann Intern Med 1996; 124: 633-42.
23. Simpson KN, Luo MP, Chumney E, et al. Cost-effectiveness of lopinavir/ritonavir versus nelfinavir as the first-line highly active antiretroviral therapy regimen for HIV infection. HIV Clin Trials 2004; 5: 294-304.
24. Health Protection Agency. Numbers of patients accessing HIV-related care: Survey of Prevalent HIV Infections Diagnosed (SOPHID) - Wales 1997 to 2006. Available at: http://www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1204100433741 (accessed 03 June 2008).
25. Commercial/academic in confidence reference.
26. British Medical Association/Royal Pharmaceutical Society of Great Britain. British National Formulary No. 55; March 2008. Available at: http://www.bnf.org (accessed 03 June 2008).
27. London New Drugs Group on behalf of the HIV Drugs and Treatments sub-group of the London HIV Consortium. Raltegravir; April 2008.
28. All Wales Medicines Strategy Group. Recommendation Statement – enfuvirtide (Fuzeon®); May 2004. Available at: http://www.wales.nhs.uk/sites3/Documents/371/ACF100F.pdf (accessed 23 03 June 2008).
29. All Wales Medicines Strategy Group. Final Appraisal Report – emtricitabine (Emtriva®); June 2007. Available at: http://www.wales.nhs.uk/sites3/Documents/371/Emtriva%20FAR%20website.pdf (accessed 03 June 2008).

30. All Wales Medicines Strategy Group. Final Appraisal Report – emtricitabine/tenofovir DF (Truvada®); June 2007. Available at: http://www.wales.nhs.uk/sites3/Documents/371/Truvada%20FAR%20website.pdf (accessed 03 June 2008).
31. All Wales Medicines Strategy Group. Final Appraisal Report – darunavir (Prezista®); August 2007. Available at: http://www.wales.nhs.uk/sites3/Documents/371/Darunavir(Prezista)%20FAR%20final.pdf (accessed 03 June 2008).
32. All Wales Medicines Strategy Group. Final Appraisal Report – tipranavir (Aptivus®); August 2007. Available at: http://www.wales.nhs.uk/sites3/Documents/371/Tipranavir%20(Aptivus)%20FARfinal.pdf (accessed 03 June 2008).

Appendix 1. Additional Clinical Information

Table 1A. Prospective studies of raltegravir in treatment-experienced adults with HIV-1 infection

Ref	Study type	No. of patients	Inclusion criteria	Baseline characteristics	Prior treatment	Treatment regimen	Outcome (Raltegravir versus Placebo)
Pivotal studies							
3, 5 BENCHMRK 1 Europe Asia/Pacific Peru	Phase III, multi-centre, double-blind, randomised placebo-controlled study. 48 wks with extension to 152 wks.	N=352 mITT population: Raltegravir, n=232 Placebo, n=118	Treatment-experienced; Plasma HIV RNA ≥1000 copies/ml; Documented resistance to 3 ART classes; ≥16 yrs old.	85.1% male 77.4% white Age*: 45 yrs CD4 cell count*: 130 copies/mm^3 HIV RNA*: 4.7 $\log_{10}$ copies/ml AIDS history: 92.3% Hep B/C: 21.7%	ART use*: 10.5 yrs; No. ARTs*: 12 % GSS: 0=29.7% 1=35.7% % PSS: 0=18.7% 1=30.3%	Raltegravir 400mg bd versus placebo added to OBT % new enfuvirtide/ darunavir in OBT: 20.7%, 26.3%	**Primary endpoint (16 wks):** % HIV RNA <400 copies/ml: 76.1% versus 40.7%, p<0.001 **Other endpoints (16 wks):** % HIV RNA <50 copies/ml at 16 weeks: 60.8% versus 33.1% Mean change from baseline in CD4 cell count (copies/mm^3): 82.7 versus 31.3
3, 6 BENCHMRK 2 North America South America	Phase III, multi-centre, double-blind, randomised placebo-controlled study. 48 wks with extension to 152 wks.	N=351 mITT population: Raltegravir, n=230 Placebo, n=119	Treatment-experienced; Plasma HIV RNA ≥1000 copies/ml; Documented resistance to 3 ART classes; ≥16 yrs old.	90.8% male 58.2% white Age*: 45 yrs CD4 cell count*: 111 copies/mm^3 HIV RNA*: 4.7 $\log_{10}$ copies/ml AIDS history: 91.4% Hep B/C: 10.6%	ART use*: 9.7 yrs; No. ARTs*: 12 % GSS: 0=22.4% 1=42.6% % PSS: 0=13.1% 1=32.0%	Raltegravir 400mg bd versus placebo added to OBT % new enfuvirtide/ darunavir in OBT: 19.3%, 46.7%	**Primary endpoint (16 wks):** % HIV RNA <400 copies/ml: 77.0% versus 42.9%, p<0.001 **Other endpoints (16 wks):** % HIV RNA <50 copies/ml: 61.7% versus 36.1% Mean change from baseline in CD4 cell count (copies/mm^3): 85.1 versus 39.7

Table 1A. Continued

Ref	Study type	No. of patients	Inclusion criteria	Baseline characteristics	Prior treatment	Treatment regimen	Outcome (Raltegravir versus Placebo)
Supporting study							
3 PN005	Phase IIb multi-centre, double-blind, randomised dose-ranging, placebo-controlled study 48 wks with extension to 144 wks	N=179	Treatment-experienced; Plasma HIV RNA >5000 copies/ml; CD4 cell counts >50cells/mm^3; Documented resistance to ≥1 ART in each of 3 classes; ≥18 yrs old	Age*: 43 yrs. AIDS history: 82%. HIV RNA >50,000 copies/ml: approx 50%	ART use*: 10 yrs No. ARTs*: 12 GSS=0: 72% (excluding enfuvirtide)	Raltegravir 200 mg bd 400 mg bd 600 mg bd, or Placebo added to OBT (tipranavir and darunavir not permitted) OBT contained atazanivir: 29%	**Primary endpoint (24 wks):** Mean change from baseline in HIV RNA (log_{10} copies/ml): 200mg bd: -1.80 400mg bd: -1.87 600mg bd: -1.84 Placebo: -0.35 **Other endpoints in the 400mg bd dose (recommended dose; 24 wks):** % HIV RNA <400 copies/ml: No atazanivir in OBT: 64.52% Atazanavir in OBT: 85.71% % HIV RNA <50 copies/ml: No atazanivir in OBT: 48.39% Atazanavir in OBT: 71.43% Mean change from baseline in CD4 cell count: No atazanivir in OBT: 102.30 Atazanavir in OBT: 137.15
ART= antiretroviral therapy; bd=twice a day; GSS=genotypic sensitivity score, defined as the total oral ARTs in OBT to which a patient's viral isolate showed genotypic sensitivity based on genotypic resistance tests; mITT=modified intention to treat population, defined as all randomised patients excluding those who did not receive any study medication; OBT=optimised background therapy; PSS=Phenotypic sensitivity scores, defined as the total oral ARTs in OBT to which a patient's viral isolate showed phenotypic sensitivity based on phenotypic resistance tests. *Median.							

Table 1B. Percentage of patients achieving HIV RNA <50 copies/ml at 48 weeks – combined results from BENCHMRK 1 and 2 studies[5,6]

	Raltegravir (n=443)	Placebo (n=228)
All patients	64%	34%
By baseline characteristics		
HIV RNA > 100,000 copies/ml	48%	16%
HIV RNA ≤ 100,000 copies/ml	73%	43%
CD4 count ≤50 cells/mm^3	50%	20%
CD4 count >50, ≤200 cells/mm^3	67%	39%
CD4 count >200 cells/mm^3	76%	44%
By ARTs in OBT		
Enfuvirtide + darunavir	89% of 44 patients	68% of 22 patients
Enfuvirtide	80% of 45 patients	57% of 23 patients
Darunavir	69% of 75 patients	47% of 47 patients
Neither	60% of 191 patients	20% of 90 patients
By OBT GSS		
0	45% of 112 patients	3% of 65 patients
1	67% of 166 patients	37% of 92 patients
≥2	75% of 158 patients	59% of 68 patients

ART=antiretroviral therapy; GSS= genotypic sensitivity scores, defined as the total oral ARTs in OBT to which a patient's viral isolate showed genotypic sensitivity based on genotypic resistance tests; OBT=optimised background therapy