All Wales Medicines Strategy Group

Grŵp Strategaeth Meddyginiaethau Cymru Gyfan

Final Appraisal Report

Etravirine (Intelence®▼) for the treatment of HIV-1 infected, antiretroviral treatment-experienced adults in combination with a boosted protease inhibitor and other antiretroviral medicinal products

Janssen Cilag Limited

Advice No: 0609 – August 2009

Recommendation of AWMSG

Etravirine (Intelence®▼) is recommended as an option for use within NHS Wales for the treatment of HIV-1 infected, antiretroviral treatment-experienced adults in combination with a boosted protease inhibitor and other antiretroviral medicinal products. Treatment should be initiated by a specialist in accordance with BHIVA guidelines.

Etravirine (Intelence®▼) is not recommended for use as first line therapy.

AWMSG is of the opinion that etravirine (Intelence®▼) is not suitable for shared care within NHS Wales.

This report should be cited as:

ABBREVIATIONS

ARV	Antiretroviral
AWMSG	All Wales Medicines Strategy Group
BHIVA	British HIV Association
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CV	Cardiovascular
EPAR	European Public Assessment Report
HAART	Highly active antiretroviral treatment
HDL	High density lipoprotein
HIV	Human immunodeficiency virus
HPA	Health Protection Agency
HSR	Hypersensitivity reaction
LDL	Low density lipoprotein
mITT	Modified intention to treat
NMG	New Medicines Group
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
OBR	Optimised background regimen
PI	Protease inhibitor
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life year
RNA	Ribonucleic acid
SPC	Summary of Product Characteristics
WMP	Welsh Medicines Partnership

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, 12th August 2009

The recommendation of AWMSG is:

Etravirine (Intelence®▼) is recommended as an option for use within NHS Wales for the treatment of HIV-1 infected, antiretroviral treatment-experienced adults in combination with a boosted protease inhibitor and other antiretroviral medicinal products. Treatment should be initiated by a specialist in accordance with BHIVA guidelines.

Etravirine (Intelence®▼) is not recommended for use as first line therapy.

AWMSG is of the opinion that etravirine (Intelence®▼) is not suitable for shared care within NHS Wales.

2.0 PRODUCT DETAILS

2.1 Licensed indication

Etravirine (Intelence®▼) in combination with a boosted protease inhibitor (PI) and other antiretroviral (ARV) medicinal products is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in antiretroviral treatment-experienced adult patients. This indication is based on week 24 analyses from two randomised, double-blind, placebo-controlled phase III trials in highly pre-treated patients with viral strains harbouring mutations of resistance to non-nucleoside reverse transcriptase inhibitors (NNRTIs) and PIs, where etravirine was investigated in combination with an optimised background regimen (OBR) which included darunavir/ritonavir[1].

2.2 Dosing

The recommended dose of etravirine is 200mg (taken as two 100mg tablets) twice daily, following a meal. See the Summary of Product Characteristics (SPC) for full details[1].

2.3 Market authorisation date

Etravirine was first licensed in August 2008[2].

2.4 UK Launch date

October 2008[3]

3.0 DECISION CONTEXT

The 2008 British HIV Association (BHIVA) guidelines emphasise that highly active antiretroviral treatment (HAART) regimens must be individualised for patients with HIV-1 in order to achieve the maximum potency, durability, adherence and tolerability, and to avoid long-term toxicities and any likely drug interactions[4]. A HAART regimen consisting of two nucleoside reverse transcriptase inhibitors (NRTIs), in addition to a NNRTI (preferably efavirenz), is the preferred first-line regimen in newly diagnosed HIV-1 patients in whom treatment is recommended. A major limitation of the NNRTI efavirenz is its low genetic barrier to resistance; a single mutation is sufficient to confer resistance to efavirenz and also cross-resistance to nevirapine[4]. Failure of one of these NNRTIs therefore limits sequential use of the other[5]. In addition, NNRTI resistance is almost always accompanied by the emergence of NRTI mutations, reducing options for this class as well[4]. Therefore, in patients who experience virological failure on this type of regimen, it is generally recommended that the regimen is switched to one including two active NRTIs plus a boosted protease inhibitor (PI). The choice of any new regimen, however, should be guided by the results of current and previous resistance testing, treatment history and the ability of the patient to adhere to and tolerate individual drugs[4].

Etravirine is a new NNRTI that appears to have a higher genetic barrier to resistance than other NNRTIs. It is not licensed, however, for first-line use in treatment-naïve patients[1]. In clinical trials, at least three etravirine-associated mutations were needed for its virological response to be significantly reduced[4]. Nevertheless, etravirine efficacy in relation to NNRTI resistance at baseline has mainly been analysed with etravirine given in combination with the ritonavir-boosted PI darunavir in highly treatment-experienced patients, and boosted PIs show a higher barrier to resistance compared to other classes of antiretrovirals. The potential for development of resistance might be higher for etravirine if it is used in an antiretroviral combination therapy regimen that does not include a boosted PI. The licensed indication, therefore, stipulates that a boosted PI should be included in the etravirine regimen[1].

4.0 EXECUTIVE SUMMARY

4.1 Review of the evidence on clinical effectiveness

The main efficacy data for etravirine are from two identical 48-week, randomised, double-blind, placebo-controlled, phase III trials (DUET-1 and -2). These were conducted in heavily pre-treated patients with three or more PI mutations and documented resistance to NNRTIs. When etravirine was added to an optimised background regimen (OBR [at least two ARV drugs: NRTI(s) with or without enfuvirtide]) plus ritonavir-boosted darunavir, the proportion of patients achieving the primary endpoint of undetectable HIV RNA (<50 copies/mL) at 24 weeks was significantly higher than with placebo. Secondary endpoints, including mean viral load reduction and CD4 cell count changes from baseline, also favoured etravirine treatment; results were consistent at 48 weeks of follow-up. The maintenance of the effect of etravirine 200mg twice daily plus OBR has also been shown to 96 weeks, particularly with regards to CD4 change from baseline. The proportion of patients achieving viral load reductions to undetectable levels was not significantly different from placebo at 24 weeks in patients who received as part of their OBR the fusion inhibitor enfuvirtide for the first time, but was significantly in favour of etravirine at 48 weeks and 96 weeks. The incidence and severity of adverse events was similar between etravirine and placebo with the exception of rash, which occurred more frequently with etravirine but rarely resulted in treatment discontinuation.

4.2 Review of the evidence on cost-effectiveness

A Markov model has been developed to conduct a primary cost utility analysis of etravirine plus OBR compared with placebo plus OBR, using efficacy data from the DUET studies. A secondary analysis that compares etravirine plus OBR against raltegravir plus OBR is also presented. As there are no direct comparative data for etravirine and raltegravir, the secondary analysis has been conducted using indirect comparisons against subgroups of patients in the BENCHMRK trials of raltegravir.

In the primary analysis, the incremental cost per quality-adjusted life year (QALY) gained for etravirine plus OBR compared with placebo plus OBR is estimated to be £26,457. Probabilistic sensitivity analysis reportedly suggests that etravirine plus OBR has 0.6%, and 81.2% probability of being cost-effective at willingness to pay values of £20,000 and £30,000 per QALY gained, respectively.

In the secondary analysis, which may involve a more relevant comparator for many heavily pre-treated patients, treatment with etravirine plus OBR is estimated to cost £18,126 less than treatment with raltegravir plus OBR, but is reported to result in a reduction of 0.256 QALYs. The incremental cost per QALY gained for raltegravir plus OBR compared with etravirine plus OBR is estimated to be £70,716. However, this result would appear subject to significant uncertainty, as dramatic changes in the model outputs are observed in response to plausible changes in several parameter values.

Limitations of the model include it being biased in favour of etravirine in relation to the proportion of patients able to experience HIV-related death. Subgroups in relation to enfuvirtide treatment are not considered.

5.0 LIMITATIONS OF DECISION CONTEXT

- The phase III clinical trials of etravirine stipulated that the OBR should contain ritonavir-boosted darunavir. Efficacy data for etravirine given with boosted PIs other than darunavir are currently limited.
- There are no direct comparative data on the efficacy of etravirine relative to other agents, such as raltegravir (Isentress®▼) or maraviroc (Celsentri®▼), which may be options for some highly pre-treated patients.
- There are limited data in patients co-infected with hepatitis B and/or C virus. Although included in the Phase IIb and DUET trials, this was only if their condition was clinically stable and did not require treatment.

6.0 CLINICAL EVIDENCE

The main efficacy data in the company submission[2] are from two identical 48-week, randomised, double-blind, placebo-controlled, phase III trials (DUET-1 and -2)[6,7]. In addition the company have provided pooled 96-week data from an optional 48-week extension study to these trials. Results of a phase IIb, active-controlled, dose-exploring study, which used a different formulation of etravirine, are also presented (study C223)[8]. The baseline characteristics and results of these studies are summarised in Table 1A in Appendix 1 and are discussed below. The data included in the company submission are based on abstracts, poster presentations, and the European Public Assessment Report (EPAR)[5].

6.1.1 Phase III placebo-controlled studies (DUET-1 and DUET-2)

DUET-1 and -2 were identical 48-week, double-blind trials that compared etravirine 200mg twice daily against placebo in heavily pre-treated patients with limited to no treatment options, documented NNRTI resistance and three or more primary PI mutations at screening[5-7]. All patients received an OBR which included at least two ARV drugs (NRTI(s) with or without enfuvirtide) plus ritonavir-boosted darunavir Patients were stratified at baseline by enfuvirtide use, with those taking enfuvirtide for the first time (*de novo*) being considered distinct from those with previous experience of enfuvirtide or those not taking enfuvirtide (not *de novo*). A difference of 20% was assumed between the etravirine group and the placebo group in the situation where *de novo* enfuvirtide was not used. The assumption was made that in subjects receiving ritonavir/darunavir and *de novo* enfuvirtide, no added benefit of etravirine could be demonstrated[4].

It was pre-specified that the results of DUET-1 and -2 would be pooled. In the overall populations, the proportion of patients achieving the primary endpoint of undetectable HIV RNA (<50 copies/mL; based on the time to loss of virologic response [TLOVR]) at 24 weeks was significantly higher with etravirine treatment compared with placebo (58.9% versus 41.1%; p<0.0001; number needed to treat [NNT] 6). As part of the primary efficacy analysis, the results were considered by enfuvirtide use[5]. A statistically significant difference was seen only in the enfuvirtide not *de novo* stratum (56.3% versus 33.6%; p<0.0001; NNT 5); there was no significant difference between etravirine and placebo in the proportion of enfuvirtide *de novo* recipients achieving undetectable HIV RNA at 24 weeks (66.7% versus 61.9%; p=0.427)[1,5]. These 24-week results were similar in the individual DUET studies[5](see Table 1A, Appendix 1). However, 48-week data indicate that a statistically significant difference was seen between etravirine and placebo in both the enfuvirtide not *de novo* (57% versus 33%; p<0.0001; NNT 5) and the enfuvirtide de novo (71% versus 58%; p=0.0116; NNT 8) strata[6].

The 48-week extension study (pooled data from both DUET trials) continued to demonstrate a statistically significant difference between etravirine and placebo at 96 weeks with regards to the percentage of the overall population achieving the primary endpoint (etravirine: 57% [344/599] versus placebo: 36% [219/604]; p<0.0001)[2]. Secondary endpoints of achieving HIV RNA <400 copies/mL, mean viral load reduction and CD4 cell count changes from baseline, all favoured etravirine treatment during the 48- and 96-week period[2,5-7] (see Table 1A, Appendix 1).

Other outcomes (measured at 48 weeks) that favoured etravirine treatment over placebo included the incidence of adjudicated AIDS-defining illness or death (5.8% versus 9.8%; p=0.041)[9], and frequency and duration of any hospitalisations[10]. Health-related quality of life (HRQoL) measurement using a HIV-specific, validated instrument also favoured etravirine treatment in several domains (24 week data)[11].

Points to note:

- Baseline phenotypic sensitivity to <u>at least one</u> PI was observed in 77.5% and 75% of all patients in DUET-1 and -2, respectively. Overall sensitivity to darunavir was 63%. The baseline phenotypic sensitivity to NRTIs was particularly poor, as there were virtually no effective marketed NRTIs for the vast majority of patients in the trials[5].
- Over 50% of patients in the placebo arms were treated with regimens with low expectation of efficacy[5].
- The difference in virological response rate was mainly due to a higher proportion of patients in the placebo groups (50.6% and 48.6% in DUET-1 and -2, respectively) as compared to the etravirine groups (31.6% and 26.8%, respectively) that never reached a suppressed viral load by week 24[5].
- Around 25% of patients were using enfuvirtide for the first time and around 40% had previously used this agent[5]. *De novo* enfuvirtide use appears to result in a numerically higher proportion of patients in both treatment groups achieving HIV RNA <50 copies/mL compared with not *de novo* use.
- As may be expected, subgroup analyses indicate that the proportion of patients achieving HIV RNA <50 copies/mL is greater in those with higher CD4 cell counts and lower viral loads at baseline; also in those with more background active ARVs[1,7].
- The K103N NNRTI-mutation was the most prevalent NNRTI mutation in these trials but was not identified as a mutation associated with resistance to etravirine. Thirteen etravirine resistance-associated mutations have been identified and virological response will be lost if three or more of these are present[5]. In the DUET studies, 86% of patients had fewer than three etravirine resistance-associated mutations[7].

6.1.2 Phase IIb dose-exploring study (study C223)

This study used a different formulation of etravirine to that which was used in the DUET studies and, to that which is commercially available[2]. Heavily pre-treated patients were randomised to 400mg or 800mg etravirine twice daily in addition to an OBR, or a standard optimised regimen and were followed up for 48 weeks[8]. If a PI was to be used in the regimen for the etravirine arm of the trial, this was to be ritonavir-boosted lopinavir, whereas any PI could be used in the active control arm[5]. Enfuvirtide was also permitted. The etravirine 800mg twice daily used in this study is bioequivalent to the 200mg twice daily dose used in the DUET studies[2], and only results from this etravirine arm are discussed here. The primary endpoint of change from baseline in viral load at 24 weeks was significantly greater in the etravirine arm than in the control arm (-1.194 versus -0.412 $\log_{10}$ copies/mL; p<0.001). The results at 48 weeks were consistent and the secondary endpoints at 48 weeks, including the proportion with HIV RNA <50 copies/mL and mean change in CD4 cell count, also favoured etravirine treatment[8] (see Table 1A, Appendix 1). However, there were some important differences between the etravirine and control arms in terms of the background regimens[5]. Enfuvirtide was used more frequently in the etravirine arms compared with the control arm (63% versus 54%, respectively) and the proportion of patients with *de novo* use of enfuvirtide was higher in the etravirine arms compared with the control arm (60-90% versus around 50%, respectively). In addition, the proportion of patients with no active agents in the background regimen was lower in the etravirine arms compared with the control arm (16% versus 26%, respectively)[5]. Collectively, these imbalances would appear to favour the etravirine arms. Committee for Medicinal Products for Human Use (CHMP) reported that the difference in the change in viral load between the etravirine and control arm of 0.7 $\log_{10}$ copies/mL is limited when these imbalances are considered[5].

Points to note:

- Ritonavir-boosted lopinavir was used by approximately half of the patients in this study[5]. Therefore approximately half of the study population did not use a boosted PI. The licensed indication for etravirine stipulates that a boosted PI must be included in the regimen[1].
- Subsequent to their original submission the company have highlighted two publications with regards to the 24 and 48 week results from this trial[12,13].

6.2 Safety

Pooled 48-week data from the DUET trials indicate that the incidence and severity of adverse events, serious adverse events, laboratory abnormalities and discontinuations due to adverse events were generally comparable between the etravirine and placebo groups, with the exception of rash[5]. Pooled 96-week data show similar findings[2]. The most common adverse event in the etravirine arms was rash (19.2% with etravirine versus 10.9% with placebo at 48 weeks (p=0.0001[6]); 21% versus 12% at 96 weeks (p<0.0001). Overall the rash occurred most frequently in the second week of treatment, was more frequent in women than in men, was generally mild-to moderate in severity, lasted a median of 15 days, and resulted in treatment discontinuation in 2.2% of the etravirine group versus 0% in the placebo group[2].

Other common adverse events reported from the pooled 48-week analysis with etravirine and placebo were: diarrhoea (18.0% versus 23.5%), nausea (14.9% versus 12.7%) and headache (11% versus 13%, respectively[6]). The frequency of nervous system (17.2% versus 19.7%) and psychiatric disorders (16.7% versus 19.5%), and hepatic adverse events (7% versus 6%) was not significantly different to placebo. There were no major differences in laboratory parameters, including lipid parameters (data available up to 96 weeks)[2]. Nevertheless, hyperlipidaemia, hepatotoxicity and pancreatitis, have been identified as important potential risks, alongside coronary artery disorders, in the risk management plan agreed with the CHMP[5]. Serious adverse events were reported to have occurred in 20% and 23%, and overall discontinuations due to adverse events were reported in 7% and 6% of the etravirine and the placebo groups, respectively. Death due to any cause occurred in 2% and 3%, respectively, No deaths in the etravirine group were considered likely to be treatment-related, and one in the placebo-group was considered possibly related to the background regimen[6].

7.0 SUMMARY OF CLINICAL EFFECTIVENESS ISSUES

7.1 Comparator medications

Etravirine belongs to the NNRTI class of antiretroviral agent. Its licensed indication is for use specifically in treatment-experienced patients[1] and the available efficacy data has been obtained mainly in patients who have been heavily pre-treated. Other available NNRTIs, efavirenz and nevirapine, are generally recommended for use as first-line agents in combination with NRTIs (efavirenz being the preferred NNRTI)[4]. These other NNRTIs would therefore not be appropriate comparators for etravirine based on its licensed indication and the available supporting trial data.

The BHIVA guidelines emphasise the need to individually tailor treatment regimens based on the results of current and previous resistance testing, treatment history and the ability of the patient to adhere to and tolerate individual drugs[4]. Agents that may be potential comparators for etravirine could include those that are indicated for use in heavily pre-treated patients, such as raltegravir[14] and maraviroc[15].

7.2 Comparative effectiveness

- The DUET trials demonstrate that etravirine has significant efficacy in patients with other NNRTI resistance associated mutations[5-7].
- Etravirine has a higher genetic barrier to resistance compared with other NNRTIs. Nevertheless, this barrier to resistance is still limited and needs to be protected by the use of active agents within the combined antiretroviral regimen[5].
- The DUET trials assessed etravirine in a highly pre-treated patient population receiving an OBR plus ritonavir-boosted darunavir[5-7]. The results of these trials have been extrapolated to include other ritonavir-boosted PIs, but specific data are lacking. Tipranavir should not be used as the PI due to a pharmacokinetic interaction that could significantly reduce etravirine exposure and the virological response[1].
- The use of enfuvirtide for the first time (*de novo* use) appeared to result in a numerically higher proportion of patients achieving HIV RNA <50 copies/mL compared with non-use or re-use (not *de novo* use) (see section 6.1.1). This finding re-emphasises the need to ensure that the OBR contains active agents.

- In addition to its significant effect on accepted surrogate markers of efficacy, such as viral load and CD4 cell count changes, etravirine was observed to reduce the frequency and duration of hospitalisations, reduce the incidence of AIDS-defining illnesses, and improve some aspects of HRQoL compared with placebo[5-7,9-11].
- As with other NNRTIs, etravirine is associated with a risk of development of rash[5]. This was mainly mild-to-moderate in severity, occurred early in treatment and was rarely responsible for treatment discontinuation[6]. Other adverse events observed in the DUET trials were comparable between etravirine and placebo. In contrast to the NNRTI efavirenz, there appeared to be no increased risk of psychiatric adverse effects compared with placebo[4]. It should be considered, however, that other NNRTIs are not appropriate comparators for etravirine (see section 7.1). There are no direct, comparative efficacy and safety data against other agents that may be appropriate comparators in this setting, such as raltegravir or maraviroc.
- Etravirine is a weak inducer of CYP3A4 and a weak inhibitor of CYP2C9 and CYP2C19. A range of drug interactions are possible. Further details are provided in the SPC[1].
- Etravirine was granted conditional approval by the European Medicines Agency. Additional clinical data are needed to further substantiate the durability of virological response and its use in combination with PIs other than darunavir/ritonavir[5]. Further analysis of 96-week data from DUET-1 and -2 is expected. A roll over study from the DUET trials (study C217) is ongoing[2].

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 the additional benefits offered by etravirine over the relevant comparator(s) justify the additional costs and if so, whether the total budgetary impact of supporting the use of etravirine is acceptable (see section 9.0).

8.2 Description and critique of the company's submission

The company's submission[2] describes a primary cost utility analysis of etravirine plus an OBR (including ritonavir-boosted darunavir) compared with placebo plus an OBR in treatment-experienced adults who have HIV-1 infection that is resistant to other NNRTIs and who have at least three primary PI mutations. A secondary, possibly more relevant, analysis has compared etravirine plus OBR against raltegravir plus OBR.

The model describes six health states relating to patients with CD4 counts of >500, 351–500, 201–350, 101–200, 51–100 and 0–50 cells/mL, and a seventh, absorbing state of death. All individuals in the model follow a natural history consisting of consecutive periods of CD4 cell increase after treatment initiation, followed by stabilisation and then decline. Patients may remain in or move between the six health states, or progress into the seventh state of death, based on their virological response to treatment (undetectable [viral load <50 copies/mL], partial suppression [detectable viral load but a minimum of a 1.0 $\log_{10}$ drop in viral load is achieved], and no suppression [< 1.0 $\log_{10}$ drop in viral load is achieved]). Upon CD4 decline, all patients are assumed to switch to a subsequent regimen. In the primary analysis this is assumed to be raltegravir plus OBR (75%) or maraviroc plus OBR (25%), and in the secondary analysis this is assumed to be maraviroc plus OBR (100%)[2].

The original submission that was made by the company used 48-week data from the DUET studies. A revised submission has been submitted, which employs newly available, confidential, 96-week data from the DUET studies. This new data has yet to be formally reported. As there are no direct comparative data for etravirine and raltegravir, the secondary analysis has been conducted using indirect comparisons against subgroups in the BENCHMRK trials of raltegravir. A validation exercise was undertaken by the company to compare the proportion of patients estimated by the model to be in each of the six CD4 categories at 48 weeks with that observed in the DUET studies. This indicates that the model may be biased in favour of etravirine in relation to the proportion of patients able to experience HIV-related death. This is not further explored in sensitivity analyses. Subgroup analyses in relation to enfuvirtide treatment are not provided, and sensitivity analyses indicate that the results of the secondary analysis that compared etravirine plus OBR against raltegravir plus OBR are subject to considerable uncertainty and should be interpreted with caution.

A revised economic model using 96-week DUET study data has been provided to WMP. The company has since reported that this revised model contained an error in relation to the probabilistic sensitivity analyses (PSA) that were conducted. Therefore, when commenting upon the first draft of the ASAR, the company has provided revised PSAs, the results of which are more favourable to etravirine and have not been verified.

8.3 Population

The modelled population is based on the DUET study populations, as described in Table 1A, Appendix 1.

8.4 Perspective and time horizon

The analysis was conducted from the perspective of NHS Wales. A lifetime horizon has been used in the base case analysis[2], which is appropriate for this disease. A three-month cycle length is used[2].

8.5 Comparator

In the primary analysis presented in the company submission, the comparator for etravirine plus OBR is placebo plus OBR[2]. Although patients in the DUET trials were highly pre-treated[5-7], other agents are licensed for use in such circumstances where appropriate. Therefore, placebo would not necessarily be an appropriate comparator for many patients meeting the licensed indication for etravirine. The secondary analysis presented in the company submission, which compares etravirine plus OBR against raltegravir plus OBR, would appear to be a more appropriate to the current decision problem.

8.6 Clinical inputs

8.6.1 Efficacy data

8.6.1.1 Virological and immunological response in the primary analysis

Efficacy data for treatment with etravirine plus OBR or placebo plus OBR are based on pooled data from the DUET studies[5-7]. The 24-week data provide the proportion of patients in each of the three virological response categories used in the model. There appears to be a minor discrepancy in the proportion of patients achieving HIV RNA <50 copies/mL reported in the company submission (59.0% for etravirine versus 40.4% for placebo) and that reported in the EPAR (58.9% versus 41.1%, respectively), which would marginally favour etravirine. The magnitude of the initial and stabilising changes in CD4 cell counts are based on the mean and standard deviation of the CD4 cell count increases at 24 and 48 weeks observed in the pooled DUET data.

CD4 cell count changes depend on virological response category and regimen; the influence of enfuvirtide de novo use or not de novo use (discussed in section 6.1.1) is not specifically considered in the base case model, but is explored in sensitivity analysis[2].

The subsequent regimen following failure with etravirine plus OBR or placebo plus OBR is assumed to consist of raltegravir for 75% of patients and maraviroc for 25% of patients, based on company-sought Welsh expert opinion[2]. For the raltegravir component, 24-week data from the BENCHMRK-1 and -2 trials are used to provide viral load outcomes for raltegravir[16]. As CD4 cell count response by virological response were not available, the response categories were assumed to be in the same ratio as those for etravirine in the DUET studies, with a scale factor applied to ensure that the weighted mean CD4 cell count change for raltegravir was the same as the published mean increase in CD4 cell count at 24 weeks in the pooled BENCHMRK trials. However, the references cited in the company submission appear to report slightly different mean CD4 cell counts for raltegravir compared with those reported in the company submission. The 48-week CD4 cell count changes for raltegravir in those with a virological response of <1-$\log_{10}$ reduction and those with a 50 copies/mL to $\geq$1-$\log_{10}$ reduction in HIV RNA are assumed to occur at the rate as occurred with etravirine in the DUET trials.

The increase in CD4 cell count with raltegravir in those with a virological response of <50 copies/mL has then been adjusted so that the weighted overall 48-week mean change in CD4 cell counts with raltegravir is the same as was reported in the pooled BENCHMRK trials[16]. As the standard deviations for these data are not available in the literature, these have been computed based on the ratio of the standard deviation to means reported for etravirine in the DUET studies[2]. The approach adopted for estimation of raltegravir efficacy in the model would appear subject to some uncertainty, although the extent to which this may or not bias the model is unclear. For the maraviroc component of the subsequent regimen, data from the MOTIVATE 1 and 2 studies[17,18] were used. Similar scale factor adjustment has been made to the maraviroc data as with the raltegravir data.

8.6.1.2 Virological and immunological response in the secondary analysis

In the secondary analysis, etravirine plus OBR is compared against raltegravir plus a comparable OBR. Virological response data from the BENCHMRK trials in the subgroup of patients who received darunavir as part of their OBR has been used in the model. Estimates for the three categories of virological response for this subgroup were generated by first adjusting the BENCHMRK data to the DUET data using the ratio of the placebo response values for the DUET and BENCKMRK studies. This was then used to adjust the probability for achieving HIV RNA <50 copies/mL for the darunavir subgroup of the BENCHMRK studies. The other two categories of virological response were apportioned based on the remaining probability in the same proportions as the unadjusted data. For CD4 cell count changes, placebo response data have not been used to adjust the raltegravir data – unadjusted treatment-specific CD4 responses are used and another approach of using the etravirine response data has been employed[2].

8.6.1.3 Transition probabilities and duration of CD4 cell count change stages

For the initial increase in CD4 cell counts, the 24-week CD4 cell count changes have been transformed into half-year values using linear extrapolation, with the three-month changes in CD4 cell counts being based on these by linear interpolation. For the subsequent regimen, a weighted average of the raltegravir and maraviroc (75:25) three-month rates of increase is used. For each of the three virological response categories, a normal distribution is defined, using the mean and standard deviation, and is applied to individuals whose CD4 cell counts are assumed to be at the midpoint in each of the six starting CD4 cell count categories. The duration of the increase in CD4 cell counts is assumed to be half a year based on the data from the DUET studies, which indicate CD4 cell counts increase rapidly in the first 24 weeks of treatment and then more slowly between weeks 24 and 48[2].

For the stable/slow increase in CD4 cell counts, the original submission used CD4 cell count increases between 24 and 48 to calculate the transition probabilities in the same way as for the initial increase stage of CD4 cell count changes. Patients were assumed to be uniformly distributed within each of the six CD4 cell count ranges. After the first year, the three-month increase in CD4 cell count for those with HIV RNA <50 copies/mL was assumed to be equal to the three-month rate observed during weeks 24 to 48 in the DUET clinical trials. In those who achieved HIV RNA <50 copies/mL the duration was estimated to be 2.5 years, and in other response categories it was one year or half a year, irrespective of whether treatment was with etravirine or placebo[2]. This provided an estimate of time taken for CD4 cell counts to start declining, at which point it was assumed all patients would switch to a subsequent regimen.

In the revised submission, new data from week 48 to 96 has been extrapolated to provide an estimate of the median time to actual treatment discontinuation beyond the first year, which is used to define the duration of the stable/slow increase in CD4 cell count phase. Additional confidential information was provided.

For the decline in CD4 cell counts, an equation that describes the linear decline in CD4 cell counts by baseline HIV RNA levels, based on data from the Multicentre AIDS Cohort Study (MACS)[19], has been populated with baseline viral load data from the DUET studies to determine the annual rate of decline in CD4 cell count for untreated patients. Based on observational data that indicates CD4 cell counts do not decline appreciably in patients who are treated and have HIV RNA levels >10,000 copies/mL[20], the linear equation was populated with a baseline HIV RNA of 10,000 and the difference between the predicted annual declines in CD4 counts was used to derive the three month decline in CD4 cell counts for all virological response categories in the model[2]. It is unclear how reliable this approach is, as the same source of this predictive equation also acknowledges that other analyses suggest a different relationship between CD4 cell count decline and viral loads[19], and most patients in the observational study that is cited here had started antiretroviral treatment with only single or dual therapy[20]. However, this uncertainty would apply to all arms of the model. Patients whose CD4 cell counts decline are assumed to immediately switch to the subsequent regimen. In those already on the subsequent regimen, they remain on this until death[2].

The company submission describes the results of a model validation exercise that was undertaken based on the modelled CD4 cell count distributions and those actually observed in the DUET studies at 48 weeks[2]. This indicated that the model underestimates the proportion of patients falling within the CD4 cell count category of $\leq$50 cells/mm^3 at 48 weeks. However, the degree of underestimation is greater in the etravirine group compared with the placebo group (the proportion of patients predicted by the model to fall into this CD4 category is only 57% of that actually observed to fall into this category with etravirine treatment, compared with 64% for the placebo group). This CD4 cell count category is assumed to be the only category in which patients may experience HIV-related death (see section 8.6.1.4). Therefore, by underestimating the proportion of patients in this category at 48 weeks to a greater extent with etravirine treatment than with placebo treatment, the model would appear to be biased in favour of etravirine. This aspect is not considered in sensitivity analyses.

8.6.1.4 Mortality

HIV-related and non-HIV-related deaths in the first year are based on the 48-week data from the DUET studies. The model assumes all HIV-related deaths occur in patients in the CD4 cell count category of $\leq$50 cells/mm^3 and that the proportion of the population in this category is a weighted average of the proportions observed in the DUET trials at baseline, week 24 and week 48 (reported to be 12.7% in the etravirine group and 18.5% in the placebo group, but not verifiable). In subsequent years in the base case analysis, and throughout the whole modelled time in the secondary analysis, annual HIV-related mortality rates were taken from a cohort of patients followed up via the EuroSIDA database[21], transformed where necessary to match the health states of the model defined by CD4 cell count, and converted to provide three month probabilities of death[2].

Non-HIV related deaths in the first year are assumed to occur equally among the CD4 cell count categories. In subsequent years in the base case analysis, and throughout the whole modelled time in the secondary analysis, non-HIV-related deaths are based on Welsh life tables, with HIV-related mortality rates subtracted. Three age ranges are considered in the model (15 to 39 years, 40 to 64 years and 65-plus) and weighted average non-HIV death rates were calculated for these, transformed into three month rates and an exponential factor has reportedly been applied in each cycle to account for population aging (not further discussed)[2].

8.6.1.5 Opportunistic infections
The model incorporates three-month probabilities of experiencing opportunistic infections for each CD4 cell count range.

8.6.2 Adverse events
The model does not specifically consider adverse events separately to the overall costs and utility values that have been assumed. The justification for this is that the only significant differences in adverse events between the etravirine and control groups in the DUET-1 and -2 studies was the occurrence of rash, which was generally mild and self-limiting and did not require treatment[2].

8.6.3 Utility weights
Utility values for the each of the CD4 cell count-defined health states of the model were obtained from a cost-effectiveness analysis of lopinavir/ritonavir versus nelfinavir as first line antiretroviral regimens[22]. This analysis used EQ5D-derived utility values obtained from around 21,000 clinical trial participants. It is unclear how long ago or what disease state these trial participants were in when these utility values were obtained and, given the advances in the treatment of HIV that have been achieved since the first antiretroviral agents became available, and the fact that patients treated with etravirine will be highly treatment experienced, it is possible these utility values might be less appropriate for the population being modelled currently. Sensitivity analysis has been conducted on these utility values using their 95% confidence intervals[2].

8.7 Healthcare resource utilisation and cost
8.7.1 Drug costs
Antiretroviral drug costs are incorporated in the model as a weighted average of those reportedly used in the DUET studies (for the etravirine and placebo arms) and the BENCHMRK and MOTIVATE studies (for raltegravir and maraviroc)[2]. It is not possible to verify the actual level of usage of each of the antiretroviral agents from the references cited in the company submission. A weighted average daily drug cost for each of the comparators is reportedly used in the model, although there is a slight anomaly in some of the daily drug costs used in the model and the current eMIMs list prices as of April 2009[23].

8.7.2 Adverse event costs
Adverse event costs are not considered on the basis that they are similar between the treatments being compared in the model[2].

8.7.3 Other resource use and costs
For the first year in the base case analysis, the mean length of hospital stay are taken from the DUET trial data[10] (2.84 days versus 4.55 days for etravirine versus placebo, respectively). The confidential cost/day of hospitalisation is reportedly based on a company-conducted update to a previous estimate[24], but few details are provided[2].

Outpatient visits are reported in the company submission to have been no different in the DUET trials (due to the study protocol), and it is stated that they are not included in the model[2]. However, the model does appear to include outpatient cost inputs, reportedly derived from the above update to a previous cost study.

Resource use after 48 weeks in the base case analysis is based on an the company-conducted UK study of resource use between 2000 and 2006 [data on file][2], which is an update to a previous study published in 1996[24]. This provides mean three-month per patient costs (2006/7 prices) by CD4 cell count range. These costs are used in all years in the secondary analysis[2].

8.8 Discounting

Costs and outcomes are discounted at 3.5% per annum[2], which is the preferred discount rate. Rates of 0% and 6% are explored in sensitivity analyses.

8.9 Results

8.9.1 Primary base-case analysis – etravirine plus OBR versus placebo plus OBR

The incremental cost per QALY gained for etravirine plus OBR compared with placebo plus OBR is estimated to be £26,457. This is based on incremental costs of around £24,749 (£283,120 versus £258,371) and a gain of 0.935 QALYs (10.951 versus 10.015 QALYs). Drug costs represent the vast majority (~85%) of the total costs for each group[2], and the company considers that the additional drug costs associated with the use of etravirine reflect the need for treatment during the additional life expectancy of patients receiving this drug[2].

8.9.2 Secondary analysis - etravirine plus OBR versus raltegravir plus OBR

In the secondary analysis, etravirine plus OBR is less effective, and less costly than raltegravir plus OBR. Treatment with etravirine plus OBR is estimated to cost £18,126 less than treatment with raltegravir plus OBR (£258,760 versus £276,887), and is reported to result in a reduction of 0.256 QALYs (10.590 versus 10.846 QALYs). The incremental cost per QALY gained for raltegravir plus OBR compared with etravirine plus OBR is estimated to be £70,716. This result would appear subject to some uncertainty, as demonstrated by the one-way sensitivity analyses (discussed in section 8.10.1.2)

8.10 Sensitivity /scenario analyses

8.10.1 One-way sensitivity /scenario analyses

8.10.1.1 One-way sensitivity analyses for the primary base case analysis

Several one-way sensitivity analyses have been conducted, which demonstrate that the model is most sensitive to the duration of slow/stable CD4 cell count phase and the cost of the PI contained within the switch regimen. None of the one way sensitivity analyses that have been conducted resulted in an incremental cost effectiveness ratio (ICER) of £20,000 or less and only when the duration of the slow/stable CD4 cell count phase was set to zero (an improbable scenario given the available trial data) and the cost of the PI was assumed to be that of ritonavir-boosted lopinavir did the ICER fall below £25,000.

The influence of *de novo* or not *de novo* enfuvirtide treatment (discussed in sections 6.1.1 and 7.2) has not been explored.

An alternative scenario has been modelled in which it is assumed that the risk of discontinuation with etravirine returns to that of placebo at 96 weeks (the end of the DUET trial observation period). The incremental cost per QALY gained for etravirine plus OBR compared with placebo plus OBR is estimated in this analysis to be £29,563, based on incremental costs of £17,749 (£263,847 versus £246,098) and a gain of 0.600 QALYs (10.575 versus 9.975 QALYs).

8.10.1.2 One-way sensitivity analyses for the secondary analysis
The one-way sensitivity analyses indicate that the model is most sensitive to the raltegravir virological response (which resulted in an ICER in excess of £200,000 when explored at the lower end of the 95% confidence interval), and the rate and duration of the slow/stable CD4 cell count phase (both of which shifted the ICER to negative values. Several other parameters also demonstrate that the model is sensitive, resulting in changes of the order of +/-£20,000 to £30,000 in the ICER (from a base value of £70,716). Collectively, these analyses suggest there is significant uncertainty in the point estimate reported in section 8.9.2.

8.10.2 Probabilistic sensitivity analysis (PSA)
8.10.2.1 PSA for the primary base case
The company has provided revised PSAs following their comments on the first draft of the ASAR, reportedly due to an error in the PSAs that were submitted. The results of these revised PSAs are more favourable to etravirine and have not been verified.

A cost-effectiveness acceptability curve (CEAC) was generated from 1,000 simulations. This indicates that at willingness to pay thresholds of £20,000/QALY, and £30,000/QALY, the probabilities of etravirine plus OBR being cost effective compared with placebo plus OBR are 0.6%, and 81.2%, respectively.

8.10.2.2 PSA for the secondary analysis
From 1,000 simulations, the revised, unverified CEAC indicates that at willingness to pay thresholds of £20,000 and £30,000 per QALY gained, the probabilities that etravirine is more cost effective than raltegravir are 99.9% and 98%, respectively. However, it should be noted that, whilst the revised PSA reportedly shows that etravirine is less costly than raltegravir in 98.2% of the cases, it also shows that etravirine is less effective than raltegravir in 76.2% of the overall cases.

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

9.0 REVIEW OF EVIDENCE ON BUDGET IMPACT

9.1 Description and critique of the company's submission
The prevalence and incidence of HIV in Wales is based on National Public Health Service for Wales data up to June 2008[25]. These have been used to construct a linear equation to estimate the number of newly diagnosed patients over the next five years, and a constant HIV-related death rate is assumed[2]. Data from a UK cohort study that followed patients attending several HIV centres between 1996 and 2002 has been used to provide estimates of the proportion of patients who are triple-class experienced and experience virological failure[26], although the extent to which data from 2002 are representative of treatment patterns today is unclear. The net cost impact is presented on the assumption that etravirine is simply added to an OBR, and does not consider the possibility of it being used as a substitute for other agents.

9.2 Perspective and time horizon
The analysis considers direct costs from the perspective of NHS Wales over a five-year period 2009 to 2013[2].

9.3 Data sources

9.3.1 Incident and prevalent cases

National Public Health Service for Wales data up to June 2008 indicates there is a cumulative total of 1,526 patients with a HIV diagnosis in Wales[25]. Despite the fact that this source advises against simply subtracting the number of deaths to derive an estimate of the current prevalence, the company submission has done this and estimate that there were 1,280 patients diagnosed with HIV in Wales at the end of June 2008[2]. Using historical estimates of new diagnoses each year, the company estimates that there would a year on year increase of around 19 patients in the number of newly diagnosed patients each year. Death rates have been assumed to be stable at 1.3% per year. The total number of patients with HIV at the end of 2009 is therefore estimated as 1,832, rising to 2,772 in 2013[2].

Based on a prospective cohort study in which all patients attending six HIV centres in the UK were followed between 1996 and 2002, it is assumed that 71.3% of patients have ever been treated with antiretroviral agents and that of these 38.3% are triple-class experienced, of which 15.3% experienced virological failure. This translates into 73 patients in 2009, rising to 111 patients in 2013 who would potentially be eligible for treatment with etravirine[2].

9.3.2 Projected rate of adoption and market share

The company estimates that 37% of potentially eligible patients would receive etravirine in 2009. In subsequent years it appears that the estimated uptake is increased 57 to 58%. The number of patients estimated to receive etravirine in 2009 is stated to be 27 in 2009, rising to 64 in 2013[2].

9.3.3 Costs and resource use

The company submission highlights that etravirine treatment was associated with a reduction in the frequency and duration of hospitalisations compared with placebo in the DUET studies[10]. The costs associated with hospitalisation are not further considered in the budget impact section.

9.4 Results

The net budget impact estimates presented in the company submission assume that etravirine is simply added to an OBR. No consideration is given to the possibility of etravirine being used instead of other agents.

In 2009, assuming 27 patients receive etravirine for a complete year the budget impact is estimated as £100,817. This is estimated to increase to 64 patients at a cost of £238,973 in 2013[2].

9.5 Sensitivity analysis

No sensitivity analysis was conducted for the budget impact analysis.

9.6 Comparator costs

Possible comparators in this patient group may include raltegravir or maraviroc. The 30 day costs of these, based on prices listed on eMIMs, April 2009[23], are presented in Table 1:

Table 1. 30-day costs etravirine and possible comparators

Antiretroviral agent	Usual dose	30-day cost[23]
Etravirine	200mg bd	£307.35
Maraviroc	300mg bd	£551.10
Raltegravir	400mg bd	£647.29
This table presents costs only and does not imply therapeutic equivalence between the agents contained herein. bd = twice daily		

10.0 ADDITIONAL INFORMATION

10.1 Guidance and audit requirements

- BHIVA issued updated guidelines on antiretroviral treatment of HIV-1 in adults online in May 2008[4], as discussed in section 3.0 and throughout the ASAR.
- The Health Protection Agency, in collaboration with National Public Health Survey for Wales, conducts an annual survey (SOPHID) of all patients seen for HIV-1-related treatment or care[27].
- Etravirine if accepted for use should be initiated by specialists, and is currently not deemed suitable for shared care.

10.3 Previous AWMSG advice

- Atazanavir (Reyataz®▼) is recommended as an option for use within NHS Wales for the treatment of HIV-1 infected adults in combination with other antiretroviral medicinal products: for treatment-naive patients, in accordance with British HIV Association (BHIVA) guidance[28].
- Atazanavir (Reyataz®▼) is recommended as an option for use within NHS Wales for the treatment of HIV-1 infected adults in combination with other antiretroviral medicinal products: for treatment-experienced patients, in accordance with British HIV Association (BHIVA) guidance[29].
- 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[30].
- Fixed-dose abacavir and lamivudine (Kivexa®) is recommended as an option for use within NHS Wales in antiretroviral combination therapy for the treatment of Human Immunodeficiency Virus (HIV-1) infection in adults and adolescents from 12 years of age[31]. Use should be in accordance with the British HIV Association (BHIVA) guidance.
- Enfuvirtide (Fuzeon®) – recommended as an option for use for the treatment of patients with HIV-1, with restrictions; May 2004[32].
- Emtricitabine (Emtriva®) – recommended as an option for use within NHS Wales for the treatment of HIV-1 infected adults in combination with other antiretroviral agents for use in treatment-naïve patients in line with current BHIVA guidelines; June 2007[33].
- Emtricitabine/tenofovir DF (Truvada®) – recommended as an option for use within NHS Wales for the treatment of HIV-1 infected adults who are treatment-naïve and in line with current BHIVA guidelines; June 2007[34].

- 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, in accordance with BHIVA guidelines; August 2007[35].
- 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, in accordance with BHIVA guidelines; August 2007[36].
- Efavirenz/emtricitabine/tenofovir (Atripla®▼) – recommended as an option for use within NHS Wales for the treatment of HIV-1 infection in adults with virological suppression to HIV-1 RNA levels of < 50 copies/ml on their current combination antiviral treatment for more than three months and in accordance with BHIVA guidelines; February 2009[37]
- Maraviroc (Celsentri®▼) – recommended as an option for use within NHS Wales for the treatment of treatment-experienced adults infected with CCR5-tropic HIV infection, in accordance with BHIVA guidelines; April 2009[38].

10.4 Patient organisation information

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

10.5 Medical expert / Clinical expert summary

A summary of medical / clinical expert views was provided to AWMSG members.

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Appendix 1. Additional Clinical Information
Table 1A. Prospective studies of etravirine in treatment-experienced patients with HIV-1

Ref	Study type	No. patients	Inclusion criteria	Baseline characteristics (approximate)	Treatment regimens	Outcomes (etravirine versus placebo)
3,4,5,6 DUET-1 and DUET-2	Randomised, double-blind, placebo-controlled, 48-week, identical, phase III trials DUET-1: France, USA, South America, Thailand DUET-2: Australia, Europe (incl. 10 patients from UK), USA and Canada	DUET-1: n=612 DUET-2: n=591	HIV-1 patients aged ≥18yrs Stable ARV regimen for ≥8 weeks, but failing HIV RNA >5000 copies/mL ≥3 primary PI mutations ≥1 NNRTI resistance associated mutations No currently active AIDS-defining illness Life expectancy ≥6 months	Age†: 45 years Males: 90% White: 70% HIV RNA†: 4.8 $\log_{10}$ copies/mL CD4†: 100 cells/mm^3 AIDS: 59% Hepatitis B/C: 12% Prior ARV use: 10-15 ARVs: 66% NNRTIs: 12% Darunavir/ritonavir: 5% Mutations: ≥2 NNRTI mutations: 69% ≥3 etravirine mutations: 14% ≥3 primary PI mutations: 62% OBR included enfuvirtide: 47% (26% de novo) Active ARVs in OBR : ≤1: 54%	DUET-1: Etravirine 200mg bd (n=304) versus Placebo (n=308) DUET-2: Etravirine 200mg bd (n=295) versus Placebo (n=296) Each in combination with OBR: at least two other ARVs (NRTI(s) with or without enfuvirtide) plus darunavir/ritonavir	**Primary endpoint:** % patients with HIV RNA <50 copies/mL at **24 weeks** (TLOVR) for etravirine versus placebo: DUET-1 results: Overall population: 55.9% versus 38.6% *De novo* enfuvirtide: 59.5% versus 55.7%; p=0.7935 Not *de novo* enfuvirtide: 54.8% versus 32.8%; p<0.0001 DUET-2 results: Overall population: 62.0% versus 43.6% *De novo* enfuvirtide: 73.4% versus 67.9%; p=0.3838 Not *de novo* enfuvirtide: 57.9% versus 34.4%; p<0.0001 Pooled results: Overall population: 58.9% versus 41.1%; p<0.0001 *De novo* enfuvirtide: 66.7% versus 61.9%; p=0.427 Not *de novo* enfuvirtide: 56.3% versus 33.6%; p<0.0001

Table 1A. continued Prospective studies of etravirine in treatment-experienced patients with HIV-1

Ref	Study type	No. patients	Inclusion criteria	Baseline characteristics (approximate)	Treatment regimens	Outcomes (etravirine versus placebo)
						Secondary/other endpoints at 48 weeks (pooled data): % patients with HIV RNA <50 copies/mL (TLOVR): 61% versus 40%; p<0.0001 % patients with HIV RNA <400 copies/mL: 72% versus 47%; p<0.0001 Mean viral load reduction (log_{10} copies/mL): -2.25 versus -1.49; p<0.0001) Mean change in CD4 cell count (cells/mm^3):+98 versus +73; p=0.0006 **Secondary/other endpoints at 96 weeks (pooled data)[37]:** Commercial in confidence data

Table 1A. continued Prospective studies of etravirine in treatment-experienced patients with HIV-1

Ref	Study type	No. patients	Inclusion criteria	Baseline characteristics (approximate)	Treatment regimens	Outcomes (etravirine versus placebo)
3,5,8 Study C223	Randomised, open-label‡, 48-week, phase IIb, dose exploring study USA	n=199	HIV-1 patients aged ≥18yrs HIV RNA >1000 copies/mL Documented NNRTI resistance ≥3 primary PI mutations	Age†: 45 years Males: 91% White: 61% HIV RNA†: 4.7 $\log_{10}$ copies/mL CD4†: 100 cells/mm^3 AIDS: >60% NB: Imbalances in enfuvirtide use and phenotypic sensitivity scores in favour of etravirine arm (refer to section 6.1.2)	Etravirine 400mg bd (n=80) (not discussed further) versus Etravirine 800mg bd* (n=79) versus Active control (n=40) Each in combination with OBR (if OBR includes PI = lopinavir/ritonavir)	**Primary endpoint:** Change in viral load ($\log_{10}$ copies/mL) from baseline at **24 weeks** (etravirine 800mg bd* versus active control): -1.194 versus -0.412; p<0.001 **Secondary/other endpoints:** Change in viral load ($\log_{10}$ copies/mL) from baseline at 48 weeks: -1.043 versus -0.368; p=0.002 % with HIV RNA <50 copies/mL at 48 weeks: 22% versus 0%; p<0.001 % with HIV RNA <400 copies/mL: 30% versus 8%; p=0.009 Mean change in CD4 cell count (cells/mm^3):+61 versus +13

ARV = antiretroviral agent; bd= twice daily; HAART = highly active antiretroviral treatment; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; OBR = optimised background regimen; PI = protease inhibitor; TLOVR = Time to loss of virological response (2 consecutive viral load values below the threshold are needed to count as a responder; 2 consecutive values above the threshold value are needed to become a non-responder; patients who discontinue early are counted as failure; re-suppression after confirmed rebound is also considered as failure); † = median; ‡= blinded only to dose of etravirine; *= 800mg bd of older formulation is bioequivalent to 200mg bd of the commercially available formulation.