European Medicines Agency

London, 23 July 2009
EMEA/CHMP/543482/2009

ASSESSMENT REPORT FOR ISENTRESS

International Nonproprietary Name:
raltegravir

Procedure No. EMEA/H/C/860/II/10

Marketing Authorisation Holder (MAH): Merck Sharp & Dohme Ltd.

Variation Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 86 68
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

1. Introduction

Isentress (raltegravir) was approved in the EU in December 2007 for the treatment of HIV-1 infection in treatment-experienced adult patients with evidence of HIV-1 replication despite ongoing anti-retroviral therapy.

In the initial application dossier safety and efficacy data to at least Week 24 were reported from the two major clinical studies (018 and 019) that supported the indication granted under a Conditional Approval. Specific Obligation 001 (SOB001) concerned the provision of Week 48 data from these studies, which were filed as variation EMEA/H/C/860/II/01 (approved on 7 January 2009).

Among the Follow-Up Measures (FUM) the MAH committed to provide completed reports on a list on ongoing and planned studies including study 021 as follows:

Area	Description	Due date
Clinical	Protocol 021: A Multicentre, Double-Blind, Randomised, Active-Controlled Study to Evaluate the Safety and Antiretroviral Activity of MK-0518 Versus Efavirenz in Treatment Naïve HIV-Infected Patients, Each in Combination With Truvada.	31-Mar-2009 (Week 48) 31-Mar-2010 (Week 96)

The MAH submitted the data required to fulfil this FUM directly as a variation (II/010) to the existing MA.

The MAH initially provided:

- The Week 48 (primary analysis) safety and efficacy data from the Phase III study 021
- A Clinical Overview and Summaries of the additional clinical pharmacology, efficacy and safety data obtained from previously ART-naïve subjects
- Proposed revisions of the SPC and PL
- A revised RMP (version 4.0).

The SPC changes that are directly related to use in ART-naïve subjects affect sections:

- 4.1 - to broaden the indication
- 4.4 - to specify populations and remove the paragraph on cancers
- 4.8 - to update the safety information with data from 021
- 5.1 - to add information on efficacy in ART-naive to Week 48.

PL changes were made accordingly to sections 1, 2 and 4.

The MAH's initial proposals for amendment of the SPC and PL are to be found in Attachment 2 to this Assessment Report.

CHMP guidelines

The CHMP guideline "Clinical Development of Medicinal Products for Treatment of HIV Infection" CPMP/EWP/633/02 (Rev. 2) is relevant for the assessment of this application. A convincing demonstration of non-inferiority at 48 weeks versus a well-recognised reference regimen may serve as a basis for approval, with data on prolonged follow up to be provided post approval. However, longer term data (i.e. > 48 weeks) might be required pre-approval if there are any specific safety concerns identified in clinical or non-clinical studies.

Additional relevant data

During the assessment period the MAH notified the CHMP in November 2008 of emerging data from studies 032 and 033, in which patients with stable viral suppression on a lopinavir/ritonavir-based regimen were switched to raltegravir without any change in backbone therapies. These studies failed

to demonstrate non-inferiority for switching to raltegravir compared to maintaining a lopinavir/ritonavir regimen and the studies have been terminated.

Provisional data reported from these studies were reviewed by the CHMP. The CHMP considered that the findings could potentially impact on the suitability of raltegravir when used in certain specific combination regimens for treatment of previously ART-naïve subjects. Therefore, the CHMP considered that an opinion on variation II/010 could not be reached until the reasons for the unexpected results had been explored.

To this end, a list of questions on studies 032 and 033 was appended to the questions specific to study 021 and it was agreed between CHMP and the MAH that the responses should be submitted concurrently.

Therefore this assessment report takes into account relevant data from studies 032 and 033 although these studies were not conducted in ART-naïve subjects.

Request for an additional year of marketing protection in accordance with Article 14(11) of Regulation (EC) No 726/2004

With submission of this application for a new indication for use in ART-naïve patients, the MAH also applied for an additional one year marketing protection period in accordance with Article 14(11) of Regulation (EC) No 726/2004. The MAH claimed that raltegravir provides a significant clinical benefit in comparison with existing standard of care in the HIV-1-infected treatment-naïve patient population.

While the data from study 021 result in a favourable risk benefit balance for use of raltegravir with two other NRTIs in previously ART-naïve patients the data do not suggest that raltegravir has superior efficacy or safety compared to the single comparative regimen studied. Therefore, the MAH's request for an additional year of marketing protection based on the new indication for use in previously ART-naïve patients is not considered to be supported (see also the Attachment to this Assessment Report).

2. Clinical aspects

2.1 Clinical Pharmacology

No pharmacokinetic data were obtained during the Phase III study 021 in ART-naïve subjects.

The application contains an updated analysis of pharmacokinetic and virological outcome data from the Phase II study 004 in ART-naïve subjects that was previously reported.

- Part I of this study consisted of 10 days of raltegravir monotherapy (100, 200, 400 or 600 mg administered twice daily as the Phase II/III/FMI poloxamer formulation) versus placebo in 35 subjects (Cohort I).
- Part II evaluated twice daily dosing with raltegravir 100, 200, 400 or 600 mg versus efavirenz 600 mg every evening, each administered in combination with tenofovir and lamivudine for 48 weeks in a total of 198 subjects (Cohort I plus Cohort II).
- Intensive PK sampling was conducted on Day 10 of monotherapy in Part I and at 2 weeks of therapy in Part II in Cohort I only.
- Sparse PK sampling was performed at Weeks 4, 8, 12 and 16. One sample was collected for all subjects (both Part I and II cohorts). At Weeks 4, 8 and 16 a single sample was collected irrespective of time relative to dosing. At Week 12 a single sample was drawn just prior to the morning dose.

In the previously reported analyses there were marked differences in the absorption profile between sampling occasions within individual subjects and across the study population. There were no strong associations with explanatory covariates available in the data set. This behaviour rendered model-

based predictions of exposure from the sparse sample dataset difficult to interpret. Therefore, three non-model-based exposure summary measures based on the observed concentration data were defined as follows (as applied already to data in treatment experienced subjects):

- Geometric Mean observed C12h (GM C12h): geometric mean of all samples for a particular patient collected between 11 and 13 h post-dose.
- Geometric Mean of All Observed Concentration (GM All): geometric mean of all samples for a particular patient, regardless of when they were collected. GM All likely provides a more reliable estimate of a subject's overall exposure to raltegravir than GM C12h.
- Minimum of All Observed Concentrations (Cmin): minimum value of all samples for a particular patient, regardless of time of collection.

The available sparse sampling dataset for study 004 consisted of data from 151 out of 160 treated with raltegravir, with all 151 having values for GM All and Cmin. A subset of 104 had samples collected between 11 and 13 h post-dose and thus had GM C12h values.

The data demonstrated a general trend of increasing concentrations with increasing dose but with considerable overlap of values among the doses evaluated and almost complete overlap between the 200 and 400 mg doses. The MAH considered that this finding was consistent with the large degree of inter-subject and inter-occasion variability observed with raltegravir in other studies.

PK/PD analyses were conducted using the 2-step approach i.e. individual PK parameter values were first determined and then a statistical analysis of the potential relationship between PK and a variety of efficacy response parameters was performed.

The concentration and efficacy dataset used for the analyses described below was the same as in the initial application and only the PK parameters calculated from the sparse sampling concentration dataset have changed. GM C12h was included in the prior analysis and the results have been re-presented for completeness.

Formal association analyses were performed for HIV RNA <400 copies/ml, HIV RNA <50 copies/ml, occurrence of virological failure and change from baseline in log10 HIV RNA at week 48. All subjects receiving any dose of raltegravir in a combination regimen were included in the analysis.

The potential association between PK summary measure values and efficacy response measures was assessed through logistic regression model, in which an odds ratio (95% CI) was determined. The odds ratio coefficient resulting from the regression model could be interpreted as the percent change in the odds (probability of the event occurring over probability of the event not occurring) of the response for each 1-unit increase on the $\log_{10}$ scale in the pharmacokinetic parameter. Baseline HIV RNA was identified as a significant predictor of treatment outcome and so was included along with the PK parameters in the logistic regression models.

In the PK/PD association analysis only a subset of subjects had data for GM C12h and there were insufficient numbers in this group with HIV RNA ≥400 copies/ml or occurrence of virological failure to allow a formal association analysis. Formal statistical analyses for the occurrence of HIV RNA <50 copies/ml and change from baseline in HIV RNA did not show any association with GM C12h.

GM All and Cmin were available for most subjects. Associations with statistically significant p-values ($p<0.05$) were observed between the PK parameters GM All and Cmin and the treatment outcome HIV RNA <400 but in the opposite direction from what would be expected such that a higher value for GM All and Cmin decreased the probability of having HIV RNA <400. This relationship was demonstrated to be heavily influenced by an outlier with a large value for the PK parameters but with some concentration values that were BLQ and the anomaly was not found when the outlier data were excluded.

No associations were observed between any PK parameter and HIV RNA <50, virological failure or change from baseline in HIV RNA. The MAH concluded that the results were consistent with a lack of

a meaningful PK/PD association over the range of doses tested and PK values observed in the treatment naïve population.

Given the high percentage of favourable efficacy responses the lack of a meaningful association between PK and efficacy response measures suggested that the relationship between raltegravir concentrations and outcomes fell near the top of the concentration-response curve, where treatment response has, at most, only a weak concentration-dependency.

Discussion on Pharmacology

The PK data demonstrated very considerable overlap in concentrations between dose groups and no clinically meaningful differences in efficacy response measures across GM C12h, GM All and Cmin. Baseline HIV RNA was negatively associated with the efficacy measures.

The overall findings reflect the very marked inter-individual (and also intra-individual) variability in raltegravir PK that has been observed previously. The PK/PD analysis is hampered by paucity of PK sampling data and the very high favourable response rates.

Overall the results can be considered consistent with the previously reported analyses in treatment experienced subjects in the two Phase III studies (018 and 019).

2.2 Clinical Efficacy

Study P021

- The study was initiated on 14 September 2006 and the last subject completed to Week 48 on 5 June 2008.
- The Week 48 data cut-off of 1 July 2008 for the current clinical study report captures all clinical data to 5 June 2008, all viral resistance data to 10 June 2008 and genotyping results up to 27 August 2008. Serious Adverse Events (SAEs) reported to the MAH's Worldwide Adverse Experience System (WAES) are included up to 31 May 2008.
- The study is ongoing to Week 96. The MAH expects to provide the data for Week 96 by 31 December 2009.

P021 is an ongoing randomised study that compares raltegravir with efavirenz in a double-blind design when each is administered to previously ART-naïve adults in combination with open-label tenofovir/emtricitabine (200 mg emtricitabine + 300 mg tenofovir disoproxil fumarate).

There were initially 69 study sites spread across North America, Latin America, Europe, India, Thailand and Australia of which 67 sites enrolled subjects.

Patient selection

Eligible HIV-infected adults were to have a screening (within 60 days of commencing study treatment) plasma HIV RNA >5000 copies/ml as determined by the central laboratory. Subjects were to be ART-naïve and local treatment guidelines were to be considered in the decision to initiate therapy.

Within 35 days of commencing treatment, laboratory studies were to establish that serum creatinine was ≤2.0 x Upper Limit of Normal (ULN) and that the liver function tests ALP, AST and ALT were all ≤5.0 x ULN. The calculated creatinine clearance (Cockcroft-Gault equation) was to be >30 ml/min.

The most pertinent exclusion criteria included documented resistance to tenofovir, emtricitabine and/or efavirenz and acute hepatitis due to any cause. Subjects with chronic hepatitis, including chronic HBV and/or HCV, were allowed to enter the study if they had stable liver function tests but

those with evidence of impaired hepatic synthetic function (e.g. hypoalbuminaemia or prolonged PT and PTT) were excluded.

Objectives

Primary:

1) To evaluate the antiretroviral activity of raltegravir 400 mg twice daily compared with efavirenz 600 mg once daily each in combination therapy with tenofovir/emtricitabine measured by proportions achieving HIV RNA <50 copies/ml at Week 48.
2) To evaluate the safety and tolerability of raltegravir compared with efavirenz by review of the accumulated safety data at Week 48.

Secondary:

1) To evaluate the antiretroviral activity of raltegravir compared with efavirenz measured by:
   (a) The proportion achieving HIV RNA <400 copies/ml at Week 48
   (b) The change from baseline in CD4 cell counts at Week 48.
2) To evaluate the antiretroviral activity of raltegravir compared with efavirenz measured by:
   (a) The proportion achieving HIV RNA <50 copies/ml at Week 96
   (b) The proportion achieving HIV RNA <400 copies/ml at Week 96
   (c) The change from baseline in CD4 cell counts at Week 96.
3) To evaluate the safety and tolerability of raltegravir compared with efavirenz by review of the accumulated safety data up to Week 96.
4) To evaluate the nervous system symptoms associated with raltegravir and efavirenz by review of accumulated safety data up to Week 8.

Statistical methods

The primary efficacy hypothesis was that the proportion achieving HIV RNA <50 copies/ml at Week 48 in the raltegravir group was non-inferior to that in the efavirenz group.

The Week 48 secondary efficacy hypotheses were:

- Proportion with <400 copies/ml at Week 48 in the raltegravir group was non-inferior to that in the efavirenz group
- Change from baseline in CD4 cell count was similar between raltegravir and efavirenz groups.

The primary analyses of efficacy was based upon the full analysis set (previously known as modified intent to treat: MITT) approach. Subjects were included in their randomised treatment group regardless of adherence to the entry criteria, actual treatment received and any deviation from the protocol.

The following approaches were used to handle missing values for those who prematurely discontinued assigned treatment:

- Observed Failure (OF): Subjects who prematurely discontinued assigned treatment due to lack of efficacy were considered as failures thereafter.
- Treatment-Related Discontinuation = Failure (TRD=F): Subjects who prematurely discontinued assigned treatment due to lack of efficacy or AE were considered as failures thereafter.
- NC=F: Subjects who prematurely discontinued assigned treatment regardless of reasons were considered as failures thereafter.

The OF and TRD=F approaches excluded missing observations from analyses while the NC=F approach considered these intermittent missing values as failures unless immediately flanked by two successes, in which case the intermittent missing value was excluded from the analyses.

The primary analysis at Week 48 used a NC=F approach in which missing values after premature discontinuation were filled in as failures. Week 48 time point proportions were computed within strata

(> or ≤ 50,000 copies/ml) and then combined using weights proportional to the size of each stratum. The 95% CIs and p-values for non-inferiority for treatment differences in response rates were calculated using Miettinen and Nurminen's method with weights proportional to the size of each stratum. The primary and secondary efficacy analyses did not adjust for covariates.

Time-to-Virological-Response (TVR) and Time-to-Loss-Of-Virological-Response (TLOVR) were estimated using Kaplan-Meier product-limit estimates and graphically displayed. A log rank test was applied to time-to-event data.

The primary analysis of safety was based upon the All Patients as Treated (APaT) approach. Only those AEs that occurred while on study therapy or within 14 days after discontinuation were included in the analysis.

The assessment of central nervous system (CNS) AEs was based on selected MedDRA terms (dizziness, insomnia, somnolence, concentration impaired, depression, nightmare, confusional state, suicidal ideation, nervous system disorder, psychotic disorder, abnormal dreams, suicide attempt, acute psychosis, delirium, depressed level of consciousness, hallucination, auditory hallucination, completed suicide and major depression) at Weeks 0 to 8 and at Weeks 0 to 48.

The differences in percentages with CNS AEs between treatments and two-sided 95% CIs using Miettinen and Nurminen's method were calculated and the statistical comparisons of the differences were based on a two-tailed Fisher's exact test. Time to first CNS AE was estimated using Kaplan-Meier product-limit methods and graphically displayed. A log rank test was applied to time-to-event data.

Results

Three of the 566 subjects who were randomised did not receive any study drug and were excluded from all analyses.

The following subjects had protocol violations but were included in the efficacy and safety analyses:

- Five had medication dispensing errors that led to them taking the wrong assigned drug for up to 2 months (mostly one month or less).
- Thirteen did not meet the inclusion criteria for obtaining specific laboratory values within 35 days prior to the treatment phase. These 13 were considered to be clinically stable by the investigator at the time of randomisation.
- Four were not completely ART-naïve. One had received several agents over >3 years, two had received zidovudine during pregnancy and one had received just a single dose of zidovudine previously. These four did not disclose the prior treatment until after randomisation.
- Six took prohibited medications during the study, mostly of short duration.
- Eight had recent signs and symptoms of active infection and/or a change in clinical status noted at least 2 weeks prior to the start of treatment in the study.
- Three (one raltegravir and two efavirenz) were prematurely unblinded to the investigator through the IVRS and without consulting the Merck Clinical Monitor. MRL data reviewers were not unblinded to this information. Data from these three were included in efficacy and safety analyses.

Baseline patient characteristics for the full analysis set showed that most (about 80%) were males with a median age of 37 years. About 15% had a prior history of AIDS and about 7% per group were co-infected with HBV or HCV. It is notable that about 50% of subjects had >100,000 copies/ml at baseline and just under 50% had CD4 counts <200 cells/mm^3. Despite the geographical spread about 80% had clade B virus. The most common (>15% in all subjects) secondary conditions reported were decreased CD4 lymphocytes (25.6%), lymphadenopathy (20.2%) and depression (18.1%).

Virological responses

The table below summarises outcomes at Week 48 based on the NC=F approach. Results for the all treated population were almost identical.

Table 1 Treatment Outcome at Week 48

Outcome at Week 48	**Raltegravir** 400 mg b.i.d. (N=281) n (%)	**Efavirenz** 600 mg q.h.s. (N=282) n (%)
Patients with HIV RNA less than 50 copies/ml[†]	241 (86.1)	230 (81.9)
Patients with HIV RNA less than 400 copies/ml[†]	252 (90.0)	241 (85.8)
Mean CD4 cell count change from baseline (cells/mm^3)[†]	189.1	163.3
Virologic Failure (confirmed)[‡]	27 (9.6)	39 (13.8)
Non responder	10 (3.6)	24 (8.5)
Rebound	17 (6.0)	15 (5.3)
Death	2 (0.7)	0 (0.0)
Discontinuation due to clinical adverse experiences	8 (2.8)	17 (6.0)
Discontinuation due to laboratory adverse experiences	0 (0.0)	1 (0.4)
Discontinuation due to other reasons[§]	12 (4.3)	15 (5.3)

[†] Approach to handling missing values: For binary endpoints (proportions), Non-Completer = Failure. For change from baseline in CD4 cell counts, Observed Failure (OF) approach assumes baseline value was carried forward for patients who discontinued assigned therapy due to lack of efficacy.

[‡] Virologic failure: defined as non responders for those with (1) HIV RNA > 50 copies/ml at the time of discontinuation for patients who prematurely discontinue study therapy or (2) HIV RNA > 50 copies/ml at Week 24; or virologic rebound for those with HIV RNA > 50 copies/ml (on 2 consecutive measurements at least 1 week apart) after initial response with HIV RNA < 50 copies/ml.

[§] Includes loss to follow-up, patient withdrew consent, noncompliance, protocol violation and other reasons.

n (%) = Number (Percent) of patients in each category.

As shown below, the analyses indicated that raltegravir was non-inferior to efavirenz with respect to the primary efficacy endpoint (< 50 copies/ml) and the secondary endpoint (<400 copies/ml). In fact, the lower bounds of the 95% CI around the differences in percentages of subjects that achieved these levels of viral suppression were both within -2%. The raltegravir group also showed a numerically greater mean change from baseline in CD4 cell count compared with efavirenz.

Table 2 Efficacy Analysis at Week 48 (NC = F approach)[†]

Parameter	Unadjusted Data Summary by Treatment Group		Treatment Effect (Raltegravir vs. Efavirenz)		Conclusion[§]
	Raltegravir 400 mg b.i.d. n/N (%)	Efavirenz 600 mg q.h.s. n/N (%)	Estimated Difference[‡] Difference in Percent Response (95% CI)	p-Value for Non-inferiority	
Proportion of patients with HIV RNA <50 c/ml	241/280 (86.1)	230/281 (81.9)	4.2 (-1.92, 10.32)	<0.001	Non-inferior
Proportion of patients with HIV RNA <400 c/ml	252/280 (90.0)	241/281 (85.8)	4.1 (-1.28, 9.68)	<0.001	Non-inferior
	Mean (95% CI)	**Mean (95% CI)**	**Mean Difference (95% CI)**		
Change from Baseline in CD4 Cell Count (cells/mm^3)	189.10 (173.9, 204.3)	163.33 (148.2, 178.4)	25.77 (4.37, 47.17)		

[†] Approach to handling missing values: For binary endpoints (proportions), Non-Completer = Failure. For change from baseline in CD4 cell counts, Observed Failure (OF) approach assumes baseline value was carried forward for patients who discontinued assigned therapy due to lack of efficacy.

[‡] The 95% CIs and p-values for non-inferiority for treatment differences in percent response were calculated using Miettinen and Nurminen's method with weights proportional to the size of each stratum (screen HIV RNA>50,000 copies/ml or ≤ 50,000 copies/ml). The 95% CI for mean difference in CD4 change was based on t-distribution.

[§] Raltegravir is concluded non-inferior to Efavirenz if the lower bound of the 95% CI for the difference in percent response is above -12 percentage points. It can be further concluded that Raltegravir is superior to Efavirenz if the lower bound exceeds zero.

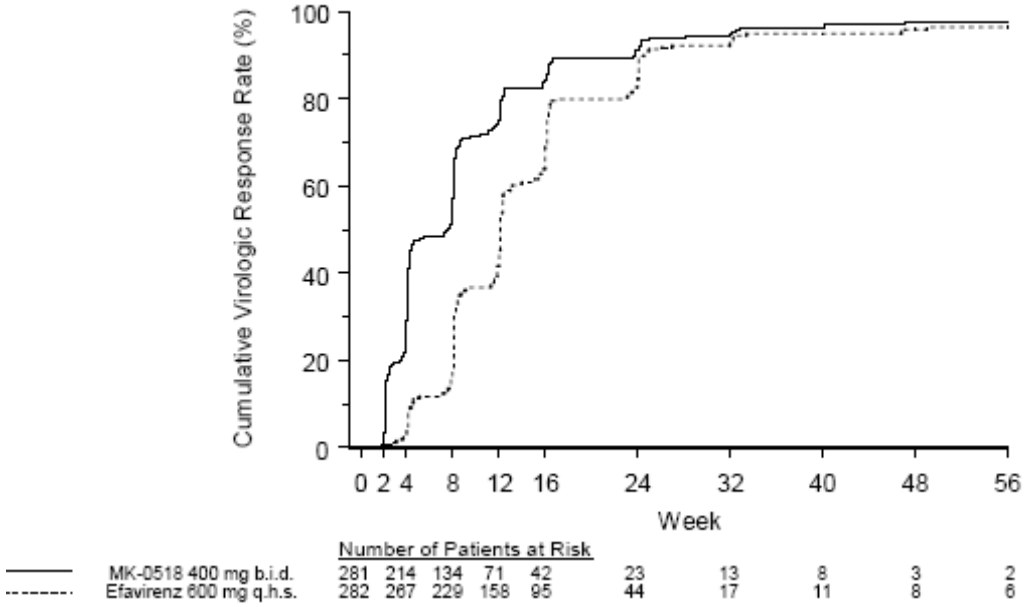
N = Number of patients in each treatment group.

The sensitivity analyses using alternative methods to account for missing data gave consistent findings, with lower 95% CI within -3%.

Starting from Week 2 onwards raltegravir was associated with a more rapid decline in viral load compared to efavirenz. The 95% CI of treatment difference for percentages with <50 copies/ml excluded zero from Week 2 to Week 16 and then spanned zero up to Week 48. Similar findings applied to the analysis of percentages achieving <400 copies/ml over time, with 95% CI that excluded zero from Weeks 2-12 and then spanning zero up to Week 48.

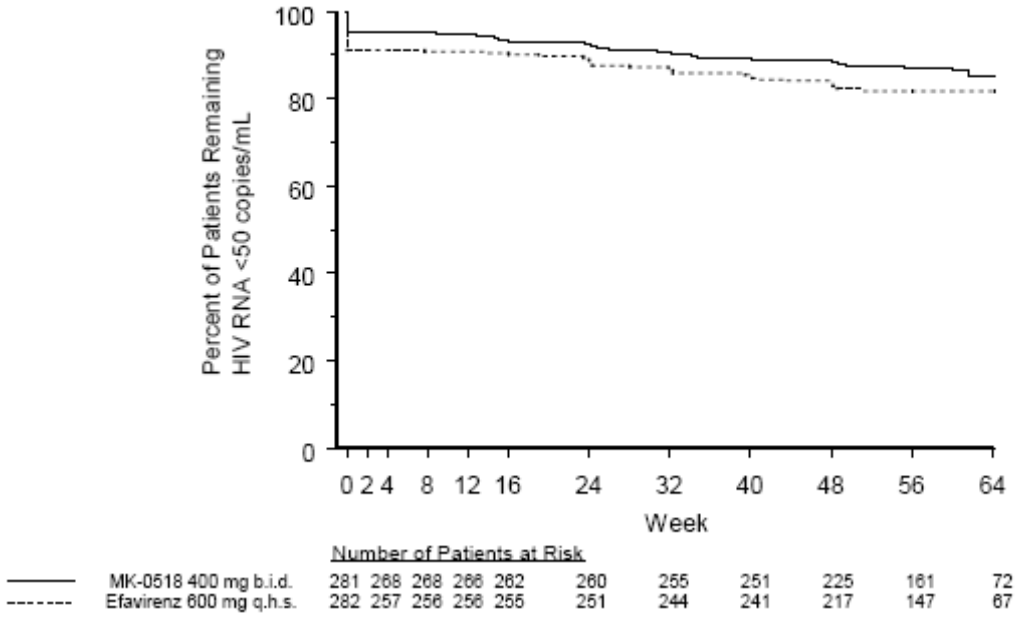
For subjects who achieved HIV RNA <50 copies/ml time to virological response was calculated as time between randomisation and the first of two consecutive values (at least 1 week apart) <50 copies/ml. For subjects who did not achieve <50 copies/ml the time to virological response was censored at the time of analysis. The time to achieve virological response was significantly shorter in the raltegravir group, as shown in the figure below.

Time to Virologic Response (TVR) - by HIV RNA < 50 copies/mL



As shown below the risk of loss of virological response was similar in the raltegravir and efavirenz groups. Generally sustained responses were observed beyond Week 48 in both treatment groups.

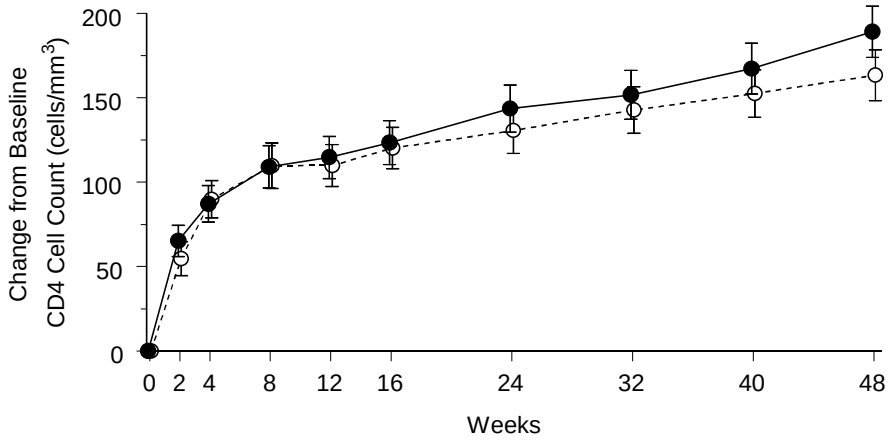
Time to Loss of Virologic Response – by HIV RNA ≥ 50 Copies/mL



CD4 counts

At Week 48 the raltegravir group showed a greater increase in CD4 count (based on nominal 95% CI of treatment difference excluding zero) compared with efavirenz.

Change From Baseline in CD4 Cell Count (95% CI) Over Time
Observed Failure Approach Protocol 021



Number of Contributing Patients

●	MK-0518 400 mg b.i.d.	281	274	277	272	270	266	260	259	258
○	Efavirenz 600 mg q.h.s.	281	272	272	268	269	266	260	254	251

Outcomes by prognostic and stratification factors

The results according to baseline viral load, CD4 count and hepatitis (OF approach) indicated that raltegravir achieved similar efficacy to efavirenz regardless of these baseline prognostic factors. Similar conclusions were drawn from the analysis based on the NC=F approach.

Analysis by subpopulations

The raltegravir treatment group showed similar efficacy compared with efavirenz regardless of baseline demographic factors. The comparisons of CD4 counts by demographic factors also gave similar findings between the treatment groups.

Resistance

The MAH previously provided phenotypic evidence that four integrase mutations (Q148H, Q148R, Q148K, and N155H) were bona fide primary raltegravir resistance mutations. In addition, mutations at position Y143 had been observed and were listed as likely primary resistance mutations but no phenotypic data had yet been generated.

Phenotypic evidence was previously provided and showed that 8 additional mutations (L74M, E92Q, T97A, E138A, E138K, G140A, G140S and V151I) could augment resistance conferred by the primary mutations and these were therefore classified as secondary raltegravir resistance mutations.

In study 021, genotyping of resistance mutations could only be performed in subjects with HIV RNA >400 copies/ml (i.e. not in all failures as defined at the <50 copies/ml level). Both the integrase gene and the reverse transcriptase gene (RT) were to be sequenced regardless of randomised therapy group.

Of the 66 subjects who met the protocol definition of virological failure (27/281 [9.6%] raltegravir and 39/282 [13.8%] efavirenz) genotyping data are available for 20, including 12 and 8 in respective groups.

The four subjects in the raltegravir group with reduced susceptibility to the agent had the following mutations in integrase at the time of failure that were not present at baseline (those in bold type are already recognised to be associated with reduced susceptibility to raltegravir):

- **G140S, Q148H**
- **L74L/M, E92Q, T97T/A, Y143Y/H**, Q95Q/R
- **G140S, Q148R**, V31V/I, V165V/I
- **Y143R**, L242L/F, R224R/W

No amino acid changes from baseline in integrase known to be associated with raltegravir resistance were found in viruses obtained from other subjects who failed in either treatment group. Viruses isolated from some subjects had amino acid changes from baseline in integrase that were thought unlikely to confer resistance to raltegravir because they represent common polymorphisms, occurred in regions of the protein not previously known to contribute to resistance and/or were detected only sporadically (e.g. in only one of multiple RT-PCR reactions). Nevertheless it cannot be ruled out that certain of these changes could contribute to resistance to raltegravir.

To identify new raltegravir resistance mutations using a phenotypic approach, amino acid changes from baseline that had been observed more frequently were introduced into a wild-type HIV-1 pro-viral clone by site-directed mutagenesis. Viral stocks produced from these vectors by transfection were tested in a single-cycle infection assay for sensitivity to raltegravir and for their replication capacity.

A total of 32 variant viruses containing one or two specific mutations have been tested including 29 that had not been tested at the time of the original MAA. These variants included 14 single mutations (L74I, L74M, L74I, T97A, Y143C, Y143H, Y143R, G163R, H183P, Y226C, Y226D, Y226F, Y226H and S230N) plus 15 double mutations (Y143C, H or R in combination with L74M, E92Q, T97A, G163R or S230R).

Y143R conferred >10-fold resistance while Y143C and Y143H conferred only ~2-fold resistance. The degree of resistance was enhanced by adding secondary mutations, with the addition of E92Q conferring the highest-level resistance (32-fold, 15-fold and 215-fold when added to Y143C, Y143H and Y143R, respectively).

Among the other single mutations tested, only two conferred measurable raltegravir resistance (E92Q, ~3-fold resistance; S230R, ~2-fold resistance). Eight other mutations conferred no resistance (L74I, L74M, T97A, G163R, V151I, Y226F and S230N). The results for L74M, E92Q, T97A and V151I were consistent with data reported previously.

Five mutations resulted in viruses with significant defects in replication capacity (L74R, H183P, Y226C, Y226D, Y226H; all with RC < 0.5% of wild-type virus) so no phenotypic data could be generated for these mutants. Nucleotide sequence analysis confirmed that only the intended mutations were introduced into the integrase genes of the proviral clones. Each of these mutant proviruses was independently constructed a second time and testing of the resulting viruses confirmed that these changes gave rise to defective infection in cell culture. The data indicate that these mutations cause severe replication defects, at least in the context of the provirus tested in the experiments.

The MAH has confirmed that mutations Y143C, Y143H, Y143R, G163R and S230R constitute *bona fide* raltegravir resistance mutations and mutations at Y143 confer primary resistance. This information was therefore added to section 5.1 of the SPC.

- ***Discussion on Efficacy***

The MAH conducted a generally satisfactory single study (although provision of a second study would have provided a more robust demonstration of efficacy) to assess the safety and efficacy of raltegravir in previously ART-naïve subjects. The submission of data to Week 48 and the size of the database were considered to be acceptable in light of the results provided thus far and also taking into account the data already available in an ART-experienced population. The results available so far support the MAH's claim for non-inferiority of the raltegravir based regimen when compared to the efavirenz one in the target patient population of ART-naïve adult patients. However, the Week 96 data from study 021 should be provided as soon as available (this is already reflected in previous commitments).

The comparative regimen of efavirenz plus tenofovir and emtricitabine (as Truvada) is very widely used in previously ART-naïve subjects and was a suitable choice for this study. While tenofovir may increase plasma exposure to raltegravir it seems rather unlikely that this would have markedly augmented the efficacy of the raltegravir-containing regimen in study 021. This conclusion is based on the MAH's population PK/PD analyses, which (although subject to several caveats due to paucity of samples and inherent inter-subject variation) have not demonstrated any clear and consistent relationships between raltegravir PK parameters and virological responses in ART-naïve subjects.

Questions were raised regarding extrapolation of the demonstration of efficacy for raltegravir when co-administered with tenofovir and emtricitabine (as Truvada, taken with food) to ART-naïve subjects to other potentially useful raltegravir-containing regimens in this population. However, this should not be an issue for ART-naïve subjects unless they have acquired a resistant HIV *de novo*. Therefore there are no grounds at present to restrict the use of raltegravir in previously ART-naïve subjects to co-administration with tenofovir/emtricitabine. However, the CHMP requested that the SPC be modified to stress the limitations of the data provided by study 021, with which the MAH complied.

Overall, the efficacy data of this trial in ART naïve patients support the extension of indication in this target population.

Data from study 021 on resistance also provided some useful updated information on raltegravir RAMs, which was added to Section 5.1 of the SPC.

2.3 Clinical Safety

The mean number of days (range) for subjects on raltegravir at any dose was 395.1 (40 to 596) days up to the cut-off for this report. The mean number of days (range) for those on the protocol dose of raltegravir (800 mg/day) was 390.2 (33 to 591) days. The difference was due to a small number of dosing errors.

Analysis of AEs

The most frequently reported (incidence >10%) clinical AEs in both treatment groups were headache (19.6% raltegravir, 23.0% efavirenz), diarrhoea (14.6%, 21.6%), nausea (13.5%, 12.1%), nasopharyngitis (13.2%, 10.6%), upper respiratory infection (12.1%, 12.4%) and insomnia (10.7%, 10.3%).

Some AEs with an incidence >10% were reported only in the efavirenz group. These were dizziness (36.2%), abnormal dreams (13.1%), fatigue (11.0%), influenza (11.0%) and rash (11.7%). There were no AEs that occurred at an incidence >10% only in the raltegravir group.

Adverse Drug Reactions (ADRs)

- Drug-related clinical AEs were reported by 341/563 (61%) treated subjects including 124 (44%) in the raltegravir group and 217 (77%) in the efavirenz group. Drug-related AEs reported in >10% occurred only in the efavirenz group (dizziness [33.7%], headache [13.8%] and abnormal dreams [13.1%]).

- Clinical AEs considered to be related to raltegravir or efavirenz alone or in combination with tenofovir/emtricitabine were reported in 337/563 (59%) including 121 (43%) in the raltegravir group and 216 (77%) in the efavirenz group.
- Drug-related clinical AEs considered to be related to tenofovir/emtricitabine were reported in 15/563 (2.7%) including 8 (2.8%) in the raltegravir group and 7 (2.5%) in the efavirenz group. No individual AE occurred with an incidence ≥ 2% in either treatment group.

Clinical AEs of moderate or severe intensity that were considered related to raltegravir or efavirenz (alone or in combination with tenofovir/emtricitabine) or tenofovir/emtricitabine alone were reported in 135/563 (24%) treated of subjects including 45 (16%) in the raltegravir group and 90 (32%) in the efavirenz group. The most commonly reported were headache (3.9% raltegravir, 4.6% efavirenz), insomnia (3.6%, 3.2%) and nausea (2.8%, 3.5%).

AEs of special interest

Nervous System (pre-planned analysis)
During Weeks 0 to 8 there were statistically significantly fewer subjects with one or more nervous system AEs in the raltegravir group (20.3%) compared to the efavirenz (52.1%) group. Between Weeks 8 and 48 an additional 18 subjects in the efavirenz group and an additional 16 in the raltegravir group reported nervous system AEs. The types of AEs were similar to those observed during Weeks 0 to 8. As in the first 8 weeks, there were statistically significantly fewer subjects with at least one nervous system AE in the raltegravir group (26.0%) compared to the efavirenz group (58.5%).

Rash
AEs of rash (including terms of rash, erythematous rash, genital rash, generalised rash, macular rash, maculo-papular rash, papular rash, pruritic rash, pustular rash and vesicular rash) were reported for 81 subjects including 23/281 (8.2%) in the raltegravir group and 58/282 (20.6%) in the efavirenz group. None of these AEs were serious but three subjects discontinued efavirenz due to rash.

There were 44 subjects (7.8%) considered to have a drug-related rash of which 5 (1.8%) were in the raltegravir group and 39 were in the efavirenz group. All rashes were considered mild in intensity, were non-serious and none resulted in discontinuation from the study.

Pruritus
Pruritus (including generalised pruritus) was reported in 9 subjects (3.2%) in the raltegravir group and 11 (3.9%) in the efavirenz group. All cases of pruritus were of mild to moderate intensity and none was serious or resulted in discontinuation. Of six cases that were considered to be drug-related there were two raltegravir and four efavirenz group subjects.

Herpes Zoster
HZ (including ophthalmic cases) was reported in 10 raltegravir and 11 efavirenz group subjects. Two of three cases considered drug-related occurred in the raltegravir group. No subject was discontinued due to HZ and most cases were of mild to moderate intensity.

Hypersensitivity
There were two cases of hypersensitivity/ drug hypersensitivity reported in each treatment group. All cases were non-serious and of mild to moderate intensity. One case per group was considered drug-related.

Immune Reconstitution Inflammatory Syndrome (IRIS)
Investigators were asked to assess the possible association of each AE with IRIS. There were 17 (6%) raltegravir and 11 efavirenz subjects (4%) reported to have AEs associated with IRIS. The range of conditions included herpes simplex, herpes zoster, oral herpes, pyrexia, skin papilloma and tuberculosis affecting the gastrointestinal tract. Drug-related clinical AEs associated with IRS occurred in 8 and 3 subjects in respective groups.
Five raltegravir and two efavirenz subjects had SAEs reported as associated with IRIS as follows:

- In the raltegravir group two had a SAE stated to be associated with IRIS that was considered to be drug-related (gonococcal arthritis of the knee and mycobacterium immune restoration disease). The other three SAEs (IRS with neurosyphilis and ophthalmic involvement, IRIS associated with signs and symptoms of pancytopenia and Kaposi's sarcoma associated with IRIS) were not considered by the investigator to be drug-related.
- In the efavirenz treatment group one of the two cases was considered drug-related (IRIS associated with *Pneumocystis jiroveci* pneumonia) while the other patient had IRIS possibly associated with cytomegalovirus colitis.

The only patient who discontinued due to an AE associated with IRIS was the raltegravir-treated patient with Kaposi's sarcoma, who later died (see further details below).

Two subjects had a laboratory AE associated with IRIS – one in the raltegravir group with absolute neutrophil count decreased and one efavirenz patient with ALT increased. Both events were considered to be drug-related but not serious and the subjects continued on study therapy.

Laboratory AEs

Some laboratory AEs were associated with non-protocol required laboratory tests or reflex tests. Because only a small number of tests were performed, the percentages of subjects with these laboratory AEs may appear inflated compared with tests done routinely.

The most frequently reported (incidence ≥2%) reported laboratory AEs were AST increased (4.6% raltegravir and 5.3% efavirenz) and ALT increased (3.2%, 5.0%), which are discussed further below. Laboratory AEs that were reported only in the raltegravir group at rates of ≥2% were blood LDH increased (in 1/2 tested), hepatitis C antibody positive (in 1/2 tested), absolute neutrophil count decreased (2.1%), atypical lymphocytes (in 1/50 tested) and prostatic specific antigen increased (in the single subject tested).

However, there were no laboratory AEs associated with standard (protocol-specified) tests with an incidence of >10% in either treatment group.

Laboratory ADRs

Overall, drug-related laboratory AEs occurred in 14 raltegravir (5.0%) and 24 efavirenz subjects (8.5%) with increases in AST most frequently reported (2.1%, 2.8%). Drug-related laboratory AEs considered to be related to raltegravir or efavirenz (alone or in combination with tenofovir/emtricitabine) were reported by 13 (4.6%) and 24 subjects (8.5%), respectively, the commonest being AST increased (2.1%, 2.8%).

Hepatitis co-infection

18/281 (6.4%) patients in the raltegravir group were hepatitis B and/or C positive and 16/282 (5.7%) patients in the efavirenz group. The safety profiles of raltegravir and efavirenz in patients with hepatitis B and/or hepatitis C virus co-infection were comparable with the profiles observed in patients without hepatitis B and/or hepatitis C virus co-infection. Transaminase elevations were more common among co-infected patients, but were generally low-grade and not of clinical significance.

SAEs and deaths

The two SAEs resulting in death that have been reported thus far occurred in the raltegravir group. Neither of these fatal adverse experiences (Kaposi's sarcoma AIDS-related and cerebral haemorrhage) was determined by the investigator to be drug-related. Details of these cases are as follows:

KS case: This was a 28 year-old black male with anxiety, arthritis, candidiasis, depression, gynaecomastia, headache, penicillin allergy, pruritus and sulfonamide allergy (and a medical history of ankle fracture, asthma, bone graft/internal fixation of fracture, pneumonia, seasonal allergy and

staphylococcal infection). Concomitant therapy included ibuprofen, fluconazole, dronabinol and doxycycline. Baseline HIV RNA was 319,000 copies/ml and CD4 count was 23 cells/microlitre.

On Day 57 (when HIV RNA was 103 copies/ml and CD4 count was 155 cells/microlitre) the patient was hospitalised and diagnosed with IRIS in association with Kaposi's sarcoma. Symptoms included severe abdominal pain, weakness, dehydration, loss of appetite, nausea, diffuse lymphadenopathy, rectal mass, bloody stools, chest pain associated with breathing, anaemia, a caecal lesion and fever. Treatment included dapsone, promethazine, hydromorphone, acetylcysteine and acetaminophen. The patient was later discharged with IRIS and Kaposi's sarcoma still continuing. The patient was re-admitted due to uncontrolled abdominal pain and he was discontinued from the study on Day 72 due to the need for chemotherapy. He eventually died despite treatment on Day 106. The investigator reported that IRIS was definitely not related to study drug and that Kaposi's sarcoma was probably not drug related.

Cerebral haemorrhage case: This was a 57 year old Asian male with concurrent conditions that included AIDS, gouty arthritis and a medical history that included cerebrovascular accident, decreased CD4 lymphocytes, gout, hypertension and hyperuricaemia. Concomitant therapy included ibuprofen, hydrochlorothiazide, allopurinol and atenolol. On Day 90 he was found unconscious and brought to the hospital. He had a head wound that was compatible with violence. A CT scan showed intracerebral haematoma at bilateral occipital lobes. He discontinued study therapy, continued to deteriorate and died on Day 96. The investigator considered that the haemorrhage was definitely not related to study therapy.

Non-fatal SAEs

There were 79 SAEs reported from 55 subjects up to the cut-off date, including 28 (10%) in the raltegravir group and 27 (9.6%) in the efavirenz group. Nine of these 79 (4 raltegravir) had SAEs that were determined by the investigators to be drug-related. The four raltegravir group subjects included one with mental disorder considered related to raltegravir, two cases of IRIS considered related to raltegravir in combination with tenofovir/emtricitabine and one accidental overdose related to tenofovir/emtricitabine.

There were two laboratory SAEs but these occurred in a single subject in the efavirenz group and were not considered drug-related.

Neoplasms

There were 7 neoplasms (benign, malignant and unspecified) in the raltegravir group (2.5%) and 15 such reports in the efavirenz group (5.3%). This number included one case of Kaposi’s sarcoma in the raltegravir group compared to 6 cases in the efavirenz group. There were also 4 and 6 cases of skin papilloma reported in respective groups. Only one of the 8 subjects with SAEs of malignancy was in the raltegravir group – this was the subject with Kaposi’s sarcoma who died as described above.

The seven malignancies reported as SAEs in the efavirenz group included anal cancer (1), bone neoplasm malignant (1) and Kaposi's sarcoma AIDS-related (5). There were another two subjects in the efavirenz group with malignancy not counted among these seven – one had worsening of Kaposi’s sarcoma that was considered non-serious and one had a SAE of B-cell lymphoma with onset >14 days after discontinuation of study therapy. Three of the cases in the efavirenz group were considered to be recurrences.

The CD4 cell counts reported at the time of onset for each cancer ranged from 17 to 618 cells/mm3 and 7/10 had HIV RNA < 400 copies/ml.

Discontinuations due to AEs

Nine raltegravir (3.2%) and 17 efavirenz subjects (6%) discontinued study therapy due to a clinical AE.

Laboratory data
The following issues merit some particular mention:

Plasma lipids
Raltegravir therapy was associated with small increases in total and LDL cholesterol and a decrease in serum triglycerides as well as a modest increase in HDL cholesterol. The mean change from baseline was significantly lower in the raltegravir group compared to the efavirenz group for serum cholesterol, HDL-C, LDL-C, triglycerides and non-HDL-C ($p<0.001$). The mean percent change from baseline for serum cholesterol, HDL-C, triglycerides and non-HDL-C was significantly lower in the raltegravir group. The differences between treatment groups were present from Week 12 onwards. Lipid-lowering therapy was commenced in three raltegravir and 11 efavirenz subjects up to Week 48 while four in each group increased their dose of such agents during the reporting period.

ALT/AST elevations
Rates of aminotransferase elevations were generally comparable between raltegravir and efavirenz. These were generally transient, not associated with clinical AEs and did not limit study therapy. Grade 2 or higher elevations in ALT occurred in 7.5% (21/281) raltegravir subjects and 9.2% (26/282) efavirenz subjects. The increases were reported as laboratory AEs in 9 and 14 subjects in respective groups (5 and 10 of which were considered drug-related with a range of 66 to 169 IU/l.

Grade 2 or higher elevations in AST occurred in 5.7% (16/281) raltegravir and 7.1% (20/282) efavirenz subjects. Increased AST was reported as a laboratory AE in 4.6% and 5.3% in respective groups of which 6 (2.1%) and 8 (2.8%) were considered drug-related with a range of 45 to 259 IU/l. Two raltegravir subjects with Grade 2 or higher AST or ALT increases experienced hepatobiliary disorders (severe cholecystitis and mild hepatomegaly) that were not considered to be drug-related and did not cause a drug interruption or discontinuation.

Bilirubin
Grade 1 elevations in total serum bilirubin occurred in 15/281 in the raltegravir group (5.3%) versus none in the efavirenz group. Additionally, 3.2% (9/281) raltegravir subjects had a Grade 2 total serum bilirubin value compared to only one (0.4%) in the efavirenz group. Grade 3 elevations occurred in two (0.7%) and none per group and there were no Grade 4 elevations in either treatment group. The elevations were primarily indirect (i.e. unconjugated) bilirubin, most were intermittent and resolved without interruption of therapy and they generally did not arise in conjunction with other liver function test abnormalities. Only one elevation was reported as a laboratory AE.

Two of the 24 raltegravir subjects with Grade 1 or 2 bilirubin abnormalities were co-infected with hepatitis B and another was co-infected with hepatitis C. One had cholecystitis while on study. Six had elevated total bilirubin prior to receiving study drug. The majority of elevations were isolated and all except three subjects had levels that were returning toward baseline at the cut-off date. These three exceptions comprised:

- Baseline Grade 1 elevation (1.8 mg/dl) but Grade 2 elevation (2.3 mg/dl) at the cut-off
- Normal baseline (0.6 mg/dl) but Grade 1 (1.4 mg/dl) elevation at the cut-off
- Normal baseline (0.9 mg/dl) but 1.3 mg/dl (Grade 1) at the cut-off.

Two raltegravir subjects had a Grade 3 elevation in bilirubin. One went from a baseline 0.4 mg/dl to a Grade 3 (3.1 mg/dl) on Day 421, considered possibly related to combination therapy. However, the bilirubin returned to baseline without any interruption to study therapy. The other went from a baseline of 0.4 mg/dl to a Grade 3 (3.1 mg/dl) on Day 169 of study therapy. Again, bilirubin subsequently returned to baseline without any interruption to study therapy.

Hepatobiliary disorders were reported in 2.1% (6/281) raltegravir and 0.4% (1/282) efavirenz subjects. Only one of these raltegravir subjects had a Grade 2 elevation in total bilirubin along with a clinical diagnosis of cholecystitis. All subjects continued on study.

In the Phase II study in the ART-naïve (study 004) Grade 1 bilirubin elevations were seen in 16 (10%) in the raltegravir group versus 1 (2.6%) in the efavirenz group while Grade 2 elevations occurred in six and no patients in respective groups. There were no Grade 3 or 4 elevations, only one raltegravir patient had a laboratory AE of elevated bilirubin, none of the cases was serious and no patient discontinued secondary to bilirubin elevation. In the Phase III studies there was a slightly higher rate of hyperbilirubinaemia in the raltegravir group even among those who did not receive atazanavir in the OBT.

As reported previously the potential for raltegravir to inhibit UGT1A1 was evaluated *in vitro* using human liver microsomes. The drug was added at various concentrations (0.07-50 μM) to a reaction mixture containing human liver microsomes, UDPGA and the UGT1A1 marker substrate oestradiol at a concentration of 100 μM. The resulting IC_{50} value was >50 μM (well above the anticipated Cmax of approximately 4.5 μM for a 400 mg BID dose) indicating that raltegravir is not a potent inhibitor of UGT1A1 in this *in vitro* system.

The findings of elevated unconjugated bilirubin show that, despite the *in vitro* findings, raltegravir has some capacity to inhibit UGT1A1 in some patients. It is not so very rare that *in vitro* data do not wholly predict the *in vivo* situation with regard to drug-drug-interactions.

While it is possible to agree with the MAH that currently there is inadequate evidence to recommend avoidance of co-administration of raltegravir with known inhibitors of UGT1A1 it cannot be ruled out that some patients could experience clinically significant drug-drug interactions. Therefore, the current statement on the interaction of raltegravir with UGT1A1 needed a thorough revision; deleting the statement that raltegravir is not an inhibitor of UGT1A1.

Serum Creatinine
The frequency of elevations in Grade 1 serum creatinine was slightly higher in the raltegravir group (4.6% [13/281] compared to 1.4% [4/282]). The mean change from baseline was negligible for both groups (0.02, -0.01). Four raltegravir subjects had Grade 1 elevations in creatinine at baseline. During the time of the elevations, there were no significant related AEs and the majority of elevations were transient. Five continued with Grade 1 elevations at the time of the cut-off but none discontinued study related to this abnormality.

<u>DEXA data</u>

Total body fat, total appendicular fat and total truncal fat levels were measured by DEXA scan in a subset of patients at baseline and at Week 48. DEXA measurement showed minimal gains in body fat, with no patterns of fat loss over 48 weeks. AEs of lipodystrophy (including fat tissue increased and lipoatrophy) were reported only in two efavirenz subjects.

<u>Drug interactions</u>

The solubility of raltegravir increases with increasing pH. Administration of omeprazole prior to administration of raltegravir in healthy subjects resulted in an approximately 3.1-fold increase in raltegravir $AUC_{0-\infty}$, 4.1-fold increase in C_{max} and 46% increase in C_{12hr}. The MAH considered that a likely mechanism to explain these results was increased bioavailability of raltegravir due to higher gastric pH.

However, the sparse PK dataset from previously reported Phase II and III studies in treatment experienced subjects did not show an effect of gastric pH-altering agents on raltegravir plasma levels. It has been reported that AIDS is associated with gastropathy and hypochlorhydria. The MAH proposed that this might explain why the findings in Phase II and III studies contrasted with those in a drug-drug interaction study in healthy subjects.

In study 021 the MAH examined the safety profile of raltegravir in those who did and did not receive concomitant agents that modify gastric pH (i.e. any PPI and/or H2 blockers at study entry and during the study). However, the analysis is severely limited by the fact that only 19/281 in the raltegravir group took one or more concomitant pH altering agents during the treatment period. Clinical AEs occurred in 18/19 (94.7%) compared to 235/262 (89.7%) not using a pH altering agent. Only 4/19 reported a SAE (secondary syphilis, limb injury, neurosyphilis and anaemia) and these SAEs were not considered drug-related by the investigator. Laboratory AEs occurred in 3/19 (15.8%) compared to 24/262 (9.2%). The frequencies of Grade 1 serum LDL-cholesterol abnormalities were 26.3% (5/19) versus 14.5% (38/262). Grade 1 abnormalities of total serum cholesterol were reported for 31.6% (6/19) versus 17.6% (46/262).

Pregnancies

One raltegravir and two efavirenz subjects reported a pregnancy during the course of the study. The raltegravir subject reported her pregnancy on Day 77, having interrupted study therapy on Day 75, and subsequently discontinued from the study. The patient continued the pregnancy to term with no complications and gave birth to a healthy baby girl via Caesarean section.

Discussion on Safety

Study 021 indicated that the safety profile of raltegravir + tenofovir/emtricitabine was generally comparable to that of efavirenz + tenofovir/emtricitabine. Some ADRs known to be associated with efavirenz use (e.g. the CNS AEs singled out for analysis by the MAH and rashes) were reported at lower rates in the raltegravir group.

Low grade (1 and 2) elevation in bilirubin occurred more commonly in the raltegravir group. Most cases involved elevations of indirect (i.e. unconjugated) bilirubin, did not lead to discontinuation of therapy and resolved while subjects remained on raltegravir. The increases in total and indirect bilirubin in the raltegravir group point to the conclusion that the *in vitro* data indicating lack of inhibition of UGT1A1 by raltegravir are not borne out in the clinic at therapeutic raltegravir doses and the SPC was modified accordingly.

The data on rates of malignancies, taken in conjunction with the update provided in variation II/01, are reassuring. Variation II/10 was filed concurrently with provision of the results of the non-clinical carcinogenicity studies (II/09), for which the CHMP adopted a positive opinion on 23 April 2009, concluding that the studies in rodents did not indicate an increased risk of cancer with the use of raltegravir. Taking into account the conclusions from that report, it can be agreed that removal of the paragraph on malignancies from section 4.4 is now possible. The paragraph in Section 4.8, however, was retained with some amendment.

The use of pH altering agents in the raltegravir group did seem to be associated with higher rates of some AEs. While the analysis is indeed severely limited the rates of clinical and laboratory AEs were higher in those taking concomitant pH-altering agents. In this regard, the MAH will conduct a study of the effects of omeprazole in HIV-infected subjects (see study 054; report on FUM 022). Meanwhile, the current SPC advice to use raltegravir with agents that increase gastric pH only if unavoidable remains appropriate.

3. Pharmacovigilance – Risk Management Plan

The version of the RMP (4.0) supplied initially with this variation to extend the indication to treatment naïve HIV-infected subjects required some revisions that were provided with the answers to the RSI. An updated RMP version 4.1, dated 6 February 2009 was submitted, with changes to the previous version highlighted. In line with the CHMP's request, inconsistencies regarding version numbers in headers and footers had been resolved.

A single table summarising the most relevant clinical trial exclusion criteria from all studies, rather than by individual study, was provided. All references to MK-0518 were changed to raltegravir, unless the former was part of a study title.

Clarification on the proposed submission date for the protocol for the collaborative study to characterise raltegravir resistance was provided, insofar as it was submitted on 17 October 2008 to the CHMP. However, no study number was provided. In version 4.1 of the RMP, no annexes had been provided and the MAH stated "not applicable" and "planned" for the protocol version and protocol status respectively. In response to these last two outstanding issues, the MAH provided a duly revised RMP version 5.0 complete with annexes in the framework of the last PSUR submission on 21 May 2009, which will be assessed separately. This version of the RMP contains the protocol for the study to characterise raltegravir resistance which is now ongoing. It is also noted in the RMP that the planned date for final submission of the data is 30th September 2010.

4. Additional Data relevant to this application – Protocols 032&033

In addition to the above discussed data, additional information on raltegravir was provided by the MAH to the CHMP on 18 December 2008.

HIV Protocols 032 and 033: Multicenter, Double-Blind, Randomized, Active-controlled Studies To Evaluate the Safety and Antiretroviral Activity of MK-0518 Versus KALETRA (lopinavir/ritonavir) in HIV-Infected Patients Switched from Stable KALETRA-Based Regimens

Introduction

Two studies with identical designs (Protocol 032 033) were initiated to evaluate the potential of raltegravir to improve the tolerability of long term antiretroviral therapy in patients with stable viral suppression on a lopinavir/ritonavir-based regimen. Patients were eligible for enrolment if they had documented HIV RNA <50 copies/ml (or bDNA ≤75 copies/ml) for at least 3 months prior to study entry while on a lopinavir/ritonavir-based regimen (dosed as 400 mg lopinavir/100 mg ritonavir twice daily). The regimen was to consist of lopinavir/ritonavir in combination with at least 2 NRTIs, without a change in ART or documentation of HIV RNA ≥50 copies/ml during the previous 3 months.

The studies randomised patients to maintain their regimen or to switch from lopinavir/ritonavir to raltegravir without changes in backbone therapy. The effects on serum lipid parameters and the overall safety/tolerability profile were to be assessed along with the ability of raltegravir to maintain HIV suppression.

Protocol 033 was the first of the studies in which all patients completed to Week 24 (the primary efficacy endpoint). A summary of the primary and secondary endpoints was provided to CHMP, which showed that switching patients on a stable lopinavir/ritonavir-based regimen to a raltegravir-based regimen was associated with some improvement in serum lipid levels and diarrhoea but the efficacy results raised concerns regarding the ability of raltegravir-based regimens to maintain HIV suppression when compared to lopinavir/ritonavir-based regimens.

The primary efficacy analysis used a Non-Completer=Failure (NC=F) approach. The observed failure (OF) approach, which focuses on the antiretroviral effect of treatment, was performed as a sensitivity analysis for the primary efficacy analysis and was the primary approach used for subgroup analyses.

Data provided in December 2008 from patients on raltegravir-based regimens showed that 88% had <50 copies/ml at Week 24 compared to 93.8% of the patients who remained on their lopinavir/ritonavir-based regimens. In particular, raltegravir did not demonstrate non-inferiority as compared to lopinavir/ritonavir with respect to the proportion of patients with HIV RNA <50 copies/ml at Week 24. At Week 24 the difference (raltegravir-lopinavir/ritonavir) was -5.8% (-12.2; 0.22).

The MAH then evaluated the primary efficacy endpoint at Week 24 for patients enrolled in Protocol 032 using preliminary un-audited data and obtained a similar result. At week 24 the difference (raltegravir-lopinavir/ritonavir) in proportion of patients with HIV RNA <50 copies/ml was -7.1% with a 95% confidence interval of (-15.0; 0.67). These efficacy results were unexpected. The MAH informed all investigators and stopped enrolment. Patients were about to be unblinded so that investigators could make appropriate clinical decisions on further therapy.

The CHMP concluded that there could be important information arising from more detailed investigation of the reasons why raltegravir failed to demonstrate non-inferiority with respect to lopinavir/ritonavir in these two studies that could potentially impact on the regimens within which raltegravir could be used in the management of previously ART-naïve patients. Therefore questions raised by studies 032 and 033 were included in the first RSI for this variation in December 2009, as the CHMP considered that the assessment of the study results could potentially impact the benefit risk assessment of raltegravir in the treatment of ART naïve patients. The following section therefore gives an assessment of the data provided in response to these questions, focusing on the impact on the target population of ART naïve patients.

Treatment histories and analysis of consequential virological outcomes

Since the original protocols did not collect the full treatment history, a supplemental case report form was designed to collect these data after the Week 24 data analysis. The overall extent of prior treatment was comparable between treatment groups for each study although the duration of prior treatment was slightly shorter in the raltegravir group compared to the lopinavir/ritonavir group in study 033. The most common agents used prior to study entry were NRTIs but there was considerable use of NNRTIs and PIs other than lopinavir/ritonavir. Prior ARTs used were generally comparable between studies and across the treatment groups.

Further data were extracted from CRFs following the Week 24 data analysis in order to clarify whether patients were on their first treatment regimen prior to enrolment or on a regimen that had been successfully instituted after failure to respond to one or more prior regimens. This supplemental treatment history was collected for all 702 patients. In both treatment groups approximately 60% of patients in 032 and 70% in 033 indicated that the lopinavir/ritonavir-containing regimen in use at screening was not their first regimen. Between 28% and 37% per study and treatment group had a history of prior virological failure with slightly higher rates in 033. Treatment groups were well balanced within each study regarding these questions although patients in 033 clearly had greater prior exposure to ARTs compared with those in 032.

The tables below show for each study the proportion of patients with HIV RNA <50 copies/ml at Week 24 by treatment history using the observed failure approach, which provides results that are consistent with all other subgroup analyses performed for these studies.

- In study 032 virological response rates were comparable between the raltegravir and lopinavir/ritonavir groups for those patients who were on their first ART regimen at entry and also for patients who had not experienced prior virological failure.

- In study 033 virological response rates were higher in the lopinavir/ritonavir group among those patients who were on their first ART regimen at entry but were more comparable between groups for patients who had not experienced prior virological failure.

- Both studies clearly showed that among those patients who had more extensive prior treatment, with or without a documented prior failure, the rates of virological suppression were higher in the groups that continued with lopinavir/ritonavir and, in complete contrast to the raltegravir group, there was no discernible effect of extent of prior treatment or failure pre-study on the response rates in the lopinavir/ritonavir groups.

Proportion of Patients With Plasma HIV RNA <50 Copies/mL at Week 24
by Treatment History - P032
(Observed Failure Approach)

Subpopulation	Response				Difference in Percent Response†
	MK-0518 400 mg b.i.d. (Group A)		KALETRA 400/100 mg b.i.d. (Group B)		
	n/N	% (95% CI)	n/N	% (95% CI)	% (95% CI)
Total	139/154	90.3 (84.4, 94.4)	152/162	93.8 (88.9, 97.0)	-3.6 (-10.0, 2.5)
Was the Kaletra-Based Regimen at Screening the Subject's First Antiretroviral Regimen?					
Yes	62/66	93.9 (85.2, 98.3)	65/69	94.2 (85.8, 98.4)	-0.3 (-9.6, 8.8)
No	77/88	87.5 (78.7, 93.6)	87/93	93.5 (86.5, 97.6)	-6.0 (-15.4, 2.7)
Has the Subject Experienced Prior Virologic Failure on Any Drug?					
Yes	34/43	79.1 (64.0, 90.0)	52/54	96.3 (87.3, 99.5)	-17.2 (-32.1, -4.8)
No	103/109	94.5 (88.4, 98.0)	97/105	92.4 (85.5, 96.7)	2.1 (-4.9, 9.6)
Missing	2/2	100.0 (15.8, 100.0)	3/3	100.0 (29.2, 100.0)	0.0 (-70.6, 61.6)

† The 95% CIs were calculated using Miettinen and Nurminen's method.
Note: MK-0518 and KALETRA were administered with background antiretroviral therapy.
N = Number of patients in each treatment group.

Proportion of Patients With Plasma HIV RNA <50 Copies/mL at Week 24
by Treatment History - P033
(Observed Failure Approach)

Subpopulation	Response				Difference in Percent Response†
	MK-0518 400 mg b.i.d. (Group A)		KALETRA 400/100 mg b.i.d. (Group B)		
	n/N	% (95% CI)	n/N	% (95% CI)	% (95% CI)
Total	154/173	89.0 (83.4, 93.3)	167/176	94.9 (90.5, 97.6)	-5.9 (-12.0, -0.2)
Was the Kaletra-Based Regimen at Screening the Subject's First Antiretroviral Regimen?					
Yes	50/55	90.9 (80.0, 97.0)	52/54	96.3 (87.3, 99.5)	-5.4 (-16.5, 4.7)
No	104/118	88.1 (80.9, 93.4)	115/122	94.3 (88.5, 97.7)	-6.1 (-13.9, 1.1)
Has the Subject Experienced Prior Virologic Failure on Any Drug?					
Yes	51/63	81.0 (69.1, 89.8)	61/65	93.8 (85.0, 98.3)	-12.9 (-25.2, -1.5)
No	99/106	93.4 (86.9, 97.3)	101/106	95.3 (89.3, 98.5)	-1.9 (-8.9, 4.9)
Missing	4/4	100.0 (39.8, 100.0)	5/5	100.0 (47.8, 100.0)	0.0 (-51.9, 46.4)

† The 95% CIs were calculated using Miettinen and Nurminen's method.
Note: MK-0518 and KALETRA were administered with background antiretroviral therapy.
N = Number of patients in each treatment group.

Analyses using the NC=F approach for the proportion of patients with plasma HIV RNA <50 copies/ml at Week 24 by treatment history for studies 032 and 033 individually showed that while the actual numbers are slightly different the pattern of findings was the same as described above using the observed failure approach.

Therefore it seems that more extensive pre-treatment with ARTs, with or without a prior failure of ART, leads to a lower likelihood of maintaining virological suppression after switching to a raltegravir-based regimen. In complete contrast, there is no discernible effect of these factors on the virological suppression rates in those who continued with lopinavir/ritonavir.

Discussion

In reflection of the inclusion criteria for these studies, the population enrolled was heterogeneous with respect to treatment histories. There was no *a priori* stratification of patients based on treatment history and it is pertinent to note that information on treatment histories was collected *a posteriori* and in response to the unexpected findings.

Virological suppression rates among patients on their first ART regimen and those with no reported history of virological failure were generally comparable between the raltegravir and lopinavir/ritonavir groups except that study 033 suggested that even in those on their first regimen there was already a disadvantage for switching to raltegravir. In contrast, patients with more extensive exposure to ARTs, with or without a prior virological failure, were more likely to maintain virological suppression if they remained on their lopinavir/ritonavir-based regimen.

Prior treatment ± failure did not impact on the lopinavir/ritonavir response rates in either study. However all the patients who entered these studies had already been on a lopinavir/ritonavir-based regimen for at least 3 months without any document viral load ≥50 copies/ml. Therefore, these patients were already selected out for a greater likelihood of a longer-term response to lopinavir/ritonavir since any patients who were not responding adequately to a lopinavir/ritonavir-based regimen within 3 months of enrolment were already eliminated. To some extent this fact implies a degree of bias in favour of continuation on lopinavir/ritonavir that would not have existed if subjects had been randomised to lopinavir/ritonavir or raltegravir *de novo* at enrolment.

Despite these considerations of potential bias, it remains a fact that switching from a successful lopinavir/ritonavir-based regimen to a raltegravir-based regimen was not an optimal treatment strategy for a substantial number of patients and this observation applied to patients on their first (in one study) or subsequent (both studies) regimens.

Since data from other sources (see study 021 above) indicate that the rate of resistance to raltegravir is probably low in previously unexposed virus, the most likely explanation for failure after switching to raltegravir is that patients had viruses that were not fully susceptible to other agents in the total regimen and, as a result, have been at particular risk of selecting for raltegravir-resistant virus during treatment. Thus, the relative importance of co-administration with active backbone therapy is greater for raltegravir than for lopinavir/ritonavir.

The advice already given in section 4.4 of the SPC on co-administration of raltegravir with at least one other active agent in all populations was prompted by concerns regarding the low genetic barrier to resistance to raltegravir and it reads as follows:

In treatment-experienced patients higher response rates were observed in patients with Genotypic Sensitivity Score (GSS)>0. Patients with GSS or Phenotypic Sensitivity Score (PSS)=0 had a higher risk of developing resistance to raltegravir (see section 5.1). In all patient populations 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.

With a formal extension of the indication to ART-naïve subjects and taking into account the results of studies 032 and 033 the CHMP requested that this paragraph should now be replaced by the following:

Raltegravir has a relatively low genetic barrier to resistance. Therefore, whenever possible, raltegravir should be administered with two other active ARTs to minimise the potential for virological failure and the development of resistance (see section 5.1).

In treatment naïve patients, the clinical study data on use of raltegravir are limited to use in combination with two nucleotide reverse transcriptase inhibitors (NRTIs) (emtricitabine and tenofovir disoproxil fumarate).

Correlation of viral suppression on raltegravir with co-administration of any specific ART

Overall, the types of concomitant therapies used were comparable between treatment groups. However, it is difficult to assess the activity of these regimens in patients with varied prior ART exposure because some patients may have had virus with pre-existing resistance mutations at baseline. Across both studies the most commonly used NRTIs were either emtricitabine or lamivudine in combination with tenofovir or zidovudine or abacavir.

In each study the difference in virological response rate between treatments was greatest among those patients who received abacavir + emtricitabine or lamivudine. What is more, although numbers are relatively small, the actual rates and therefore difference in rates between treatments was almost exactly the same within each study for patients who received these ARTs (i.e. 80% vs. 95.7% and 81.8% vs. 94.7%). On looking at each study separately it also becomes clear that the lower response rates to raltegravir were more apparent in study 033 than in study 032.

Proportion of Patients With Plasma HIV RNA <50 Copies/mL at Week 24
by Concurrent ART – P032
(Observed Failure Approach)

	Response				Difference in Percent Response†
	MK-0518 400 mg b.i.d. (Group A)		KALETRA 400/100 mg b.i.d. (Group B)		
Subpopulation	n/N	%(95 CI)	n/N	%(95 CI)	%(95 CI)
Total	139/154	90.3 (84.4, 94.4)	152/162	93.8 (88.9, 97.0)	-3.6 (-10.0, 2.5)
Concurrent Background ART					
tenofovir (+) emtricitabine or lamivudine	72/ 79	91.1 (82.6, 96.4)	69/ 75	92.0 (83.4, 97.0)	-0.9 (-10.4, 8.8)
abacavir (+) emtricitabine or lamivudine	20/ 25	80.0 (59.3, 93.2)	22/ 23	95.7 (78.1, 99.9)	-15.7 (-35.9, 4.1)
zidovudine (+) lamivudine	22/ 22	100.0 (84.6, 100.0)	27/ 27	100.0 (87.2, 100.0)	0.0 (-15.1, 12.7)
other combination of 2 ARTs	14/ 14	100.0 (76.8, 100.0)	17/ 18	94.4 (72.7, 99.9)	5.6 (-17.1, 26.2)
3 or more ARTs	11/ 14	78.6 (49.2, 95.3)	14/ 16	87.5 (61.7, 98.4)	-8.9 (-38.3, 19.7)

† The 95% CIs were calculated using Miettinen and Nurminen's method.

Note: MK-0518 and KALETRA were administered with background antiretroviral therapy.

N = number of patients in each treatment group.

n = Number of patients in each subcategory.

Proportion of Patients With Plasma HIV RNA <50 Copies/mL at Week 24
by Concurrent ART – P033
(Observed Failure Approach)

	Response				Difference in Percent Response†
	MK-0518 400 mg b.i.d. (Group A)		KALETRA 400/100 mg b.i.d. (Group B)		
Subpopulation	n/N	%(95 CI)	n/N	%(95 CI)	%(95 CI)
Total	154/173	89.0 (83.4, 93.3)	167/176	94.9 (90.5, 97.6)	-5.9 (-12.0, -0.2)
Concurrent Background ART					
tenofovir (+) emtricitabine or lamivudine	54/ 58	93.1 (83.3, 98.1)	42/ 43	97.7 (87.7, 99.9)	-4.6 (-14.6, 5.9)
abacavir (+) emtricitabine or lamivudine	18/ 22	81.8 (59.7, 94.8)	18/ 19	94.7 (74.0, 99.9)	-12.9 (-34.7, 9.5)
zidovudine (+) lamivudine	50/ 57	87.7 (76.3, 94.9)	54/ 59	91.5 (81.3, 97.2)	-3.8 (-16.1, 8.0)
other combination of 2 ARTs	18/ 21	85.7 (63.7, 97.0)	36/ 38	94.7 (82.3, 99.4)	-9.0 (-30.3, 6.2)
1 ART	3/ 3	100.0 (29.2, 100.0)	1/ 1	100.0 (2.5, 100.0)	0.0 (-63.1, 83.7)
3 or more ARTs	11/ 12	91.7 (61.5, 99.8)	16/ 16	100.0 (79.4, 100.0)	-8.3 (-36.0, 12.6)

† The 95% CIs were calculated using Miettinen and Nurminen's method.

Note: MK-0518 and KALETRA were administered with background antiretroviral therapy.

N = number of patients in each treatment group.

n = Number of patients in each subcategory.

Discussion

These analyses show a particular and consistent problem for use of raltegravir with abacavir + emtricitabine or lamivudine despite the low denominators. This issue is discussed further below. The data from 033 suggest a benefit from having tenofovir in the regimen but the data are inconsistent between studies and do not allow for any firm conclusion that this is related to any possible effect of tenofovir on raltegravir exposure.

Geno- & phenotype resistance at baseline

The supplementary CRF was also used to request if information regarding pre-study resistance testing was available and if so, the nature of the results. Based on the limited amount of pre-study resistance testing data available the investigators reported that in 179 patients the HIV contained mutations associated with resistance to at least one antiretroviral drug. Of these 179 patients, 59% (106/179) had virus with NNRTI mutations, 70% (126/179) had NRTI mutations and 75% (134/179) had PI mutations. It is unknown how many of the remaining 523 patients were infected with HIV that contained resistance mutations.

Concentrating just on the 49 total patients who failed therapy, investigators reported that 14 of these patients had HIV that contained mutations associated with resistance to at least one ART. Of these 14 patients, 57% (8/14) had virus with NNRTI mutations, 79% (11/14) had NRTI resistance, and 86% (12/14) had PI mutations. It is unknown how many of the remaining 35 patients were infected with HIV that contained resistance mutations.

Looking specifically at the 32 patients who failed raltegravir therapy, there were only 8 patients with data who had virus with mutations associated with resistance to at least one ART. Of these 8 patients, 38% (3/8) had virus with NNRTI mutations, 75% (6/8) had NRTI mutations and 88% (7/8) had PI mutations. It is unknown how many of the remaining 24 patients were infected with HIV that contained resistance mutations.

Overall, the MAH considered that the data from these analyses and from those reported above support the hypothesis that the increased rates of virological failure in the raltegravir groups in the two studies most likely reflect compromised activity of agents in the backbone regimen due to viral resistance. Thus the results are consistent with those in the studies in even more treatment experienced subjects (i.e. as in studies 005, 018 and 019) in which it was clear that virological response rates to raltegravir correlated with the number of agents in the OBT predicted to be active.

The MAH maintained that the results of studies 021 and 004 in treatment-naïve patients provide unequivocal evidence of the efficacy of raltegravir in combination with two NRTIs in subjects infected with HIV that is susceptible to both the NRTIs.

Discussion

Based on the limited amount of pre-study resistance testing data available it becomes clear that rates of resistance-associated mutations (RAMs) to NRTIs, NNRTIs and PIs were comparable between all patients with data and all failed patients with data. As far as can be discerned from the few raltegravir failures with data, the rates were also comparable for these eight patients.

Implications for use in ART-experienced patients

The increased risk of virological failure in the raltegravir groups in studies 032 and 033 most likely reflects compromised activity of one or more co-administered agents in the backbone regimen due to viral resistance. In turn, this increased the risk of selecting for raltegravir-resistant virus during treatment. Thus the results are consistent with those in the studies in even more treatment experienced subjects (i.e. as in studies 005, 018 and 019) in which it was clear that virological response rates to raltegravir correlated with the number of agents in the OBT predicted to be active.

The need to combine raltegravir with an active ART backbone is consistent with the advice already included in Section 4.2 of the SPC, which cross-refers to sections 4.4 and 5.1.

However, the CHMP requested that the SPC be updated to reflect the broadening of the indication and to advise that whenever possible raltegravir should be co-administered with at least two other agents predicted to be active (see also above). In addition, section 5.1 was updated to state that it is not recommended to switch patients who have achieved and maintained virological suppression on their current regimen to a raltegravir-based regimen.

Implications for use in ART-naïve patients

The findings in studies 032 and 033 do not affect the conclusions drawn from study 021 in treatment-naïve patients for use of raltegravir in conjunction with tenofovir/emtricitabine. However, initial therapy for HIV often involves use of tenofovir/emtricitabine or abacavir/lamivudine plus an NNRTI or a boosted PI. Studies 032 and 033 suggest a consistent problem with the use of raltegravir plus abacavir + emtricitabine or lamivudine despite the low denominators.

No PK interaction would explain the finding since there is no effect of co-administration of raltegravir with lamivudine. No effect would be expected with emtricitabine and any interaction with abacavir might, if anything, increase plasma levels of one or both agents due to competition for glucuronyltransferase. In addition, there is no obvious mechanism for a pharmacodynamic interaction to occur between raltegravir and these NRTIs.

Therefore it seems most likely that the higher risk of failure on an abacavir-containing regimen reflects pre-existing resistance to one or more of abacavir and emtricitabine/lamivudine (for which there is cross-resistance) leading to a particular risk of selecting for raltegravir-resistant virus during therapy. This should not be an issue for ART-naïve subjects unless they have acquired a resistant HIV *de novo*. In addition, data from study 021 suggest that pre-therapy resistance to raltegravir is not currently problematical.

Meanwhile the data from 032 and 033 strongly underline the need to administer raltegravir with other active agents to reduce the risk of virological failure, which in many but not all instances is associated with appearance of raltegravir RAMs. As already reflected in the SPC, studies 018 and 019 indicated that at least one other active agent was needed. Routine practise would suggest that whenever possible raltegravir should be co-administered with at least two other agents predicted to be active. Thus, the MAH agreed to update the SPC to reflect this need.

The data also suggest that tenofovir/emtricitabine might to some extent be superior to abacavir/lamivudine in terms of virologic suppression, in which case co-administration of raltegravir with abacavir/lamivudine might carry a higher risk of selecting for raltegravir resistance than would co-administration with tenofovir/emtricitabine. However, the data are not sufficient to make any clear recommendation in this regard. Therefore there are no grounds at present to restrict the use of raltegravir in previously ART-naïve subjects to co-administration with tenofovir/emtricitabine. However, the SPC was modified to stress the limitations of the data provided by study 021.

5. Changes to the Product Information

As discussed in detail above, sections 4.1, 4.2 and 4.4, as well as 5.1 of the SPC were updated to both include the new patient population of previously ART naïve patients, together with the results of the relevant clinical study, but also to underline both the limitations of the study in naïve patients (only one backbone therapy) as well as the low genetic barrier to resistance that raltegravir has. In addition, updated information about additional integrase mutations was added to section 5.1, as well as information about raltegravir's non-B subtype antiviral activity *in vitro*.

The safety analysis of the trials led to updates in section 4.8 of the SPC, most notably to a modification of the information of prevalence of cancer in the raltegravir arms of previous studies, as this trend could not be confirmed within the currently assessed studies. Nevertheless, skin papilloma

was added to the list of at least possibly causally related adverse drug reactions with a frequency of "uncommon".

The findings of elevated unconjugated bilirubin show that, despite the *in vitro* findings, raltegravir has some capacity to inhibit UGT1A1 in some patients. Therefore, the statement in section 4.5 of the SPC in regards to the potential of raltegravir to inhibit the UDP glucuronosyltransferases (UGTs) 1A1 and 2B7 was revised to mention that some inhibition of UGT1A1 may occur *in vivo* based on effects observed on bilirubin glucuronidation.

Also, upon request of the CHMP, the MAH added the information in section 4.5 that no interactions were observed when raltegravir was co-administered with etravirine, maraviroc and methadone. Even though information about lack of interactions is normally not mentioned in this section, the CHMP found that these 3 compounds are of particular interest for the prescribing physician and that the information about their lack of interaction would be important to add in the SPC.

The Package Leaflet was updated in accordance, especially section 4 "Possible Side Effects", in line with the updates in section 4.8 of the SPC.

Finally, the MAH took this opportunity to update the contact details of the local representative in Iceland.

6. Overall conclusions and Benefit/Risk Assessment

The MAH conducted a generally satisfactory single study (although provision of a second study would have provided a more robust demonstration of efficacy) to assess the safety and efficacy of raltegravir in previously ART-naïve subjects. The submission of data to Week 48 and the size of the database were considered to be acceptable in light of the results provided thus far and also taking into account the data already available in an ART-experienced population. The results available so far support the MAH's claim for non-inferiority of the raltegravir based regimen when compared to the efavirenz one in the target patient population of ART-naïve adult patients. The Week 96 data from study 021 are expected end October 2009.

The comparative regimen of efavirenz plus tenofovir and emtricitabine (as Truvada) is very widely used in previously ART-naïve subjects and was a suitable choice for this study. While tenofovir may increase plasma exposure to raltegravir it seems rather unlikely that this would have markedly augmented the efficacy of the raltegravir-containing regimen in study 021. This conclusion is based on the MAH's population PK/PD analyses, which (although subject to several caveats due to paucity of samples and inherent inter-subject variation) have not demonstrated any clear and consistent relationships between raltegravir PK parameters and virological responses in ART-naïve subjects.

Questions were raised regarding extrapolation of the demonstration of efficacy for raltegravir when co-administered with tenofovir and emtricitabine (as Truvada, taken with food) to ART-naïve subjects to other potentially useful raltegravir-containing regimens in this population. This potential concern over extrapolation was augmented by the interim data received from studies 032 and 033. Although these studies were performed in ART-experienced subjects the results from each study pointed to a particularly high risk of loss of virological suppression when patients were switched to raltegravir with abacavir + lamivudine or emtricitabine.

Nevertheless, it seems most likely that the higher risk of failure on an abacavir-containing regimen reflected pre-existing resistance to one or more of abacavir and emtricitabine/lamivudine (for which there is cross-resistance) leading to a particular risk of selecting for raltegravir-resistant virus during therapy. This should not be an issue for ART-naïve subjects unless they have acquired a resistant HIV de novo. Therefore there are no grounds at present to restrict the use of raltegravir in previously ART-naïve subjects to co-administration with Truvada. However, the SPC was modified to stress the limitations of the data provided by study 021.

The data received from studies 032 and 033 also underlined the continuing concern regarding the low genetic barrier for resistance to raltegravir. Previous data suggested that the risk of selecting for raltegravir-resistant virus was higher when it was used as functional monotherapy or with only one other agent predicted to be active. The data from 032 and 033 strongly suggest that failure to maintain viral suppression after switching to a raltegravir-based regimen was associated with use of a sub-optimal total ART regimen due to pre-existing resistance. This situation is much less likely to occur in the ART-naïve population. In addition, data from treatment experienced patients not previously exposed to raltegravir suggest a low risk of pre-existing raltegravir RAMs.

Study 021 indicated that the safety profile of raltegravir + Truvada was generally comparable to that of efavirenz + Truvada. The increases in total and indirect bilirubin in the raltegravir group point to a conclusion that the *in vitro* data indicating lack of inhibition of UGT1A1 by raltegravir are not borne out in the clinic and the SPC was modified accordingly.

The data on rates of malignancies, taken in conjunction with the update provided in variation II/01, are reassuring. Variation II/10 was filed concurrently with provision of the results of the non clinical carcinogenicity studies (II/009) and a separate report had been issued (CHMP Opinion issued on 23 April 2009). Taking into account the conclusions from that report, it was agreed that removal of the paragraph on malignancies from section 4.4 was now possible. The paragraph in Section 4.8 remained, but with some amendment.

The use of pH altering agents in the raltegravir group did seem to be associated with higher rates of some AEs. While the analysis is indeed severely limited the rates of clinical and laboratory AEs were higher in those taking concomitant pH-altering agents. In this regard, the MAH will conduct a study of the effects of omeprazole in HIV-infected subjects (see study 054; report on FUM 022). Meanwhile, the current SPC advice to use raltegravir with agents that increase gastric pH only if unavoidable remains appropriate.

Overall, the data recently made available from studies 032 and 033 do not have a direct impact on the suitability of raltegravir for previously ART-naïve subjects.

The CHMP therefore concluded that the benefit risk balance for the extension of indication of raltegravir to add ART-naïve patients is positive.

While the use of raltegravir in ART-naïve patients is considered to be approvable, there are insufficient data to be able to conclude that raltegravir-containing regimens that might be used in the ART-naïve would provide a significant benefit in terms of safety or efficacy compared to other suitable regimens for this patient population. Therefore it is not possible to agree that the data support an additional year of marketing protection based on the new therapeutic indication for raltegravir in treatment naïve patients (see also the Attachment to this Assessment Report).

6. Outcome

On 23 July 2009 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics, Annex II and Package Leaflet.

Furthermore, the CHMP reviewed the data submitted by the MAH taking into account the provisions of Article 14(11) of Regulation (EC) No. 726/2004, taking into account the provisions of the "*Guidance on elements required to support the significant clinical benefit in comparison with existing therapies of a new therapeutic indication in order to benefit from an extended (11-year) marketing protection period (November 2007)*", and did not consider that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies (see the Attachment to this Assessment Report).

ATTACHMENT

CHMP AR on the novelty of the indication/significant clinical benefit in comparison with existing therapies dated 23 July 2009

1. Introduction

The MAH Merck Sharp & Dohme Ltd. submitted on 8 October 2008 an extension of indication variation application for Isentress (raltegravir) adding treatment naïve patients to the existing population of antiretroviral experienced HIV-infected adults.

With submission of this extension of indication application in treatment naïve patients the MAH also applied for an additional one year marketing protection period in accordance with Article 14(11) of Regulation (EC) No 726/2004.

2. Justification of significant clinical benefit as presented by the applicant

Significant clinical benefit based on improved efficacy

Although several recommended regimens are available for the initial treatment of HIV-1 infection patient and provider preferences, underlying co-morbidities, acute adverse drug effects and long-term complications continue to limit the success of ART in patients who are naïve to therapy. Moreover, significant drug resistance mutations, particularly to NNRTIs, are increasingly prevalent in the ART-naïve population and drug interactions among ARTs provide challenges to prescribing and monitoring therapy for these patients. There is a need for new agents and drug classes in order to expand the options for the initial treatment of HIV-1 infection and maximise the probability of achieving and maintaining optimal virological suppression and immune reconstitution with first-line regimens.

Data from the phase III study in treatment-naïve patients (Protocol 021) demonstrated that raltegravir has potent and durable antiretroviral and immunological effects in treatment-naïve patients. In addition, it has an excellent safety and tolerability profile. In this study raltegravir was compared to efavirenz, both in combination with tenofovir/emtricitabine. The results demonstrated statistically non-inferior efficacy compared to efavirenz at Week 48 in treatment-naïve patients. Compared to efavirenz, a numerically higher proportion achieved HIV RNA suppression to < 50 copies/ml as early as Week 2 and remained higher through Week 48.

The raltegravir-containing regimen resulted in greater immunological effect as measured by the change from baseline in CD4 cell count compared to the efavirenz-containing regimen. Consistent efficacy was observed across important subgroups including patients with baseline CD4 cell counts ≤200 cells/mm3 and viral RNA > 100,000 copies/ml, patients infected with non-clade B virus, and patients co-infected with hepatitis B and/or C.

The resistance profile of raltegravir was evaluated by performing genotypic analysis of the integrase coding region in patients who had virological failure in both Protocol 021 and Protocol 004. Overall, there were few treatment failures in these studies. Resistance evaluation was done for patients who were protocol defined virological failures and who also had HIV RNA > 400 copies/ml, the standard limit for routine genotyping assays. In the treatment naïve studies (Protocol 021 and 004), samples were evaluable from 15 patients who failed therapy in the raltegravir groups and 10 from the efavirenz groups. In the raltegravir groups approximately half did not have any detectable changes in integrase correlating with reduced susceptibility.

Significant clinical benefit based on improved safety

Review of the double-blind treatment-naïve population receiving raltegravir showed that the overall clinical adverse experience profile was consistent with that previously described in treatment-experienced patients. Numbers (%) of patients with AEs and with drug-related AEs, in the raltegravir group were significantly lower than for the efavirenz group based on the nominal p-values (0.002 and <0.001, respectively). There were no other statistically significant differences between the two groups.

Discontinuations due to clinical adverse experiences were uncommon but slightly higher in the efavirenz group (3.2% [9/281] versus 6.0% [17/282]). In a pre-specified analysis, the proportion of

patients with one or more central nervous system symptoms accumulated up to week 8 as well as week 48 was significantly lower in the raltegravir group.

Detailed review of the laboratory adverse experiences and laboratory abnormalities demonstrated that the laboratory safety profile of raltegravir in treatment-naïve patients is consistent with the overall safety profile reported previously. Since many antiretroviral agents have unfavourable effects on lipids, a pre-specified analysis of the change from baseline in serum lipids was performed. Through 48 weeks of therapy, raltegravir demonstrated minimal effects on serum lipids with small increases in total, LDL and non-HDL cholesterol and a decrease in serum triglycerides. In contrast, the efavirenz-treated group had statistically significantly higher percent increases in total cholesterol, LDL-C, non-HDL-C and triglycerides. Modest increases in HDL were observed in both groups, significantly higher for efavirenz. Body composition, measured by DEXA scan, showed no evidence of lipodystrophy or lipoatrophy in patients treated with raltegravir for 48 weeks.

Last, the updated malignancy data including Protocol 021 demonstrated that there is no specific cancer risk associated with raltegravir treatment as noted in the conclusions reached in the 48 Week Treatment Experienced Supplemental Application.

Significant clinical benefit based on major contribution to patient care

According to current HIV treatment guidelines efavirenz, which is recommended in combination with two NRTIs for initial therapy of HIV infection, has demonstrated durable efficacy and a favourable adverse event profile. In this application, raltegravir has demonstrated potent and durable antiretroviral and immunological effects in treatment-naïve patients, with a better tolerability and safety profile than efavirenz.

Additionally, raltegravir is active against virus resistant to NNRTIs and PIs and will be an important treatment option in patients infected with resistant virus. Raltegravir does not interact with the cytochrome P-450 system and has a favourable drug interaction profile and does not require dose adjustment when co-administered with commonly prescribed antiretroviral therapies. This simplifies dosing instructions, facilitating compliance which plays an important role in maintaining complete viral suppression.

These results demonstrate that raltegravir is an important addition to the HIV treatment-naïve armamentarium and an important new treatment option for first-line therapy of HIV-infected patients.

3. Assessment of the applicant's justification of significant clinical benefit

Significant clinical benefit based on improved efficacy

The data from study 021 showed that the specific combination regimen of raltegravir + tenofovir/emtricitabine is as effective as efavirenz + tenofovir/emtricitabine in treatment naïve patients but it cannot be concluded that the raltegravir regimen is significantly improved when compared to the latter. Over the total treatment period the results for both groups were generally comparable and it was only in the very first weeks that there might be an advantage for raltegravir.

It is understood that the regulation states that even without showing greater efficacy a medicinal product could be considered to confer significant clinical benefit if it acts through a different principal mechanism of action and thus provides a treatment alternative or it produces a response different from other treatments in a substantial part of the targeted population. In this respect it is therefore important to note that, although it has a different mechanism of action, based on the numbers available there was no advantage for raltegravir over efavirenz in the populations with the highest viral loads and lowest CD4 counts at baseline.

In addition, there are doubts raised on the extrapolation of results with this specific raltegravir-containing regimen to other possible combination regimens. While the MAH repeatedly claims a low

potential for drug-drug interaction it has been discussed previously that the very large inter-individual variation in PK could be the result of many factors that have not yet been identified. Therefore much caution is needed in assuming that any raltegravir-containing regimen would provide similar efficacy to that observed in study 021 in combination with tenofovir/emtricitabine.

Significant clinical benefit based on improved safety

The MAH's arguments focus almost completely on comparisons between raltegravir and efavirenz when each is given in combination with tenofovir/emtricitabine. While the efavirenz-containing regimen is widely used it is by no means the only possible primary regimen and therefore it is not appropriate to conclude that the specific raltegravir regimen studied would necessarily have a better safety profile than other useful first-line regimens.

To focus so heavily on the comparison with efavirenz is considered to be inappropriate. Indeed, if the CNS effects are separated it would not appear that there is any significant benefit for the raltegravir regimen in terms of clinical AEs. While the rates of lipid abnormalities were lower for the raltegravir regimen versus the efavirenz regimen there were many other laboratory data that did not show a difference between regimens and there was a higher rate of elevations in bilirubin with raltegravir that may reflect inhibition of UGT1A1.

Generally, a comparison against a single regimen with respect to specific types of adverse event must be viewed with much caution.

Significant clinical benefit based on major contribution to patient care

Again the MAH focuses strongly on a claim that raltegravir has demonstrated antiretroviral and immunological effects and a better tolerability and safety profile than efavirenz. These claims are anyway not considered to be wholly justified and the picture may be different for alternative raltegravir-containing regimens and/or comparisons with other first-line regimens suitable for the ART-naïve.

In addition, the MAH stresses that raltegravir is active against virus resistant to NNRTIs and PIs and will be an important treatment option in patients infected with resistant virus. At the same time though the risk of selecting for raltegravir-resistant virus must be borne in mind and much more data are needed in larger numbers and over longer periods before the true risk can be assessed.

While the MAH claims that raltegravir has a favourable drug interaction profile and does not require dose adjustment when co-administered with commonly prescribed antiretroviral therapies it is necessary to bear in mind that the reasons for the large intra- and inter-individual variability in PK remain poorly understood and could in part reflect issues such as interferences at the level of absorption. In addition, the effects on bilirubin could reflect a clinically important effect on UGT1A1 despite the nonclinical study predictions that inhibition was unlikely to occur in man at the approved dose.

4. CHMP Conclusion

Overall, there are insufficient data to be able to conclude that raltegravir-containing regimens that might be used in the ART-naïve patients would provide a significant benefit in terms of safety or efficacy compared to other suitable regimens for this patient population. Therefore it is not possible to agree that the data support an additional year of marketing protection based on the new therapeutic indication for raltegravir in treatment naïve patients.

The CHMP concluded that the efficacy and safety results supported a positive benefit risk balance for the extension of indication application for Isentress in treatment naïve patients. However, the lack of proof of superior efficacy results in the submitted trial did not support the claim for a significant efficacy benefit. Furthermore, the CHMP considered the safety profile of raltegravir not to be

significantly better. Finally, the CHMP judged the provided justification on improved patient care to not be sufficiently substantiated.
Overall, in the absence of significant clinical benefit based on improved efficacy, safety and contribution to patient care, in comparison both to the comparator as well as other antiretroviral medicines indicated for treatment naïve patients, the CHMP considered that the justification for an additional year of marketing protection was insufficient. Therefore, the CHMP did not support the MAH's justification for an additional year of marketing protection based on the new therapeutic indication for Isentress in treatment naïve patients.

5. Outcome

The CHMP reviewed the data submitted by the applicant taking into account the provisions of Article 14(11) of Regulation (EC) No. 726/2004, taking into account the provisions of the "*Guidance on elements required to support the significant clinical benefit in comparison with existing therapies of a new therapeutic indication in order to benefit from an extended (11-year) marketing protection period (November 2007)*", and did not consider that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies.