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ASSESSMENT REPORT
FOR
CELSENTRI

International non-proprietary name:
maraviroc

Procedure No. EMEA/H/C/000811/II/0006

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

Introduction

Maraviroc is a member of a therapeutic class called CCR5 antagonists, which selectively binds to the human chemokine receptor CCR5, preventing CCR5-tropic HIV-1 from entering cells. It has been shown active *in vitro* against a wide range of clade B and non clade B clinical isolates, including those resistant to existing drug classes. Maraviroc has no antiviral activity *in vitro* against viruses which can use CXCR4 as their entry co-receptor (dual-tropic or CXCR4-tropic viruses).

Celsentri (maraviroc), film-coated tablets is appproved since September 2007, in combination with other antiretroviral medicinal products, for treatment-experienced adult patients infected with only CCR5-tropic HIV-1 detectable. The recommended daily dose is 150 mg, 300 mg or 600 mg twice daily depending on interactions with co-administered antiretroviral therapy and other medicinal products.

Data from two phase II dose-ranging studies for dose-selection, (A4001007[1], A4001015[2]) assessed during the MAA and data from a retrospective study of two large antiretroviral-naïve cohorts[3,4], showed a high percentage of treatment-naïve patients infected only with CCR5-tropic HIV-1. The potential benefit of a CCR5 antagonist as HAART component for treatment-naïve patients was therefore evaluated in study A4001026, *a multicentre, randomised, double-blind, comparative trial of a novel CCR5 antagonist, maraviroc, in combination with zidovudine/lamivudine versus efavirenz in combination with zidovudine/lamivudine for the treatment of antiretroviral naïve HIV-1 infected subjects*.

Based on the results of 96 week data for study A4001026, the MAH applied for an extension of the therapeutic indication of Celsentri to include treatment-naïve CCR5-tropic HIV-1 infected adult patients in the present type II variation.

Non-clinical aspects

Environmental risk assessment (ERA)

An updated ecotoxicology/environmental risk assessment according to the current applicable guidelines was provided.

In Phase I a worst-case PEC in surface water of 3.0µg/l was calculated. This was higher than the action limit of 0.01µg/l and a Phase II environmental fate and effects analysis was performed.
The phase II analysis did not indicate any environmental concern with the use of maraviroc at maximum daily dose of 600 mg.

In order to enhance environmental protection even for medicinal products that do not require special disposal measures, section 6.6 of the SPC for Celsentri was amended to reflect the recommended standard statement.

[1] A randomised, double blind, placebo, controlled, multicentre study of maraviroc 25 mg QD, 50 mg BID, 100 mg BID and 300 mg BID in asymptomatic HIV infected patients to investigate pharmacodynamics, pharmacokinetics, safety and toleration.

[2] An investigation into the effects of food and dose regimen on viral load response in HIV infected patients on short term monotherapy with maraviroc.

[3] Brumme ZL, Goodrich J, Mayer HB, et al., Molecular and clinical epidemiology of CXCR4-using HIV-1 in a large population of antiretroviral-naïve individuals. Journal of Infectious Diseases 2005; 192 (3): 466-74.

[4] Moyle GJ, Wildfire A, Mandalia S, et al., Epidemiology and predictive factors for chemokine receptor use in HIV-1 infection. Journal of Infectious Diseases 2005; 191 (6): 866-72.

Clinical aspects

The clinical development of maraviroc in treatment-naïve adult patients infected with CCR5-tropic HIV-1 consisted in one phase III, randomised, double-blinded, comparative study (A4001026) of maraviroc at two different doses *versus* efavirenz, each in combination with zidovudine /lamivudine.

The 96 week results of this study were submitted in this variation application.

Clinical efficacy

Study A4001026 (MERIT study)

A phase III, multicentre, randomised (1:1:1), double-blinded study comparing maraviroc at two different doses (300 mg QD, 300 mg BID) *versus* efavirenz (600 mg QD), each in combination with zidovudine 300mg/lamivudine 150 mg (BID, Combivir) in treatment-naïve adult patients infected with CCR5-tropic HIV-1 following 96 weeks.

There was an interim analysis at week 16, a primary efficacy analysis at week 48 and a final analysis at week 96.

Study Population

Male and female subjects, ≥16 years of age (not pregnant), infected with CCR5-tropic HIV-1 with a viral load ≥2000 copies/ml at screening. The subjects could not have received any antiretroviral therapy for more than 14 days and could not have an active or recent (previous 30 days) opportunistic infection or a suspected primary HIV-1 infection. All subjects underwent genotypic and/or phenotypic testing for the presence of CCR5-tropic HIV-1 prior to the first dose of study drug.

Study Treatments

Subjects were randomised to receive one of the following double-blinded treatments:

- Maraviroc 300 mg QD + lamivudine 150 mg/zidovudine 300 mg BID,
- Maraviroc 300 mg BID + lamivudine 150 mg/zidovudine 300 mg BID or,
- Efavirenz 600 mg QD + lamivudine 150 mg/zidovudine 300 mg BID.

Following the interim analysis at week 16, the maraviroc 300 mg QD treatment group was discontinued (09 January 2006) due to the pre-specified criteria for non-inferiority to efavirenz not being met. Subjects on this treatment group were assessed for eligibility to receive open label maraviroc 300 mg BID based on safety criteria and virologic response. Hence, week 16 onwards there were two maraviroc 300 mg BID treatment groups: a double-blinded and an open-labeled.

Study Objectives

The primary objective was to assess whether the antiviral activity (i.e. plasma viral load <400 and <50 copies/ml at week 48), of each of two doses of maraviroc in combination with zidovudine/lamivudine was non-inferior to a reference regimen of efavirenz plus zidovudine/lamivudine in antiretroviral-naïve, CCR5 tropic HIV-1 infected subjects.

The secondary objectives were:

- to assess whether the antiviral activity (i.e. plasma viral load <400 and <50 copies/ml at week 24 and at week 96), of each of two doses of maraviroc in combination with zidovudine/lamivudine was non-inferior to a reference regimen of efavirenz plus zidovudine/lamivudine in antiretroviral-naïve, CCR5 tropic HIV-1 infected subjects;
- to compare the TLOVR through weeks 48 and 96 for each of the two maraviroc regimens *versus* the efavirenz regimen;
- to compare the reduction of plasma $\log_{10}$ viral load from baseline through weeks 24, 48 and 96 for each of the two maraviroc regimens *versus* the efavirenz regimen;

- to compare the differences in the magnitude of changes in cluster of differentiation 4 receptor (CD4) and 8 (CD8) cell counts from baseline through weeks 24, 48 and 96 for each of the two maraviroc regimens *versus* the efavirenz regimen;
- to compare the TAD in $\log_{10}$ viral load at weeks 24, 48 and 96 for each of the two maraviroc regimens *versus* the efavirenz regimen;
- to assess HIV-1 genotype and phenotype at the time of failure;
- to assess HIV-1 tropism at baseline and at the time of failure;
- to compare the safety and tolerability of each of the two maraviroc regimens *versus* the efavirenz regimen.

Statistical methods

Efficacy analyses at week 96 were considered secondary to the primary analysis at week 48. The analyses were performed on the full analysis set (FAS[5]) and per protocol (PP[6]) populations comparing maraviroc 300 mg BID and efavirenz 600 mg QD for each endpoint.

The principal endpoint was the percentage of subjects with undetectable viral load at week 96 by the standard and more sensitive methods (<400 copies/ml and <50 copies/ml, respectively). The difference in the percentage of subjects with the specified response was assessed by using a 1-sided 97.5% confidence interval (CI; adjusted for the randomisation strata) and calculated for the difference between maraviroc 300 mg BID and efavirenz 600 mg QD. If the lower bound of the CI was above -10%, non-inferiority between maraviroc 300 mg BID and efavirenz 600 mg QD could be concluded.

The CHMP noted that this study, analogous to an adaptive design with dose (regimen) selection at the interim analysis, has the potential to inflate type I error and interference should have been based on adjusted confidence intervals. A 97.5% two-sided interval would have been appropriate. The MAH used a 1-sided 98.75% (equivalent to a 97.5% two-sided confidence limit) in a secondary analysis performed for illustrative purposes *as per* study protocol. A comparison of results obtained for the primary endpoint and for TLOVR using lower bound of the 1-sided 97.5% CI and 1-sided 98.75% was presented.

Results

The original Trofile assay (Monogram Biosciences) was used in this study. An enhanced sensitivity Trofile assay with an increased sensitivity for detection of CXCR4-tropic virus was in the meantime available. The results for study A4001026 were obtained using the original Trofile assay but a retrospective re-analysis of the results using the enhanced sensitivity Trofile assay was performed.

All data presented concerns the double-blind treatment group of maraviroc 300 mg BID and efavirenz 600 mg QD.

Patients' disposition

Of the 1730 subjects planned for enrollment, 917 were randomised:

- 360 to receive maraviroc 300 mg BID;
- 361 to receive efavirenz 600 mg QD;
- 174 to receive maraviroc 300 mg QD;
- 22 were randomised but have not received any study medication.

[5] FAS analysis set: included all randomised subjects who received at least 1 dose of study medication.

[6] PP analysis set: included all randomised subjects who received at least 1 dose of study medication (FAS) for at least 14 days, were more than 80% compliant and did not had any protocol violation (as *per* protocol-defined including patients who switched to CXCR4 positive viral tropism from screening to baseline).

Discontinuation rates at week 48 and week 96 are summarised in the following table:

Number of subjects	Maraviroc 300 mg BID N=360		Efavirenz 600 mg QD N=361	
	Week 48	Week 96	Week 48	Week 96
All	97 (26.9%)	129 (35.8%)	91 (25.2%)	123 (34.1%)
Subject died	1 (0.3%)	2 (0.6%)	0	2 (0.6%)
Related to study drug				
Adverse event	12 (3.3%)	15 (4.2%)	39 (10.8%)	44 (12.2%)
Lack of efficacy	43 (11.9%)	55 (15.3%)	15 (4.2%)	23 (6.4%)
Not related to study drug				
Adverse event	3 (0.8%)	7 (1.9%)	10 (2.8%)	12 (3.3%)
Other reason	13 (3.6%)	14 (3.9%)	9 (2.5%)	12 (3.3%)
Pregnancy	0	5 (1.4%)	0	7 (1.9%)
Subject defaulted	25 (6.9%)	31 (8.6%)	18 (5.0%)	23 (6.4%)

Overall, there was a high discontinuation rate similar in both treatment groups. However, in the maraviroc group due to lack of efficacy, while in the efavirenz group due to efavirenz-related adverse events. The high rate of discontinuations observed in the efavirenz group at week 96 (34.1%) is similar to the rate reported in other treatment naïve studies with efavirenz + zidovudine/lamivudine regimens.

Demographic and baseline characteristics

There were no significant differences between the maraviroc 300 mg BID group and efavirenz 600 mg QD group. A high proportion of females (29% maraviroc group and 28% efavirenz group) and black patients (34.2% maraviroc group and 36.8 % efavirenz group) was noted.

Efficacy results

Proportion of subjects with undetectable virus (principal endpoint)

The following table shows the proportion of patients with viral load <400 and <50 copies/ml at week 48 and at week 96 (FAS-As Treated analysis set).

	Maraviroc 300 mg BID N = 360	Efavirenz 600 mg QD N = 361	Difference in % Difference in Percentages	Lower Bound of 1-Sided 97.5% CI*	Lower Bound of 1-Sided 98.75% CI**
Week 48					
<400 copies/ml	70.6% (n=254)	73.1% (n=264)	-3.0	-9.5	-10.4
<50 copies/ml	65.3% (n=235)	69.3% (n=250)	-4.2	-10.9	-11.9
Baseline Viral Load					
<100.000 cps/ml	69.6%	71.6%			
>100.000 cps/ml	59.6%	66.0%			
Week 96					
<400 copies/ml	61.4% (n=221)	64.5% (n=233)	-3.2	-10.2	-11.2
<50 copies/ml	56.9% (n=205)	62.6% (n=226)	-5.8	-12.8	-13.8
Baseline Viral Load					
<100.000 cps/ml	61.8%	64.9%			
>100.000 cps/ml	50.6%	59.3%			

* one-sided 97.5% lower confidence limit (original pre-specified criterion)

**one-sided 98.75% lower confidence limit (equivalent to 97.5% two-sided lower confidence limit)

The established difference in response rates of -10% for non-inferiority was not met.

The results obtained with efavirenz are similar to those seen in other studies of efavirenz where lamivudine/zidovudine was used as a backbone (70-75% of patients < 50 copies/ml after 48 weeks of treatment). Maraviroc efficacy was affected by baseline viral load (10% difference between those with viral load < and > 100.000 copies/ml).

Similar results were observed for subjects with viral loads of <400 copies/ml or <50 copies/ml using the PP – As Treated population. These results are qualitatively similar to the previously reported primary analyses at week 48 (slightly higher - 5% proportions of patients with viral load <400 and <50 cps/ml than in the FAS- AT population in both treatment groups). The analysis of the difference in percentage using this population did not meet the pre-defined criteria for non-inferiority, as well.

Time to Loss of Virologic Response (TLOVR)
The results, using the TLOVR algorithm for subjects with a viral load of <400 copies/ml, showed that the lower confidence bound of the 1-sided 97.5% CI was -9.7% for the FAS - As Treated population. These results are similar to those reported for the FAS - As Treated population at week 48 (the 1-sided 97.5% CI was above -10%).
However, for subjects with a viral load of <400 copies/ml in the PP – As Treated population, and for subjects with a viral load of <50 copies/ml in the FAS – As Treated and PP –As Treated populations the results showed that the lower confidence bound of the 1-sided 97.5% CI for each analysis was below -10%.

Overall, the analysis using the TLOVR algorithm is consistent with a significant loss of efficacy at week 48 for the maraviroc group, maintained until week 96.

Change from baseline in CD4+ and CD8+ cell counts
The following table represents the immunologic recovery at week 48 and week 96 (FAS-As Treated analysis set).

Treatment Group	N	Baseline Mean	Mean Change from Baseline	Adjusted mean[a] (S.E, n)	Treatment Difference (Maraviroc-Efavirenz)	
					Estimate	95% CI
CD4+ Cell Count (cells/µl) – Week 48						
Maraviroc 300 mg BID	360	264.7	192.6	169.8 (6.9, 352)		
Efavirenz 600 mg QD	361	271.9	165.4	143.5 (7.0, 348)	26.3	7.0, 45.6
CD4+ Cell Count (cells/µl) – Week 96						
Maraviroc 300 mg BID	360	264.5	252.5	206.9 (8.1, 352)		
Efavirenz 600 mg QD	361	271.9	212.9	171.5 (8.1, 348)	35.4	13.0, 57.9
CD8+ Cell Count (cells/µl) – Week 48						
Maraviroc 300 mg BID	360	938.8	24.18	41.8 (17.7, 352)		
Efavirenz 600 mg QD	361	935.8	-138.9	-124.5 (17.8, 348)	166.3	117.1, 215.5
CD8+ Cell Count (cells/µl) – Week 96						
Maraviroc 300 mg BID	360	938.8 (503.4, 360)	-1.74 (434.0, 232)	24.5 (18.0, 352)		
Efavirenz 600 mg QD	361	935.8 (476.6, 360)	-158.3 (411.4, 233)	-147.7 (18.1, 348)	172.2	122.2, 222.2

There is a benefit in favour of maraviroc for the difference in CD4 cell count and CD8 cell count at week 96 between the maraviroc 300 mg BID and efavirenz 600 mg QD treatment groups. Based on current available data it is not clear if the difference would translate into a clinical benefit.

Results of sub group analyses
Poorer response rates were observed for maraviroc in black subjects, in southern hemisphere patients, in patients with subtype C virus and in female subjects.

This may indicate that maraviroc performs less well in patients with non-B subtypes (prevalent in treatment-naïve patients in Europe). This could also be related with the Trofile assay, since 23% of those with subtype C had non-reportable viral tropism at screening, as compared to 6% of those with subtype B. This issue is undergoing discussions on improvement by modifying primers.

The above findings could also point to a significant impact of genetic determinants in terms of response. Further clarifications were provided by the MAH on the overall impact of genetic variability and the relationship between exposure and response to treatment. Including a number of summaries on simulations (modulations where the 300 mg dose is justified as adequate) to address the CHMP presumption that the 300 mg BID dose (in combination with two NRTIs) used in this study might have been too low. The CHMP noted that in one analysis, the number of patients with < 400 copies/ml at week 48 would increase around 6%, according to the simulation (70=>76%), when the dose was increased from 300 to 450 mg BID. Neither race nor clades were identified as prognostic factors in the model for study A4001026.

Viral resistance and Tropism

At time of treatment failure, 33 (60.0%) subjects in the maraviroc 300 mg BID treatment group and 8 (34.8%) subjects in the efavirenz 600 mg QD treatment group had resistance to zidovudine/lamivudine. One (1.8%) subject in the maraviroc 300 mg BID treatment group and 14 (60.9%) subjects in the efavirenz 600 mg QD treatment group had resistance to efavirenz.

At the time of treatment discontinuation, 40 (31.0%) subjects in the maraviroc 300 mg BID treatment group and 8 (6.5%) subjects in the efavirenz 600 mg QD treatment group showed resistance to zidovudine/lamivudine. One (0.8%) subject in the maraviroc 300 mg BID treatment group and 16 (13.0%) subjects in the efavirenz 600 mg QD treatment group showed resistance to efavirenz.

The following table shows the percentage of subjects with a change in tropism results from CCR5 tropic to CXCR4 or dual/mixed tropic between baseline and time of treatment failure or discontinuation:

	Maraviroc 300 mg BID	**Efavirenz 600 mg QD**
Time of treatment failure		
N	43	22
n (%)	12 (27.9)	0
Difference	12 (27.9)	N/A
95%CI (%)	14.5, 41.3	N/A
Time of discontinuation		
N	106	105
n (%)	14 (13.2)	0
Difference	14 (13.2)	N/A
95%CI (%)	6.8, 19.7	N/A

Hence, the majority of those failing with maraviroc, still had CCR5-tropic virus at time of treatment failure. The impact of the switch in the clinical outcome in treatment naïve patients including risk for disease progression and the potential for reversion to the previous CCR5 tropism was further discussed by the MAH *per* CHMP request.

At week 96, 12 subjects (28%) with CCR5 tropism at baseline failed with CXCR4-using virus.

Considering the mean increases in CD4+ cell count from baseline to time of failure in the maraviroc group including in subjects who had CCR5 tropic virus at baseline and failed with CXCR4-using virus; and the slightly lower incidence of CDC category C infection and malignancy events in subjects receiving maraviroc, it seems that there is no adverse immunological outcome in subjects failing maraviroc with CXCR4-using virus.

Available data from the study off drug (ISOD) with maraviroc shows that the majority of subjects with CCR5 at baseline failing with CXCR4-using virus reverted back to CCR5-tropism. This reversion is consistent with data obtained in treatment-experienced patients.

Based on the current available data it is agreed that the impact of the tropism switch in the clinical outcome does not constitute a concern. The MAH committed to follow-up this issue in the 5 years data from study A4001026 (see Letter of Undertaking attached to this report).

Re-analysis of efficacy results using the enhanced Trofile assay

Data from *in vitro* mixing experiments showed that an enhanced Trofile assay detected CXCR4 variants 100% of the time when they comprised 0.3% of the total viral population as opposed to 10% with the original Trofile assay.

Of the 721 subjects randomised to maraviroc 300 mg BID (n=360) and to efavirenz 600 mg QD (n=361) and classified as CCR5-tropic at screening by the original Trofile assay, 106 (14.7%) were re-classified as dual mixed/CXCR4-tropism by the enhanced Trofile [48 (13.3%) and 58 (16.1%) in the maraviroc and efavirenz groups, respectively]**.**

The number of treatment naïve patients that were not eligible for maraviroc therapy due to the presence of CXCR4-virus following re-analysis is significant.

Results of the primary endpoint in the FAS-As Treated analysis set for the original assay and following the retrospective re-analysis by the enhanced Trofile assay at week 48 and 96 are presented in the below table:

		Maraviroc 300 mg BID % (n/N)	Efavirenz 600 mg QD % (n/N)	Difference in % Difference in Percentages	Lower Bound of 1-Sided 97.5% CI	Lower Bound of 1-Sided 98.75% CI
Week 48						
<400 copies/ml	Trofile	70.6% (254/360)	73.1% (264/361)	-3.0	-9.5	-10.4
	Enhanced Trofile	73.3% (228/311)	72.3% (219/303)	0.6	-6.4	-7.4
<50 copies/ml	Trofile	65.3% (235/360)	69.3% (250/361)	-4.2	-10.9	-11.9
	Enhanced Trofile	68.5% (213/311)	68.3% (207/303)	-0.2	-7.4	-8.4
Baseline Viral Load <100.000 copies/ml	Trofile	69.6% (142/204)	71.6% (151/211)			
	Enhanced Trofile	71.8 (127/177)	72.1 (132/183)			
>100.000 copies/ml	Trofile	59.6% (93/156)	66.0% (99/150)			
	Enhanced Trofile	64.2 (86/134)	62.5 (75/120)			
Week 96						
<400 copies/ml	Trofile	61.4% (221/360)	64.5% (233/361)	-3.2	-10.2	-11.2
	Enhanced Trofile	64 % (199/311)	64.4% (195/303)	-0.4	-7.9	-9.0
<50 copies/ml	Trofile	56.9% (205/360)	62.6% (226/361)	-5.8	-12.8	-13.8
	Enhanced Trofile	58.8% (183/311)	62.7% (190/303)	-3.9	-11.5	-12.6
Baseline Viral Load <100.000 copies/ml		61.8%	64.9%			
>100.000 copies/ml		50.6%	59.3%			

Similar findings were observed in the PP-AT population. The lower confidence bound for <50 copies/ml at week 48 decreased from -10.9 to -7.4 with one-sided 97.5% lower confidence interval and from -11.9 to -8.4 with one-sided 98.75% lower confidence interval. This retrospective analysis, using a new method and without further data to support the revised results is considered not valid and not sufficient for consideration to the applied extension of the therapeutic indication.

Re-analysis of virology results at week 96 using the enhanced Trofile assay

The analysis consisted of responders and virologic failures as defined using the time to loss of virologic failure algorithm with a plasma HIV-1 RNA cut-off of 50 copies/ml (TLOVR50). Those discontinuing the study for other, non-virologic reasons were omitted from this analysis. This resulted in a total population of 253 in the maraviroc group and 220 in the efavirenz group.

There were similar numbers of responders in both groups (maraviroc n=188/253; efavirenz: n=184/220). In the maraviroc group there was a higher number of subjects who experienced virologic failure (maraviroc: n=65/253; efavirenz: n=36/220). Most subjects who experienced virological failure with CCR5-tropic virus had CXCR4-using virus at time of failure as shown in the following table.

Treatment group	**Viral tropism at the time of virologic failure**[a]			
	CCR5-tropic **n (%)**	CXCR4-using **n (%)**	**No Result** Plasma HIV-1 RNA <500 copies/ml n (%)	Undeterminable (NR/NP)[b] n (%)
maraviroc 300 mg BID (N=65)	41 (63)	11(17)	10 (15)	3 (5)
efavirenz 600 mg QD (N=36)	27 (75)	0	5 (14)	4 (11)

[a] Time to discontinuation (or week 96 visit) having never suppressed or time of first plasma HIV-1 RNA rebound above 50 copies/ml.
[b] No result/not phenotypable.

The incidence and type of resistance to maraviroc or efavirenz and background NRTIs is as follows:

	Subpopulation	N[a]	Maraviroc/Efavirenz resistance n (%)	Lamivudine resistance (M184V) n (%)	Zidovudine resistance (TAMs) n (%)
Maraviroc	**CCR5-tropic**	32	5 (16)[b]	20 (63)	2 (6)
	CXCR4-using	10	10 (100)[c]	10 (100)	2 (20)
	Total	42	15 (36)	30 (71)	4 (10)
Efavirenz	**Total**	25	17 (68)[d]	10 (40)	2 (8)

[a] Maraviroc population included all virologic failure subjects with complete virology data set (i.e. valid tropism and reverse transcriptase genotype result and with a successful maraviroc susceptibility test for subjects failing with CCR5-tropic virus.
Efavirenz population included all subjects with a valid reverse transcriptase genotype result.
[b] reduced susceptibility to maraviroc establish with phenotypic assay
[c] reduced susceptibility due to detection on-therapy of previously existing CXCR4-using virus
[d] resistance establish with genotype analysis: the main efavirenz-associated resistance mutation was K103N (n=12)

As seen, and as with the original Trofile assay, the majority of patients failing with maraviroc, still had CCR5-tropic virus, and with CCR5-tropic virus still sensitive to maraviroc *in vitro* (27/42 failures). For the others, sensitivity to maraviroc was lost due to a switch to CXCR4-virus (10/42) or mutations in the CCR5-virus, related to reduce activity (5/42); the latter in a way representing ”traditional antiretroviral resistance”. Importantly, the proportion and number of patients who acquired resistance to the NRTI backbone was much higher in the maraviroc group.

This indicates a less favourable resistance profile in terms of the options of NRTI backbone for future treatments in the population previously exposed to maraviroc.

Discussion and conclusion on efficacy

Study A4001026, designed to compare maraviroc at two different doses (300 mg QD and 300 mg BID) *versus* efavirenz (600 mg QD), each in combination with zidovudine 300mg/lamivudine 150 mg BID, failed to demonstrate the non-inferiority of maraviroc 300 mg BID regimen over a standard regimen with efavirenz 600 mg QD for the treatment-naïve adult patients infected with CCR5-tropic HIV-1.

Results of an interim analysis at week 16 precluded the continuation of maraviroc 300 QD treatment group due to failure in meeting pre-defined criteria for non-inferiority to efavirenz. The sample size decreased and the study continued with two treatment groups. The primary efficacy endpoint at 48 weeks of treatment failed to demonstrate non-inferiority of maraviroc 300g BID. Further analysis at 96 weeks confirmed the lack of demonstration of non-inferiority.

Efficacy results were retrospectively re-analysed by using an enhanced sensitivity Trofile assay including patients without detectable CXCR4-virus at screening: 106 patients were reclassified (58 in the efavirenz group and 48 in the maraviroc group). In this re-analysis, non-inferiority of maraviroc over efavirenz at week 48 was shown but failed to be demonstrated at week 96.

At week 96 the overall discontinuation rate was similar between the two treatment groups being lack of efficacy the main reason in the maraviroc group and treatment-emergent adverse events in the efavirenz group.

In those patients with virological failure on maraviroc treatment, around two out of three showed a virus still sensitive to maraviroc, while resistance to lamivudine was very common (around three out of four patients). This indicates a less favourable resistance profile in terms of the options of NRTI backbone for future treatments in the population previously exposed to maraviroc.

Virological failure with resistance development will always be a major threat to HIV treatment with direct acting antiretrovirals. Hence, the CHMP had major concerns on the clearly lower virological efficacy of maraviroc in treatment-naïve patients infected with CCR5-tropic HIV-1 as compared to efavirenz and with the resistance to other agents which were 3-4 times more commonly seen with maraviroc regardless of the Trofile assay used.

These concerns were expressed to the MAH, who did not provide any new relevant data. In conclusion, the CHMP was of opinion that the use of maraviroc is not approvable for treatment-naïve patients based on the results of study A4001026, due a high rate of virological failure and resistance. However, the CHMP agreed that the study results should be reflected in the safety section of the Celsentri product information to warn against the use of maraviroc in CCR5-tropic HIV-1 infected

treatment naïve adult patients. A summary of the study results supporting the warning should also be included in the product information.

Further discussions were held, culminating with the MAH acknowledging these major concerns and not pursuing an extension of the therapeutic indication for maraviroc to include treatment-naïve patients.

Clinical safety

Patient exposure
The safety analysis was primarily based on the 360 subjects who received maraviroc 300 mg BID and on 361 subjects who received efavirenz 600 mg QD in study A4001026. The mean duration of exposure was similar between treatment groups (672 days, median).

Adverse events (AEs).
A similar proportion of patients in the maraviroc group and in the efavirenz group experienced an AE. Treatment related AE were more frequently reported in the efavirenz group.

Serious adverse events (SAEs) and Death
A total of 12 deaths (6 in each treatment group) were reported until the 96 week cut-off. However, 5 subjects (2 on maraviroc group and 3 on efavirenz group) died during the course of study or within 28 days of study discontinuation. The remaining 7 deaths occurred more than 28 days after permanent study discontinuation (4 on maraviroc group and 3 on efavirenz group).

Treatment-emergent SAEs considered related to treatment were reported in 2.8% (10/360) subjects treated with maraviroc 300 mg BID and in 4.8 % (17/361) of subjects treated with efavirenz 600 mg QD.
The SAEs related to maraviroc treatment were: deep vein thrombosis, nasopharyngeal cancer (patient died), vomiting, nausea, transaminases increased, anorexia, abdominal pain, blood creatinine phosphokinase increased, neutropenia, Hodgkin's disease, anaemia, syncope, diffuse large B-cell lymphoma (patient died), depression and transaminases increased.

The SAEs related to efavirenz treatment were: Pancytopenia, anaemia, haematuria, flank pain, myocardial infarction, rash macular, hepatic enzyme increased, rash, GGT increased, AST increased, blood creatinine phosphokinase increased, hepatitis, hypersensitivity, abortion spontaneous, multiple drug overdose intentional and suicide attempt. No deaths in the efavirenz group were associated with SAE related with efavirenz.

Adverse events of interest
Infections, AIDS events and malignancies
The incidence of infections and infestations (62.5% in maraviroc group vs 62.3% in the efavirenz group, for all causality) and category C AIDS events (2.5 % in maraviroc group vs 3.3% in the efavirenz group) were overall similar between both treatment groups.

There was no clear difference in severity of the infections and infestations between the treatment groups, with most being Grade 1 or 2. In category C AIDS events, in the maraviroc group one patient reported *pneumocytiis jiroveci* pneumonia and another tuberculosis while in the efavirenz group, 6 patients reported pulmonary tuberculosis and another tuberculosis.

The incidence in terms of malignancies was: 1.4 % (5 subjects) in the maraviroc group and 3.3% (12 subjects) in the efavirenz group. Of these, 3 subjects in the maraviroc group *vs* 0 in the efavirenz group had reported malignancies considered to be related to the study drug. The adverse events related to malignancies resulted in discontinuation in 3 subjects in the maraviroc group and 4 subjects in the efavirenz group.

Laboratory findings
Overall, lipid changes were lower with maraviroc as compared to efavirenz. Liver enzymes were raised more frequently in the efavirenz group. No significant differences were found in other laboratory findings.

Discontinuation due to AES
The percentage of patients who permanently discontinued the study due to adverse events was lower in the maraviroc group 7.5% (27 subjects) as compared with efavirenz group 18.6% (67 subjects). The most common reasons for discontinuation were related to increased transaminases, nausea and pregnancy in the maraviroc group and rash, pregnancy, tuberculosis, dizziness and nausea in the efavirenz group.
The proportion of patients who temporarily discontinued study was similar between both treatment groups (5%).

Discussion and conclusion on safety

In general the safety profile of maraviroc in the HIV-infected treatment-naïve patients was not different from the already known safety profile in treatment-experienced patients. When compared to efavirenz, maraviroc is overall better tolerated, as reflected by the proportion of subjects that discontinued in each treatment arm due to safety reasons.

The most frequently reported treatment-emergent adverse events were nausea (36.1% for maraviroc, 34.6% for efavirenz), headache (25.3% for maraviroc, 25.2% for efavirenz), diarrhoea (8.1% for maraviroc, 12.7% for efavirenz) and fatigue (16.1% for maraviroc and 14.1% for efavirenz). The incidence of Grade 3 treatment-emergent adverse events was greater in the efavirenz arm. However, Grade 4 was similar for both treatment arms.

A total of 94 subjects permanently discontinued from the study due to treatment emergent adverse events; 27 (7.5%) subjects were receiving maraviroc and 67 (18.6%) subjects were receiving efavirenz. The most common reasons for discontinuation were related to increased transaminases, nausea and pregnancy in the maraviroc group and rash, pregnancy, tuberculosis, dizziness and nausea in the efavirenz group.

As regards adverse events of interest for maraviroc no differences could be detected in this study. However, with regard to infections and infestations a substantially higher proportion of subjects with pulmonary tuberculosis were reported in the efavirenz group. This finding may be related to eventual differences either in terms of the recovery of immune function or to specific interference of maraviroc in the immune response to *M. tuberculosis* infection. This was further discussed and at the present time with the data available no conclusion can be made.

Overall conclusion and Benefit-Risk assessment

Study A4001026, the only comparative study of maraviroc as a first line treatment in treatment-naïve CCR5 infected HIV-1 adult patients in combination with zidovudine/lamivudine as compared to efavirenz in combination with zidovudine/lamivudine, failed to demonstrate the non-inferiority of maraviroc. Although the NRTI backbone used in this study is no longer recommended in first line, it was a reasonable therapeutic option at the time the study was planned.

The efficacy results observed with the efavirenz group are similar to those seen in other randomised studies (typically around 70% after 48 weeks of therapy). The loss of efficacy for maraviroc occurred already during early treatment, and was for the most not related to a switch in viral tropism.

The number of discontinuations due to lack of efficacy was 2-3 times higher with maraviroc and in summary, around 3-4 times as many patients in the maraviroc group developed resistance to the NRTI backbone (in particular lamivudine). Lamivudine and the closely related emtricitabine (also cytosine analogue with same resistance pattern) are medicinal products currently used in first line regimens.

A somewhat improved outcome was shown in a retrospective re-analysis of the efficacy and safety results by using an enhanced sensitivity Trofile assay to detect very low levels of CXCR4-virus.

Hence, the need for a very sensitive assay to select patients without detectable CXCR4-virus was clear from the data presented. However, also in this censored population lack of efficacy and resistance development to the NRTI backbone was considerably more common with maraviroc.

It could be argued that poor conduct of this study, with a higher proportion of patients discontinuing therapy than in other recent and important studies in treatment naïve patients, could be one reason for the results obtained. The drop-out rate could also indicate that the actual compliance was low.

However, the fact that virological failure and resistance development was much more common with maraviroc than with efavirenz – this last with a low barrier to resistance and with a high tendency for resistance development – could be interpreted as maraviroc being a medicinal product of rather low potency and where failure is associated with a high risk of resistance.

The safety profile of maraviroc in the treatment naïve patient population was not different from the already known mid-term profile in treatment-experienced patients. The impact of CCR5-inhibition on immune function, including for example risk for malignancy must be studied at longer term and in larger populations before a final conclusion is made.

Based on results of study A4001026, the presently favourable safety profile of maraviroc does not outweigh the high risk for virological failure and resistance development in the treatment of CCR5-tropic HIV-1 infected adult antiretroviral-naïve patients. However, results of study 1026 are relevant to be reflected in the Celsentri product information.

The MAH, acknowledging the CHMP concerns, proposed not to pursue with an extension of indication for Celsentri in treatment-naïve CCR5 infected HIV-1 adult patients, however agreed to reflect the results of this study in the SPC in the relevant sections.

Changes to the Product Information

As above discussed, it was agreed that the results for study A4001026 should be mentioned in the SPC as follows:

- **Section 4.4 "Special warnings and precautions for use"**

CELSENTRI is not recommended to be used in treatment naïve patients based on the results of a clinical study in this population (see section 5.1)

- **Section 5.1 "Pharmacodynamic properties"**

In vivo:
~~*Treatment naïve patients*~~
~~*"The resistance profile in treatment-naïve patients has not been characterized."*~~

Studies in Treatment Naïve Patients
An ongoing randomised, double-blinded study (MERIT), is exploring CELSENTRI versus efavirenz, both in combination with zidovudine/lamivudine (n=721, 1:1). After 48 weeks of treatment, CELSENTRI did not reach non-inferiority to efavirenz for the endpoint of HIV-1 RNA < 50 copies/ml (65.3 vs. 69.3 % respectively, lower confidence bound -11.9%). More patients treated with CELSENTRI discontinued due to lack of efficacy (43 vs.15) and among patients with lack of efficacy, the proportion acquiring NRTI resistance (mainly lamivudine) was higher in the CELSENTRI arm. Fewer patients discontinued CELSENTRI due to adverse events (15 vs.49).

Furthermore, section 6.6 was amended to include standard statement on disposal measures.

- **Section 6.6 “Special precautions for disposal”**

~~*No special requirements*~~*Any unused product or waste material should be disposed of in accordance with local requirements.*

Conclusion

On 24 September 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, subject to the commitment undertaken.