London, 05 October 2005
Product name: **Ziagen**
Procedure No. **EMEA/H/252/II/20**

SCIENTIFIC DISCUSSION

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.eu.int http://www.emea.eu.int

1. Introduction

The proposed amendments relate to an update of the Summary of Product Characteristics (SPC) and consequential changes to the Package Leaflet of Ziagen film coated tablets and Ziagen oral solution, to introduce a 600 mg (two tablets) once daily dosing regimen for in adults and adolescents over 12 years.

The currently approved dose of Ziagen is one 300 mg tablet orally twice daily in adolescents and adults and 8mg/ kg orally twice daily (BID) up to a maximum of 600mg/ day (300mg/ dose) in paediatric patients.

Moreover, as part of this variation and further to the renewal of Ziagen in May 2004, the MAH was requested to update section 5.1 of the SPC with results of study CNA30024.

2. Non-clinical aspects

Results of pharmacological and toxicological studies of abacavir were submitted and assessed with the original marketing authorisation application for Ziagen and subsequent variations.

The increase in plasma drug concentrations associated with the proposed alternative dosage regimen are unlikely to present any safety issues since the concentrations achieved during the toxicological evaluation of abacavir still provide large margins of safety.

Therefore, no additional pre-clinical data were submitted to support the use of the new alternative dose regimen.

The MAH submitted however results of an *in vitro* mitochondrial toxicity investigating abacavir and lamivudine as single agents, both in combination and in combination with other NRTIs in CCRF-CEM human lymphoblastoid cells. No synergetic effects due to the combination have been observed in comparison with abacavir and lamivudine as single agents.

3. Clinical aspects

To support the introduction of the abacavir once daily dosing for adults and adolescents over 12 years of age, the MAH submitted:

- One clinical pharmacology study CNA10905 to characterise the pharmacokinetics of plasma abacavir and intracellular Carbovir Triphosphate (CBV-TP) at steady-state following administration of an abacavir 300 mg twice daily containing regimen.
- One pivotal clinical trial CNA30021 comparing abacavir 600mg once daily versus abacavir 300 mg dosed twice daily, each in combination with lamivudine once daily and efavirenz once daily over 48 weeks.

In addition, the supporting clinical trial EPV 40001 is submitted. The 24 and 48 weeks results of this study were part of the previous submission for Epivir 300 mg tablets application and have already been assessed by the CHMP. In view of the previously highlighted limitations of the study EPV40001, this study is not summarised in this Assessment Report.

Subsequently the MAH completed the clinical dossier by providing preliminary 24 weeks data of two new phase III studies (CAL 30001 and ESS 30008) in antiretroviral treatment experienced patients using the once daily fixed dose combination abacavir/ lamivudine (Kivexa).

Moreover, as part of this variation and further to the renewal of Ziagen in May 2004, the MAH was requested to update section 5.1 of the SPC with results of study CNA30024. The report of study CNA 30024 performed with abacavir and lamivudine administered as a twice daily regimen had been provided in the dossier submitted for Marketing Authorisation of Kivexa, a fixed combination of

abacavir and lamivudine administered once daily. The CHMP concluded that the results of this study were of poor interest to support the Marketing Authorisation of Kivexa (a once daily regimen) and didn't warrant to be mentioned in the SPC. However, these results deserved to be included in the SPC of Ziagen. Indeed, whereas the clinical development of Ziagen was mainly performed in combination with zidovudine and lamivudine, this study provides further efficacy/ safety data within a different triple combination.

An overview of the clinical studies submitted to support the once a day regimen is presented in table 1.

Table 1: Overview of the clinical programme

Study	Study Objective	Study Population	Doses of Abacavir	Duration of Treatment	No. of Patients Randomised	Study Design
Pharmacokinetics						
CNA 10905	To characterise the pharmacokinetics of abacavir and its intracellular anabolite carbovir triphosphate	HIV infected patients	300 mg BID	7 – 30 days	20 (9 on Ziagen and 11 on Trizivir)	Open label, single arm
Efficacy and Safety						
CNA 30021	To evaluate the safety and efficacy of abacavir once daily versus abacavir twice daily	Therapy naïve HIV-1 infected patients	600 mg once daily versus 300 mg twice daily	72 weeks	784 (392 in each arm)	Randomised, double blind, multicentre
CAL 30001	To evaluate the safety and efficacy of abacavir/ lamivudine fixed dose combination (FDC) once daily versus abacavir twice daily and lamivudine once daily in combination with tenofovir and a new PI or NNRTI	Treatment experienced HIV-1 infected patients	600 mg once daily versus 300 mg twice daily	24 weeks	186 (95 on abacavir/ lamivudine FDC; 91 on abacavir BID and lamivudine OD)	Randomised, open-label, parallel, multicentre
ESS 30008	To evaluate the safety and efficacy of the abacavir/ lamivudine FDC tablet administered once a day versus abacavir and lamivudine administered twice daily in combination with a PI or NNRTI	Treatment experienced HIV-1 infected patients	600 mg once daily versus 300 mg twice daily	24 weeks	260 (130 in each arm)	Randomised, open-label, multicentre

EPV 40001	To explore the early antiviral activity and tolerability of abacavir and lamivudine once daily within a triple combination regimen including abacavir, lamivudine, and zidovudine compared to the triple combination regimen twice daily	Antiretroviral naïve, HIV-1 infected subjects.	600 mg once daily versus 300 mg twice daily	48 weeks	159 (53 on abacavir OD; 106 on abacavir BID)	Randomised, open label, multicentre pilot study

739 patients received abacavir twice daily and 670 patients received abacavir once daily in combination with other antiretroviral agents.

3.1 Clinical Pharmacology

Study CNA 10905

The primary objective of this study was to evaluate the pharmacokinetics of intracellular carbovir triphosphate (CBV-TP), in order to support the abacavir 600 mg OD regimen. The study was performed in HIV infected patients treated with abacavir 300 mg BID. Therapy has been withheld beyond 24 hours for the purposes of pharmacokinetic sampling and the last abacavir dosing was therefore 300 mg (and not 600 mg).

Ages ranged from 29 to 55 years, body weights ranged from 53.4 to 131.9 kg, and heights ranged from 156 to 183 cm. Total CD4 cell counts ranged from 298 to 1133 cells/mm^3, with a median of 572 cells/mm^3. 17 patients had an undetectable viral load at baseline (VL < 400 copies/ ml).

Pharmacokinetic results

Figure 1: Mean (SD) Concentration-time Profiles of Plasma abacavir and Intracellular CBV-TP up to 24 Hours Post Dose at Steady State Following a abacavir 300mg Twice Daily Containing Regimen

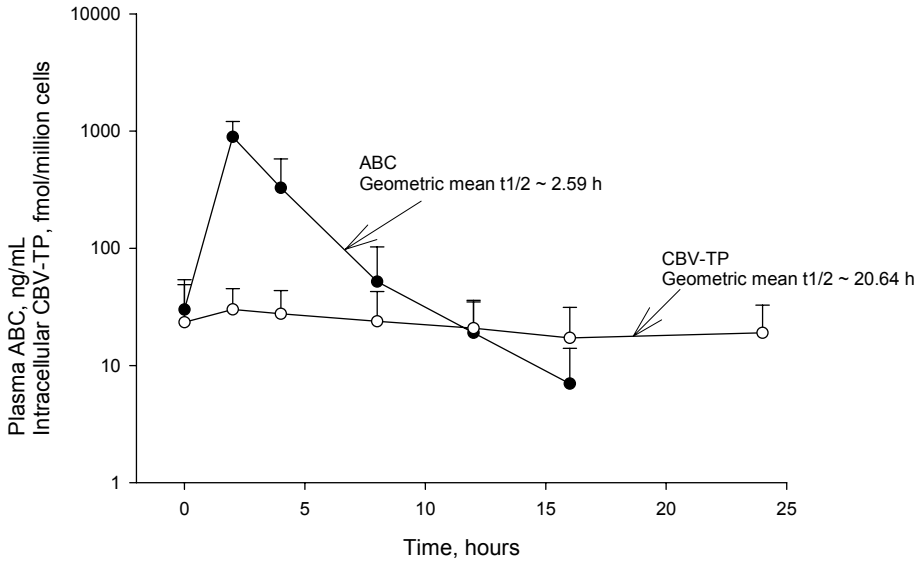

Table 2: Abacavir and carbovir-TP pharmacokinetic parameters

	Abacavir: Geo. Mean (95% CI)	Intracellular carbovir-TP: Geo. Mean (95% CI)
C_{max}	µg/ml 0.88: (0.75 - 1.03)	fmol/10^6cells : 29.7 (22.1 – 39.9)
AUC0-24	µg.h/ml: 2.56 (2.13 - 3.06)	fmol.h/10^6cells : 252.78 (190.05 – 336.21)
T1/2 h	2.59 (2.04 - 3.29)	20.6 (16.4 – 26.0)
T_{max} h	2.00 (2.00 – 3.92)	2.00 (0.00 – 12.00)
C12		fmol/10^6cells median (range): 18.1 (4.7 – 51.6)
C24		fmol/10^6cells median (range): 16.3 (3.1 – 61.1)

The CHMP noted that the observed plasma pharmacokinetics of abacavir were different to those described in previous studies in HIV infected patients. Mean (CV) steady state C_{max} of abacavir in plasma is approximately 3.0 µg/ml (99%) as described in the SPC compared with 0.88 (34%) in this study. In the same way, the mean (CV) steady state AUC over a dosing interval of 12 hours is 6 µg.h/ml (29 %) in the SPC while the AUC0-24ss Geometric mean (95% CI) is 2.56 (2.13 –3.06) in the study.

Moreover, the MAH referred to the original marketing authorisation for Ziagen tablets to describe the abacavir PK after a 600 mg abacavir tablet dose: the mean abacavir C_{max} was approximately 4.26 +/- 1.19 µg/ml and the mean AUC was 11.95 +/- 2.51 µg.h/ml. It is worth noting that these data are still different to the ones mentioned in the SPC.

The primary differences in plasma abacavir pharmacokinetic parameters provided in the SPC and those reported for Study CNA10905 are attributable to the differences in pharmacokinetic objectives and associated differences in blood sampling schedules, which result in different abacavir pharmacokinetic parameter estimates (longer time to peak concentration (t_{max}), lower peak concentration (C_{max}) and lower area under the concentration-time curve (AUC) over a 12-hour dosing interval).

The CHMP concluded that this study demonstrates that carbovir-TP has a long half-life *in vivo,* but does not demonstrate that the carbovir-TP concentrations will support once daily dosing.

An important shortcoming of the pharmacokinetic development programme to support this type II variation is the lack of submission of comparative pharmacokinetic data between abacavir once and twice daily. Therefore, the applicant was requested to compensate for this deficiency by submitting comparative pharmacokinetic data between 600 mg OD and 300 mg BID. This will also allow substantiating the pharmacokinetic profile of the 600 mg OD in terms of plasma and intracellular levels.

Pharmacokinetic data in paediatric patients

The MAH will provide the pharmacokinetic data in paediatric patients to support the use of the OD abacavir regimen in children. The data to support the once daily regimen in paediatric patients are particularly awaited since the gap between the posology recommendation in adults and children is particularly unfortunate.

3.2 Clinical Efficacy

Study CNA30021

This was a randomised, double-blind, multicentre clinical trial comparing abacavir 600 mg once daily versus abacavir 300 mg twice daily, when used in combination with lamivudine 300 mg once daily and efavirenz 600 mg once daily over 48 weeks in antiretroviral naïve patients.

Methods

Study Participants

Adults above 18 years of age with documented HIV-1 infection who were antiretroviral (ART)-naïve (defined as less than 7 days of any approved or experimental ART) or had 14 days or less of zidovudine monotherapy exposure were eligible for this study. Patients were required to have a screening plasma HIV-1 RNA level > 400 copies/ml and a CD4 cell count >50 cells/mm^3 on at least one occasion within 21 days of study entry.

Treatments

Patients who permanently discontinued randomised (assigned) study treatment (abacavir once daily or abacavir twice daily) due to an adverse event (AE) were permitted to substitute other licensed antiretroviral medicinal products and continue in the study. For analysis purposes, these patients were considered as treatment failures at the time of switch. Patients could substitute other authorised antiretroviral medicinal products for background (non-assigned) study compounds (lamivudine or efavirenz) due to an AE and continue in the study. A switch of background study agents was not considered a treatment failure; however, an intensification of study treatment by addition of a fourth active antiretroviral agent was defined as a treatment failure.

Outcomes/ Endpoints

The primary efficacy measure was the comparison of the proportion of patients with plasma HIV-1 RNA levels <50 copies/ml at Week 48 and adjusted by the randomisation strata (screening plasma HIV-1 RNA < 100,000 copies/ml versus >100,000 copies/ml).

The analysis for the primary efficacy endpoint was based on the Intention-To-Treat (ITT)-Exposed Population, which included patients exposed to at least one dose of study drug. The evaluation of non-inferiority was based on a two-sided 95% CI stratified by baseline HIV-1 RNA. A responder at 48 weeks was defined as a patient who had achieved confirmed plasma HIV-1 RNA <50 copies/ml and had not yet lost the virological response by Week 48 as defined by the time to loss of virological response (TLOVR) algorithm.

Sample Size and Statistical Methods

A total of 730 subjects with a 1:1 randomisation stratified by screening HIV-1 RNA would provide 90 % power to assess the non-inferiority of abacavir once daily compared with the standard twice daily dose of abacavir at the 0.05 level of significance. This sample size calculation assumed identical 50 % success rates in the treatment groups at 48 weeks. Non-inferiority was defined as a two-sided 95 % confidence interval (CI) adjusted for randomisation strata that excluded differences as large as 12 % in the direction of inferiority of the abacavir once daily group.

Results

Patients' disposition

The population enrolled with a median age of 36 years old mainly consisted in White (54 %) male (81%) patients. The mean viral load at baseline was 4.91 (3.05-6.99) log copies/ml, including 44 % of patients with a viral load > 100 000 copies/ml) and 31% with a CD4 cell count at baseline < 200 cell/mm^3 (mean CD4 cell count: 262 (21-918). Within this treatment naïve patient population, 20% (133/770) of the patients in the study had symptomatic HIV-1 infection and only 7% (53/770) had AIDS.

The details of patients analysed is given in table 3. 24% discontinued the study, the reasons were overall balanced between abacavir once and twice daily.
Of note, a significant proportion (approximately 10%) of the subjects were lost to follow up. This does not speak in favour of an optimal monitoring of the study. Adverse events were part of the main reasons for premature study drug discontinuation.

Table 3: Patients disposition

	Abacavir OD n (%)	**Abacavir BID n (%)**	**Total n (%)**
Total Randomised (N)	392 (100%)	392 (100%)	784 (100%)
Not treated	8 (2%)	6 (2%)	14 (2%)
Treated	**384**	**386**	**770**
Completed	290 (76%)	294 (76%)	584 (76%)
Discontinued	94 (24%)	92 (24%)	186 (24%)
<48 weeks of treatment	58 (15%)	63 (16%)	121 (16%)
≥48 weeks of treatment	36 (9%)	29 (8%)	65 (8%)
Reason for Discontinuation			
Number discontinued	94	92	186
Adverse event	**22 (23%)**	**25 (27%)**	**47 (25%)**
Consent withdrawn	12 (13%)	9 (10%)	21 (11%)
Lost to follow-up	32 (34%)	35 (38%)	67 (36%)
Clinical progression	1 (1%)	1 (1%)	2 (1%)
Protocol violation	4 (4%)	2 (2%)	6 (3%)
Insufficient viral load response	6 (6%)	5 (5%)	11 (6%)
Other	17 (18%)	15 (16%)	32 (17%)

Efficacy results

The results are presented in the tables 4 & 5.

Table 4: Virologic Response at Week 48 Based on Plasma HIV-1 RNA <50 copies/ml using the TLOVR algorithm (ITT-Exposed Population)

Strata	**ABC OD N=384** n (%)	**ABC BID N=386** n (%)	**Point Estimate (%)**	**95% Confidence Interval**
Stratified			-1.7	-8.4, 4.9
≤100,000 copies/ml	141/217 (65%)	145/217 (67%)	-1.8	-10.8, 7.1
>100,000 copies/ml	112/167 (67%)	116/169 (69%)	-1.6	-11.6, 8.4
Unstratified			-1.7	-8.4, 4.9
Total	253/384 (66%)	261/386 (68%)		

Table 5: Proportion of patients with Plasma HIV-1 RNA <50 copies/ml at Week 48 (As-Treated Population)

Strata	**ABC OD N=266 n (%)**	**ABC BID N=265 n (%)**	**Point Estimate (%)**	**95% Confidence Interval**
Stratified			0.4	-5.3, 6.2
≤100,000 copies/ml	132/145 (91%)	126/145 (87%)	4.1	-3.1, 11.3
>100,000 copies/ml	99/121 (82%)	103/120 (86%)	-4.0	-13.3, 5.3
Unstratified			0.4	-5.3, 6.2
Total	231/266 (87%)	229/265 (86%)		

Results are in accordance with the predefined hypothesis of non-inferiority between the abacavir once daily group compared with the abacavir twice daily group.

The distribution of patients in both arms in the subcategories of baseline viral load < 100 000 copies/ml (50-1000; 1000-10 000 and 10 000-100 000) was well balanced between the arms. This further substantiates the non-inferiority demonstration between abacavir once and twice daily regimen.

In the abacavir once daily group, 66% (253/384) of patients were defined as responders, as compared with 68% (261/386) of patients in the ABC twice daily group.

There was no significant difference in terms of CD4 cell count change from baseline between the once daily or twice daily regimen.

The number of subjects defined as virological failures (10% in the OD group (38/384) and 8% in the BID group (32/386)) was low and comparable in both groups. Genotypic data at baseline and post-baseline were available for 31 patients with plasma HIV-1 RNA >500 copies (16 in the abacavir OD group and 15 in the abacavir BID group). There was a high proportion of patients with any treatment emerging mutations in both groups (abacavir OD: 81% (13/16) and abacavir BID: 67% (10/15), p=0.433)). There was a trend towards a higher number of NRTI emerging mutations in the abacavir OD group 69 % (11/16) compared with the abacavir BID group 33 % (5/15) (p=0.0076). Within the patients with virus harbouring no mutations at baseline, 7/11 (63%) patients in the abacavir OD group versus 3/13 (23%) in the abacavir BID patients presented on-therapy NRTI mutations.

Overall, there was a trend in favour of a higher rate of emergence of resistance in the in the abacavir once daily regimen compared to the BID regimen. However, the sample size of the genotypic analysis warrants particular precaution in the interpretation of the data. Moreover, it should be kept in mind that similar virologic suppression was observed between abacavir once and twice daily regimen.

Although the results in terms of percentage of patients with virological response were compatible with a non-inferiority margin, there was a major concern about the potential loss of chance for patients in relation to the change in the daily regimen from twice to once daily. Therefore, the MAH was requested to discuss what represented the 8.4% in the ITT analysis in terms of fraction of the efficacy that was expected to be contributed by abacavir in the tritherapy. In the absence of available bitherapy studies with lamivudine and efavirenz allowing direct evidence of the contribution of abacavir to a regimen containing abacavir, lamivudine, efavirenz, the MAH reviewed historical comparative data of triple therapy including dual NRTI and double NRTI therapy. Given the evolution of HIV treatment strategies, this indirect approach was considered valid.

According to this analysis, the range of treatment differences was approximately 30 – 60% for the various triple versus dual regimens, with an average benefit of triple therapy over double therapy of 45%. Despite the inherent limitations in the historical comparisons especially in the evolving field of HIV infection, it appears that 8.4 % would account for approximately 20 % (8.4/45), of the overall activity (45 % in average) expected to be provided by abacavir within a triple combination. This is expected to be counterbalanced by the potential improvement in terms of adherence resulting from a simplified schedule regimen, especially when considering that non-adherence represents a critical cause of failure to treatment.

To investigate the duration of response, a total of 163 and 162 patients were treated for at least 72 weeks in the once daily and twice daily groups, respectively. Over this extended follow-up, the efficacy of abacavir OD was comparable to abacavir BID as shown by a Kaplan Meier estimate based on the TLOVR algorithm or on review of the proportions of patients with undetectable viral load at each time point.

Study CAL 3001

This is a randomised, open-label, parallel, multicentre study to evaluate treatment with the fixed-dose combination of abacavir/lamivudine (600mg/300mg) once-daily versus abacavir (300mg) twice daily and lamivudine (300 mg) once daily in combination with tenofovir (TDF) once-daily and a new protease inhibitor (PI) or non-nucleosidic reverse transcriptase inhibitor (NNRTI) for 48 weeks in antiretroviral (ART)-experienced HIV-1 infected patients.

Methods

Study Participants

The study enrolled male or non-pregnant female HIV-1 infected adults (≥ 18 years) who are ART experienced but TDF naïve patients, currently receiving a stable regimen containing 3 NRTIs, or

2 NRTIs and 1 PI or 2 NRTIs + and 1 NNRTI for at least 3 months and having ≤ 3 NRTI-associated mutations (including M184V), but without K65R, L74V, 69S insertion, Q151M, M41L, L210W, or ≥ 3 thymidine analogues mutations (TAMs).
Patients were required to have HIV-1 RNA level > 1000 copies/ml and CD4 cell count > 50 cells/mm^3 on at least one occasion within 21 days of study entry.

Treatments

Patients were stratified at baseline according to plasma HIV-1 RNA level (< 5000 copies/ml and ≥ 5000 copies/ml) and genotype (with or without mutation M184V).

Patients who either met the definition of virologic failure or had an insufficient virologic response according to the investigator's opinion or had an adverse event that required permanent discontinuation of any of the study agents could change their study regimen during the study.
Patients had the choice either to continue randomised study agents and continue background antiretroviral agents, or to continue randomised study agents and substitute the background PI or NNRTI with another, or to permanently discontinue randomised study agents and substitute with any other licensed antiretroviral agent. Patients who switched to the last option were considered as treatment failure at the time of change.

Outcomes/endpoints

The primary efficacy measure was to test the non-inferiority of abacavir in a fixed dose combination tablet administered OD versus abacavir administered BID with lamivudine OD over 24 and 48 weeks, based on the comparison of plasma HIV-1 RNA average area under the plasma HIV-1 RNA curve minus baseline (AAUCMB) in the two arms through week 24 and adjusted by the randomised strata.

Sample size and statistical methods

A sample size of 83 patients per arm with an 1.1 allocation stratified by screening plasma HIV-1 RNA and genotype was required to test the non-inferiority between the two treatment groups for approximately 90% power and $\alpha = 0.05$ in the two-sided confidence interval. This sample size calculation assumed that the expected difference in the median time-weighted change in plasma HIV-1-RNA defined as AAUCMB was 0.0 log10 copies/ml and that the common standard deviation was 0.80 log10 copies/ml. The non-inferiority margin was defined as 0.4 log10 copies/ml in the direction of inferiority of the FDC OD group.

Results

Patients' disposition

A total of 186 patients were enrolled and randomised. The demographic characteristics were overall well balanced between the two arms. Patients included were approximately 38 years old, mainly White (66%) and male (76%).
At baseline there was an imbalance between both arms with respect to median viral load (3.92 log10 copies/ml in OD arm versus 4.22 in the BID). In terms of previous medications, 63 % patients in the OD arm and 53 % in the BID have already been treated with lamivudine prior to the study. Abacavir containing regimens were used prior to study entry in 12 (13 %) and 15 (17 %) patients in the OD and BID arms, respectively.
In terms of background therapy the most commonly used fourth product was lopinavir/ritonavir and efavirenz.

Table 6: Patients disposition (Total randomised and ITT exposed population)

	ABC/LAM FDC OD N (%)	**ABC BID + LAM OD N (%)**	**Total N (%)**
Total randomised (N)	**95**	**91**	**186**
Not treated	1 (1)	3 (3)	4 (2)

Total ITT Exposed Population	**94**	**88**	182
Discontinued (N, ITT exposed)	**7 (7)**	**15 (17)**	**22** (12)
Primary reason for study discontinuation (ITT exposed; N, %)			
Adverse event	3 (3)	2 (2)	5 (3)
Consent withdrawn	0	2 (2)	2 (1)
Lost to follow-up	3 (3)	3 (3)	6 (3)
Protocol Violation	1 (1)	2 (2)	3 (2)
Other[1]	0	6 (7)	6 (3)

[1]Other included: subject discontinuing treatment, professional reason, compliance, investigator decision and alcohol abuse

There was an imbalance in the rate of discontinuation (17% versus 7% respectively in the BID and OD regimens).

Efficacy results

Only results at week 24 were provided (see table 7).

Table 7: Plasma HIV-RNA AAUCMB results and statistical evaluation of non-inferiority of virologic response at week 24 (log10 copies/ml – ITT, Switch included)

	ABC/LAM FDC OD (N=94)	**ABC BID + LAM OD (N=88)**	**Median AAUCMB Difference (OD-BID)**	**95% Confidence interval**
No M184V, <5000c/ml				
N	**10**	**7**		
Median baseline HIV-1 RNA	3.31	4.20		
Median AAUCMB	-1.21	-1.76	**0.72**	**0.18, 1.34**
Range (min, max)	-1.58, 1.42	-2.44, -1.04		
No M184V, ≥ 5000c/ml				
N	**20**	**21**		
Median baseline HIV-1 RNA	4.31	4.49		
Median AAUCMB	-1.77	-2.06	**0.15**	-0.44, **0.73**
Range (min, max)	-3.11, 00	-3.10, 0.13		
M184V, <5000c/ml				
N	**24**	**20**		
Median baseline HIV-1 RNA	3.41	3.71		
Median AAUCMB	-1.41	-1.61	**0.21**	-0.21, **0.61**
Range (min, max)	-2.22, 0.58	-2.56, 0.18		
M184V, ≥ 5000c/ml				
N	**40**	**39**		
Median baseline HIV-1 RNA	4.09	4.32		
Median AAUCMB	-1.94	-1.93	**-0.03**	-0.35, **0.28**
Range (min, max)	-2.75	-2.99, 0.39		
Overall				
N	**94**	**87**		
Median baseline HIV-1 RNA	3.92	4.22		
Median AAUCMB	-1.60	-1.87	**0.16**	-0.06, **0.37**
Range (min, max)	-3.11, 1.42	-3.10, 0.39		

Results are in accordance with the predefined hypothesis of non-inferiority (upper limit of the 95 % CI of the difference in terms of AAUCMB between both treatment arms being inferior to 0.4 log10 copies/ml). This was also seen in the overall analyses on the as-treated population.

Nevertheless, this study has some limitations and therefore the results should be interpreted with caution. Firstly, the population enrolled was likely in second or third line therapy when referring to the high rate (60%) of patients with no TAM mutation at baseline. Moreover, the patients enrolled were receiving a quadritherapy whereas, in clinical practice, the resort to a quadritherapy would be particularly unlikely in non heavily pretreated patients. Secondly the use of AAUCMB as a primary endpoint, even if acceptable, is not an optimal endpoint as compared to the more clinically meaningful percentage of patients with undetectable viral load. Finally there was a noticeable imbalance in the rate of discontinuation (17% versus 7% respectively in the BID and OD regimens) and in terms of baseline viral load (lower viral load in the OD arm).

In terms of adherence, there were no statistically significant differences between groups during the randomised follow-up period in terms of total satisfaction scores. There was a trend towards greater adherence with the fixed dose combination over the control arm (pill count overall adherence 55 % versus 37 %).

STUDY ESS30008

This is a randomised, open-label, multicentre study comparing the switch to the abacavir/lamivudine fixed dose combination tablet administered once a day to the continued treatment with abacavir and lamivudine administered twice a day in combination with a PI or NNRTI in antiretroviral experienced patients.

Methods

Study participants

This study enrolled male or non-pregnant female HIV-1 infected adults (≥18 years), treated with an initial antiretroviral regimen containing abacavir 300 mg BID and lamivudine 150mg BID in combination with either a PI or NNRTI for ≥ 24 weeks. Patients were required to have plasma HIV-1 RNA < 400 copies/ml for 3 months immediately preceding screening and at study entry and CD4 cell count ≥ 50 cells/mm^3.

Treatment

Patients were stratified according to PI or NNRTI use at entry and randomised 1:1.

Outcome/endpoints

The primary objective was to establish that abacavir/lamivudine FDC administered OD is virologically non-inferior to the individual tablets administered BID (proportion of non virologic failures (responders)). Virologic failure was defined as plasma HIV-1 RNA ≥ 1265 copies/ml (0.5 log10 copies/ml increase over 400 copies/ml) on two consecutive occasions, at least 2-4 weeks apart. Patients who did not have two consecutive plasma HIV-1 RNA values ≥ 1265 copies/ml were considered responders or "non-virologic failures" for the purposes of the primary endpoint.

Sample size and statistical methods

A total of 240 patients (120 per treatment group) would provide at least 80% power (α=0.05) to establish the non-inferiority via a lower 95% confidence bound (equivalent to a two sided 90% confidence interval) for the difference in proportions of the two treatment groups. This sample size calculation assumes a 0.85 success rate for each treatment group at 48 weeks and a non-inferiority margin of –12% for the OD treatment group minus BID treatment group difference.

Results

Patients' disposition

A total of 260 patients were enrolled and randomised. Patients were approximately 38 years old and the majority was male (82%). The population consisted mainly of asymptomatic well-controlled patients (80 %). The mean baseline HIV RNA was 1.73 log10 copies/ml (± 0.216) and the mean CD4 cell count was 554 cells/mm^3 (89-1638). Patients were mainly treated with NNRTI (65 %) with approximately 60% consisting in efavirenz containing HAART. Ritonavir and fosamprenavir were the most frequent combined protease inhibitors in both groups (20% and 16% in the abacavir and lamivudine arm, respectively, and 20 % and 18 % in the fixed dose combination OD arm, respectively).

Patients were well balanced in terms of prior exposure to abacavir (the median time of exposure to abacavir and lamivudine prior to study entry was 22 and 23 months for the abacavir and lamivudine BID and fixed dose combination OD treatment groups respectively).

Table 8: Patients disposition at week 24 (ITT population)

	ABC + LAM BID N=130 N (%)	**ABC/LAM FDC OD N=130 N (%)**	**Total N=260 N (%)**
Total randomised (N)	**130**	**130**	**260**
Completed 24 weeks	123 (95%)	124 (95%)	247 (95%)
Discontinued (<24 weeks of treatment)	7 (5%)	6 (5%)	13 (5%)
Reason for discontinuation			
Adverse event	1 (14%)	0	1 (8%)
Consent withdrawal	1 (14%)	0	1 (8%)
Lost to follow-up	2 (29%)	2 (33%)	4 (31%)
Protocol-defined virologic failure	0	2(33%)	2 (15%)
Protocol violation	1 (14%)	0	1 (8%)
Other	2 (29%)	2 (33%)	4 (31%)

Efficacy Results

Only 24 weeks data have been provided and the results on the primary endpoints are displayed in table 9.

Table 9: Proportion of non virologic failures (responders) through week 24 (proportion of subjects who did not have confirmed plasma HIV-1 RNA ≥ 1265 copies/ml on two consecutive occasions (ITT M=F population, ITT observed population and ITT As-treated population)

Strata	ABC + LAM N=130 N (%)	ABC/LAM FDC N=130 N (%)	Point estimate	90% Confidence Interval
In the ITT population – Missing=Failure				
Total	**120 (92%)**	**124 (95%)**	-3.1	**-8.0**, 1.8
Stratified			-3.1	-8.0, 1.8
Background PI	41 (93%)	43 (93%)		
Background NNRTI	79 (92%)	81 (96%)		
In the ITT observed population				
Total	**128 (98%)**	**128 (98%)**	0.0	**-2.5**, 2.5
Stratified			0.0	-3.1, 3.0
Background PI	43 (98%)	45 (98%)		
Background NNRTI	85 (99%)	83 (99%)		
In the ITT as-treated population				
Total	**126 (98%)**	**128 (98%)**	-0.0	**-2.6,** 2.5
Stratified			-0.1	-3.1, 3.0
Background PI	41 (98%)	45 (98%)		
Background NNRTI	85 (99%)	83 (99%)		

The results are in accordance with the predefined hypothesis of non-inferiority (12%).

This study has some limitations that should be taken into account in the interpretation of the results. The population enrolled mainly consisted in asymptomatic well controlled patients under first line therapy. Therefore, this population is closer to a population of antiretroviral naïve than antiretroviral experienced patients. The primary endpoint was the proportion of patients with "non virologic failure", with a rather unusual definition of the failure HIV-RNA >1265 copies/ml (0.5 log copies/ml increase over 400 copies/ml) instead of the more conservative definition of HIV-RNA > 400 copies/ml or even >50 copies/ml.

STUDY CNA 30024

This was a randomised, double-blind, controlled, multicentre clinical trial comparing abacavir 300 mg twice daily versus zidovudine when used in combination with lamivudine 150 mg twice daily and efavirenz in antiretroviral naïve patients.

Methods

Study Participants

Adults above 18 years of age with documented HIV-1 infection who were ART-naïve (defined as less than 7 days of any approved or experimental ART). Patients were required to have a screening plasma with HIV-1 RNA level > 400 copies/ml and a CD4 cell count >50 cells/mm^3 on at least one occasion within 21 days of study entry.

Treatments

Patients who permanently discontinued randomised (assigned) study treatment (abacavir or zidovudine) due to an adverse event were permitted to substitute other licensed antiretroviral medicinal products and continue in the study. For analysis purposes, these patients were considered as treatment failures at the time of switch. Patients could substitute other authorised antiretroviral medicinal products for background (non-assigned) study compounds (lamivudine or efavirenz) due to an adverse event and continue in the study. A switch of background study agents was not considered a treatment failure; however, an intensification of study treatment by the addition of a fourth active antiretroviral agent would be defined as a treatment failure.

Outcomes/Endpoints

The primary efficacy measure was the comparison of the proportion of patients with plasma HIV-1 RNA levels <50 copies/ml at Week 48 and adjusted by the randomisation strata (screening plasma HIV-1 RNA ≤ 100,000 copies/ml versus >100,000 copies/ml).

The analysis for the primary efficacy endpoint was based on the Intention-To-Treat (ITT)-Exposed Population, which included patients exposed to at least one dose of study drug. The evaluation of non-inferiority was based on a two-sided 95% CI stratified by baseline HIV-1 RNA. A responder at 48 weeks was defined as a patient who had achieved confirmed plasma HIV-1 RNA <50 copies/ml and had not yet lost the virological response by Week 48 as defined by the time to loss of virological response (TLOVR) algorithm.

Sample Size and Statistical Methods

A total of 628 patients with a 1:1 randomisation stratified by screening HIV-1 RNA would provide 85 % power to assess the non-inferiority of abacavir compared to zidovudine at the two-sided 0.05 level of significance. This sample size calculation assumed identical 50 % success rates in the treatment groups at 48 weeks. Non-inferiority was defined as a 95 % CI adjusted for randomisation strata that excluded differences as large as 12 % in the direction of inferiority of the abacavir & lamivudine & efavirenz treatment arm. If non-inferiority was established, the superiority of the abacavir & lamivudine & efavirenz arm was tested

Results

Patients' dispositions

The population enrolled with a median age of 35 years old mainly consisted in male (81%) patients. The mean viral load at baseline was of 4.79 (1.95 – 5.88) log copies/ml, including 39 % of patients with a viral load > 100 000 copies/ml; the mean CD4 cell count was 264 (25-1883 celles/mm^3). Within this treatment naïve patient population, 77 % (497/649) had asymptomatic HIV infection and only 5% (33/649) had AIDS.

The details of patients analysed is given in the table below. 24 % discontinued the study. Of note, a significant proportion (approximately 9%) of the subjects were lost to follow up. This does not speak in favour of an optimal monitoring of the study.

Table 10: Patients' disposition

	ABC + 3TC + EFV n (%)	**ZDV + 3TC + EFV n (%)**	**Total n (%)**
Total Randomised (N)	327 (100%)	327 (100%)	654 (100%)
Not treated	3 (<1%)	2 (<1%)	5 (<1%)
Completed at least 48 Weeks of study	253 (78%)	250 (77%)	503 (78%)
Discontinued	71 (22%)	75 (23%)	146 (24%)
<48 weeks of treatment	49 (15%)	57 (18%)	106 (16%)
>48 weeks of treatment	22 (7%)	18 (6%)	40 (6%)
Reason for Discontinuation			
Adverse event	16 (23%)	25 (33%)	41 (28%)
Consent withdrawn	12 (17%)	6 (8%)	18 (12%)
Lost to follow-up	26 (37%)	34 (45%)	60 (41%)
Clinical progression	2 (3%)	1 (1%)	3 (2%)
Protocol violation	3 (4%)	0	3 (2%)
Insufficient viral load response	2 (3%)	2 (3%)	4 (3%)
Other	9 (13%)	7 (9%)	16 (11%)
Missing	1 (<1%)	0	1 (<1%)

Efficacy Results

The results are presented in tables 11 & 12.

Table 11: Virologic Response at Week 48 Based on Plasma HIV-1 RNA <50 copies/ml using the TLOVR algorithm (ITT-Exposed Population)

Strata	**ABC + 3TC + EFV N=324 n (%)**	**ZDV + 3TC + EFV N=325 n (%)**	**Point Estimate**	**95% Confidence Interval**
Stratified			0.8	-6.3, 7.9
<100,000 copies/ml	142/198 (72%)	140/199 (70%)		
>100,000 copies/ml	84/126 (67%)	84/126 (67%)		
Unstratified			0.8	-6.3, 7.9
Total	226/324 (70%)	224/325 (69%)		

Table 12: Proportion of patients with Plasma HIV-1 RNA <50 copies/ml at Week 48 (As-Treated Population)

Strata	**ABC + 3TC + EFV N=240 n (%)**	**ZDV + 3TC + EFV N=227 n(%)**	**Point Estimate**	**95% Confidence Interval**
Stratified			-6.5	-11.4, -1.6
<100,000 copies/ml	134/140 (96%)	132/138 (96%)		
>100,000 copies/ml	77/100 (77%)	83/89 (93%)		
Unstratified			-6.8	-11.8, -1.7
Total	211/240 (88%)	215/227 (95%)		

In the abacavir & lamivudine & efavirenz group, 70% (226/324) of patients were defined as responders, as compared with 69% (224/325) of patients in the zidovudine & lamivudine & efavirenz group.

The number of patients defined as virological failures (6% in the abacavir group and 4% in the zidovudine group) was low and similar between arms.

Median change from baseline in CD4 cell count at Week 48 was +209 cells/mm^3 in the abacavir group and +155 cells/mm^3 in the zidovudine group [Difference: +54 cells/mm^3; p = 0.0050 (based on AAUCMB)]. Of note, results in favour of the abacavir arm were also significant in the as treated analysis. These results might be explained by the lymphopenia induced by zidovudine.

Results of the ITT and per protocol analysis are compatible with a non-inferiority demonstration based on a 12% margin between the abacavir & lamivudine & efavirenz and zidovudine & lamivudine & efavirenz arms. A trend towards a better response in the zidovudine arm was seen at Week 48 in the per protocol analysis (patients with an HIV-1 RNA <50 copies/ml at Week 48: 88% in the abacavir arm versus 95% in the zidovudine arm) and this tendency is even more noticeable when considering the population with viral load >100,000 copies/ml.

Discussion on clinical efficacy

The pivotal randomised double blind study CNA 30021 compared abacavir once (n=384) and twice daily (n=386) regimen within triple combination involving lamivudine and efavirenz in antiretroviral naïve patients. The primary endpoint of this study was the proportion of patients with undetectable viral load using the Time to Loss of Virological Response (TLOVR) algorithm (composite of safety and antiviral activity). At 48 weeks, in the ITT exposed population, the proportion of patients with virological response was 66% in the OD regimen versus 68 % in the BID regimen of abacavir [95% CI of the difference in the percentages (-8.4%; 4.9%)] and 87 % versus 86 % respectively for the OD and BID regimens of abacavir in the As treated population [95% CI of the difference in the percentages (-5.4; 6.2%)]. These results were compatible with the predefined 12% non-inferiority margin. There was a concern however about the potential loss of chance for patients in relation to the change in the daily regimen of abacavir from BID to OD. The applicant addressed this satisfactorily by showing that this potential loss of chance would not exceed one fifth of the overall estimated efficacy contribution of abacavir with a tritherapy.

The fact that the clinical development of abacavir OD only targeted the population of antiretroviral naïve patients was also perceived as a major shortcoming by the CHMP.

The applicant subsequently completed the clinical dossier to support the variation by providing the preliminary 24 weeks data of two new phase III studies in antiretroviral experienced patients (CAL 30001 and ESS 30008) using the fixed dose combination of abacavir and lamivudine once daily.

In study CAL 30001, preliminary data at 24 weeks showed that the fixed combination abacavir/lamivudine once daily was non-inferior to the abacavir BID and lamivudine OD group. In study ESS30008 preliminary data at 24 weeks showed the non-inferiority between patients who switched to the fixed dose combination or continued their treatment with abacavir BID and lamivudine taken concurrently as part of an initial triple therapy.

However, due to the limitations of the studies in terms of design and patients disposition (CAL 3000: quadritherapy used in a population of moderately experienced patients (60% with no TAM mutation at baseline), imbalance in the patient disposition, significant imbalance in the viral load at baseline: ESS 30008: population well controlled under a first line therapy closer to a population of antiretroviral naïve than experienced patients), results should be taken with caution. The MAH undertook to submit the final reports from these studies as part of the follow-up measures to be fulfilled post-authorisation of this variation.

The applicant undertook also to provide all comparative resistance data between abacavir OD and BID regimen as part of the follow-up measures.

Data from all these studies suggest that abacavir once daily is no more sensitive to missed doses than abacavir twice daily. In addition, there is a trend in CAL30001 to suggest that abacavir/ lamivudine fixed dose combination once daily may improve adherence relative to abacavir twice daily & lamivudine and that this trend may lead to some improvements in efficacy.

3.3 Clinical Safety

Database and Patient exposure

The safety of abacavir has been established in adults and children in multiple controlled clinical trials and corroborated by several years of post-marketing experience. The worldwide estimated cumulative patient exposure to abacavir (Ziagen & Trizivir) since first marketing approval is estimated to be approximately 508,958 patient-years of treatment up to the end of December 2003.

The evaluation of the safety profile of abacavir twice daily is based on the demonstration that the once daily dose of abacavir (600 mg) had a similar safety profile to twice daily dose (2 x 300 mg) and the incidence and/or presentation of abacavir hypersensitivity was not altered by dosing it once daily instead of twice daily.

For this type II variation, the safety data derived mainly from study CNA30021 which provides up to 72-week data on the safety of abacavir 600 mg OD or 300 mg BID in antiretroviral treatment naïve patients. In addition, data from study EPV40001 and study CNA 30024 (using abacavir twice daily) support the safety and tolerability of abacavir. Finally, preliminary 24 weeks data have also been submitted from the two Phase III trials in antiretroviral experienced patients using the fixed dose combination abacavir/ lamivudine once daily.

Study CNA30021

The incidence of adverse events was similar in both treatment groups (incidence of Grade 2 to 4 adverse events abacavir OD 70% *vs* abacavir BID 72%). Psychiatric disorders (abacavir OD: 35%; abacavir BID: 36%), nervous system disorders (abacavir OD: 32%; abacavir BID: 28%) and gastrointestinal disorders (abacavir OD: 30%; abacavir BID: 29%) were the most frequent drug-related adverse events. Psychiatric and nervous system disorders were more likely due to efavirenz. No new safety concerns were identified with abacavir 600 mg once daily.

With regard to HSR, which is the most significant adverse event associated with abacavir, the incidence was comparable between abacavir 600 mg once daily and abacavir 300 mg twice daily, as well as associated symptoms, with the exception of abdominal pain, most reported with abacavir 300 mg twice daily, although there was a trend for a higher rate of hypersensitivity reaction in the OD group (36/384; 9%) versus BID group (28/386; 7 %).

The incidence of suspected abacavir HSR was 9% and 7% respectively for abacavir OD and abacavir BID.

Study CAL 30001

The incidences of drug related adverse events are generally comparable between treatment groups (47% of patients in the fixed dose combination OD group and 45% in the abacavir BID & lamivudine OD group) with the exception of fatigue and hypersensitivity reaction which were reported in a higher number of patients in the fixed dose combination OD group than in the abacavir BID & lamivudine OD group, as shown in the table 13:

Table 13: Most Common (≥5% Incidence) Drug-related Adverse Events

Drug-Related Adverse Event	ABC/LAM FDC OAD N=93; n (%)	ABC BID + LAM OD N=89; n (%)
Subjects with ANY drug-related adverse event	44 (47)	40 (45)
Nausea	11(12)	12(13)
Diarrhoea	10(11)	7(8)
Drug hypersensitivity[1]	8(9)	4(4)
Dizziness	3(3)	5(6)

Fatigue	6(6)	2(2)
Vomiting	5(5)	2(2)
Headache	1(1)	5(6)

[1] Diagnosed as ABC hypersensitivity reaction. In accordance with GSK policy all cases of ABC hypersensitivity were classified as serious adverse events regardless of ICH seriousness criteria

There were more patients in the fixed dose combination OD group (11%) than in the abacavir BID & lamivudine OD group (6%) who had adverse events leading to permanent discontinuation of treatment. For both groups, the most commonly reported adverse event that resulted in the permanent discontinuation was hypersensitivity, all related to abacavir.

Serious adverse events, none fatal, were reported in 14% of patients in the fixed dose combination OD group and 8% in the abacavir BID & lamivudine OD group. This difference was driven mainly by hypersensitivity.

A total of nine patients (10%) in the fixed dose combination OD group experienced a drug-related serious adverse event compared with four (4%) in the abacavir BID & lamivudine OD group. The only other drug-related serious adverse event reported was increased blood creatinine phosphokinase, which was reported in one patient only in the fixed dose combination OD group.

Study ESS30008

The number of patients experiencing at least one adverse event was higher in the fixed dose combination OD group in comparison with the abacavir and lamivudine BID group (15/130 (12 %) versus 6/130 (5%), but this might be related to the open label design, with investigators more likely notifying adverse events in a treatment arm consisting in a new schedule regimen with a new fixed combination. No case of HSR was reported which could be explained by the fact that the patients were treated with abacavir for at least 24 weeks prior to inclusion (of note, median time for occurrence of HSR is 11 days). It is assumed that treated patients who had experienced HSR were not present at the time of inclusion.

Study CNA 30024

The incidences of drug-related adverse events were similar between the two treatment groups (ABC 69% *vs* ZDV 76%).

The body systems with the highest incidence of drug-related adverse events included neurological (ABC 44%; ZDV 54%), gastrointestinal (ABC 31%; ZDV 46%), non-site specific (ABC 24%; ZDV 26%), skin (ABC 40%; ZDV 41%) and psychiatric (ABC 10%; ZDV 11%).

Differences in drug-related adverse events between the two treatment groups followed the known safety profiles of abacavir and zidovudine. Nausea (ABC 17%; ZDV 31%), vomiting (ABC 5%; ZDV 13%) and fatigue (ABC 10%; ZDV 17%) were most frequent in the zidovudine group, whereas allergic reactions (all considered as ABC HSR cases) were most frequent in the abacavir group. Rash was equally common in both groups (ABC 10%; ZDV 13%).

Adverse events reported in the abacavir and zidovudine groups did not raise any new safety concerns and were consistent with the known safety profiles of the different compounds. The incidence of suspected abacavir HSR was 7%.

Hypersensitivity reaction

Hypersensitivity reaction is the key safety concern associated with abacavir. It is a recognisable syndrome occurring in approximately 5 % of patients and is characterised by the presence of multiple symptoms that indicated involvement of several organs or systems. Rechallenge can be more severe and in some cases life threatening or fatal.

A concern was raised by the CHMP as in the pivotal study CNA 30021, the incidence of cases of hypersensitivity reaction with abacavir were higher (9% for abacavir OD and 7 % for abacavir BID) than expected (5% of subjects exposed to abacavir in clinical trials according to cumulative data from the last PSUR of abacavir and in line with the current SPC).

In study CAL 30001 in antiretroviral experienced patients, the rate of HSR was higher in the OD regimen (9 %) of abacavir than the BID regimen (4 %). Even if it cannot be ruled out that some factors might have artificially led to such finding (e.g. higher rate of combined NNRTI in the abacavir OD arm, known confusion factor for HSR diagnosis, open-label design) the CHMP agreed that this should be further investigated (especially in terms of biological plausibility).

Since 1999, the MAH has used a new standard abacavir hypersensitivity reaction case report form (HSR CRF) module. The MAH addressed the above concern showing that when data are pooled from all studies that used the HSR CRF module, the incidences of HSR are 8.1% and 7.6% for once and twice daily dosing, respectively. In addition, the combination with efavirenz might have also contributed to the increased rate of HSR observed in these studies (rash induced by efavirenz could have been a confusion factor in the HSR diagnosis). This issue is under assessment to revise the general description of HSR in the SPC of medicinal products containing abacavir.

Moreover, the MAH provided a complementary analysis showing that the difference observed is much more likely the result of an artificial finding in a small open label study. An updated multivariable risk factor analysis provided evidence that abacavir once daily was not a predictor of HSR. As a matter of fact, as underlined in published literature (Naisbitt and al; 2003) abacavir HSR reaction has typical clinical features of an immune-mediated reaction considered as dose-independent. More recently, a strong association has been shown between abacavir HSR and haplotype including HLA-B57.

Discussion of clinical safety

Study CNA30021 did not reveal any increased risk with the OD regimen of abacavir versus BID, although there was a trend for higher rate of hypersensitivity reaction in the OD group (9%) versus BID group (7 %). A concern was raised nevertheless as in this study, the incidence of cases of hypersensitivity reaction were slightly higher than expected (5% of patients exposed to abacavir in clinical trials according to cumulative data from the last PSUR of abacavir and in line with the current SPC). In addition in study CAL 30001 in antiretroviral experienced patients, the rate of HSR was higher in the OD regimen (9 %) of abacavir than in the BID regimen (4 %).

This concern over a potential deterioration of the safety profile associated with a once daily regimen of abacavir was especially critical since the benefit in terms of adherence was felt insufficiently substantiated. The MAH was therefore requested to discuss the biological plausibility of an increased risk of HSR associated with a change in the dosing regimen of abacavir.

The MAH performed a retrospective analysis which supported that the strongest predictor for reporting an abacavir HSR was the use of the new abacavir case report form module as HSR is more readily identified by the study investigator. In addition the MAH provided a complementary analysis showing that the difference observed is much more likely the result of an artificial finding in a small open label study since the abacavir dosing frequency (OD versus BID) is not a risk factor for HSR.

4. Overall Discussion and benefit/ risk assessment

Pharmacokinetic data

Study CNA1095 demonstrates that carbovir-TP has a long half-life *in vivo*, but does not demonstrate that the carbovir-TP concentrations will support once daily dosing.

An important shortcoming of the pharmacokinetic development programme to support this type II variation was the lack of submission of comparative pharmacokinetic data between abacavir once and

twice daily. The MAH only referred to the original Marketing Authorisation for Ziagen tablets to describe the abacavir pharmacokinetics after a single dose of 600 mg abacavir tablet dose.

Therefore, the MAH undertook the commitment to provide as follow-up measures post approval of this variation the requested comparative pharmacokinetic study of abacavir once versus twice daily regimen, that could further substantiate the demonstration on the non-inferiority between abacavir once and twice daily by providing reassuring data on the C_{min} values (in relation to the risk of emergence of resistance). In addition the study will address the issue of the potential gender difference in the phosphorylation capacity, as reported in for several NRTIs in recent publications (Anderson et al. AIDS 2003; 17:2159-2168 Antiviral dynamics and sex differences of zidovudine and lamivudine triphosphate concentrations in HIV-infected individuals, Harris et al AIDS 2002; 16: 1196-1197 Intracellular carbovir-triphosphate levels in patients taking abacavir once a day).

The MAH will provide the pharmacokinetic data in paediatric patients to support the use of the OD abacavir regimen in children. The data to support the once daily regimen in paediatric patients are particularly awaited since the gap between the posology recommendation in adults and children is particularly unfortunate.

Clinical efficacy

The pivotal randomised double blind study CNA 30021 compared abacavir once (n=384) and twice daily (n=386) regimen within triple combination involving lamivudine and efavirenz in antiretroviral naïve patients. At 48 weeks, in the ITT exposed population, the proportion of patients with virological response based on plasma HIV-1 RNA < 50 copies/ml was 66% in the OD regimen versus 68 % in the BID regimen [95% CI of the difference in the percentages (-8.4%; 4.9%)]. In the As treated population the proportion accounted for 87 % versus 86 % respectively for the OD and BID regimens of abacavir [95% CI of the difference in the percentages (-5.4; 6.2%)]. These results were compatible with the predefined 12% non inferiority margin. Although the non-inferiority was demonstrated, there was a concern over the lower limit of the 95 % confidence interval. This issue was satisfactorily addressed. It was shown that with 95 % confidence, treatment with abacavir once daily should not yield success rates worse than treatment with twice daily by more than 8.4 % and that this potential difference was sufficiently small to draw an overall conclusion of non-inferiority of once daily over twice daily dosing regimen.

The fact that the clinical development of abacavir OD only targeted the population of antiretroviral naïve patients was also perceived as a major shortcoming. The MAH subsequently completed the clinical dossier to support the variation by providing the preliminary 24 weeks data of two new phase III studies in antiretroviral experienced patients (CAL 30001 and ESS 30008) using the fixed dose combination abacavir/lamivudine once daily. In study CAL3001, at 24 weeks the fixed combination abacavir/lamivudine once daily was non-inferior to the abacavir BID and lamivudine OD group. In ESS 30008, at 24 weeks there was non-inferiority between patients who switched to the fixed dose combination or patients who continued their treatment with abacavir BID and lamivudine taken concurrently as part of an initial triple therapy. The MAH undertook to submit the final reports from these studies as part of the follow-up measures to be fulfilled post-authorisation of this variation to confirm these preliminary results.

The applicant undertook also to provide all long-term data (> 48 weeks) of abacavir once daily from studies in antiretroviral naïve and experienced patients as well as comparative resistance data between abacavir OD and BID regimen as part of the follow-up measures to be fulfilled post-authorisation of this variation.

The CHMP had raised a concern in terms of adherence. Although adherence was poorly substantiated (not explored in a study in antiretroviral naïve patients, conflicting results observed in other studies), it has to be recognised that such a benefit is difficult to capture within isolated studies because of the large sample size that is required. In addition, it has been demonstrated within the published scientific literature that a reduction of the pill burden and/or of frequency of intake could be translated into improved adherence.

Clinical safety

The adverse reactions reported with abacavir once daily were comparable with those reported with abacavir twice daily. Hypersensitivity reaction is a key safety concern associated with abacavir. There was a trend towards a higher risk of hypersensitivity reactions in the abacavir once daily dosing arm. Further analyses showed that such a risk is not linked to a change in dosing regimen. Indeed abacavir HSR is very likely to be classified among immune-mediated reactions considered as dose-independent. The risk factor analyses of HSR showing that the abacavir dosing frequency (OD versus BID) is not a risk factor further support this conclusion. Therefore, the higher frequency of HSR observed with the OD regimen of abacavir in the CAL 30001 study especially, seems rather the result of an artificial finding in a small open label study. The MAH is committed to pursue the educational programme initiated since the original marketing authorisation of abacavir to continue to ensure the safe use of abacavir in the context of the change of the dosing regimen, as well as to closely monitor HSR and to submit updates within PSURs and safety reviews.

Benefit/Risk assessment

The pivotal study CNA 30021 has provided efficacy and safety data with abacavir once daily in antiretroviral naïve patients. Preliminary data in antiretroviral experienced patients indicate non-inferiority of the once daily fixed dose combination abacavir/ lamivudine over abacavir BID plus lamivudine.

A risk of a possible deterioration of the safety profile (increased risk of HSR) with a change in the dosing regimen of abacavir does not appear to exist. The MAH is committed to pursue the educational programme initiated since the original Marketing Authorisation of abacavir to continue to ensure the safe use of abacavir in the context of the change of the dosing regimen, as well as to closely monitor HSR and to submit updates within PSURs and safety reviews, HSR being the unique significant limiting factor of the use of abacavir.

Simplified schedule regimens are especially critical when considering that HIV infection has become a chronic disease and that non-adherence negatively impacts on response to treatment. Abacavir once daily has the potential to simplify the daily life of patients.

Considering the above the CHMP considered that the benefit/risk assessment of abacavir once daily was favourable.

5. Changes to the Product Information

Further to the assessment of the different proposals of the Marketing Authorisation Holder to amend the Product Information and in the light of the assessment of the submitted data, the CHMP requested the following additional amendments of the SPC:

Section 4.1 "Therapeutic indication"

Due to the availability of further clinical studies detailed in section 5.1, this section has been revised to inform that the demonstration of the therapeutic benefit has been mainly based on the results of studies performed with the twice daily regimen in treatment-naïve adult patients. The reference to the combination therapy with lamivudine and zidovudine has been moved to section 5.1.

Section 4.4 "Special warnings and special precautions for use"

Kivexa has been added in the list of medicinal products containing abacavir.

Critical aspects of the validation of the abacavir once daily regimen have been included, namely that the benefit of abacavir as a once daily regimen is mainly based on a study performed in combination with efavirenz and lamivudine, in antiretroviral-naïve adult patients (with a cross reference to section 5.1).

Section 4.8 "Undesirable effects"

A statement has been added informing prescribers that in clinical studies with abacavir 600 mg once daily the reported rate of hypersensitivity remained within the range recorded for abacavir 300 mg twice daily.

Section 5.1 "Pharmacodynamic properties"

Under clinical experience an introduction paragraph has been added informing prescribers that the demonstration of the therapeutic benefit of Ziagen is mainly based on the results of studies performed with the twice daily regimen in adult treatment-naïve patients in combination with zidovudine and lamivudine. Thereafter results of abacavir twice daily and once daily are presented, detailing results of studies in therapy naïve and therapy experienced patients, respectively.

A paragraph presenting the results of study CNA 300024 has been included.

The paragraph on study CNA30021 has been revised to include only essential information on the study design, outcome and virological failure and the occurrence of NRTI-associated mutations. The lower limit of the confidence interval is emphasized to warrant attention of prescribers on a potential but limited and acceptable loss of chance associated with a change in the dosing regimen of abacavir. It also informs that long term data (beyond 48 weeks) with abacavir once daily are currently limited.

Results of studies CAL30001 and ESS30008 have been included, highlighting the limitations and warranting caution when interpreting the results.

The information on the intracellular pharmacokinetics has been moved to section 5.2.

Section 5.2 "Pharmacokinetic properties"

The paragraph on the bioavailability has been revised, including a clear description of the pharmacokinetic parameters with CV.

The information on the intracellular pharmacokinetics has been moved here from section 5.1.

Where relevant changes are also reflected in the Package Leaflet. In addition the CHMP requested the MAH to revise the paragraph regarding the Methadone interaction in line with the SPC.

III. CONCLUSION

The CHMP considered this Type II variation to be acceptable and agreed on the proposed wording to be introduced into the Summary of Product Characteristics and Package Leaflet based on the observations and the appropriate conclusions, subject to the additional follow-up measures undertaken by the Marketing Authorisation Holder (see Annex 12 of this Assessment report).

The CHMP adopted on 16 September 2004 an Opinion on a Type II variation to be made to the terms of the Community Marketing Authorisation, as amended.