SCIENTIFIC DISCUSSION

1. Introduction

Kivexa, which contains 600 mg abacavir and 300 mg lamivudine in each film-coated tablet, is intended for the treatment of Human Immunodeficiency Virus (HIV) infection in adults.

Kivexa is a new fixed dose combination of previously known active substances. Medicinal products containing lamivudine (150 mg, 300 mg film-coated tablets and 10 mg/ml oral solution) and abacavir (300 mg film-coated tablets and 20 mg/ml oral solution) have already been approved via the centralised procedure for the treatment of HIV infection. The recommended dose for lamivudine is either 150 mg twice daily or 300 mg once daily in adults. For abacavir the approved dose was initially only 300 mg twice daily but a once daily dosing regimen has just been recommended (600 mg abacavir once daily). In addition, two fixed dose combinations have already been approved via the centralised procedure: the first one consisting of lamivudine 150 mg and zidovudine 300 mg as film-coated tablets and the second one consisting of 300 mg abacavir, 150 mg lamivudine and 300 mg zidovudine as film-coated tablet.

In the context of a chronic disease where non-adherence is a critical problem with potential consequence in term of risk of emergence of resistance, the development of a fixed combination with a once daily administration could be a way in alleviating the constraints of patients.

The approved indication is: "Kivexa is a fixed-dose combination of two nucleoside analogues (abacavir and lamivudine). It is indicated in antiretroviral combination therapy for the treatment of Human Immunodeficiency Virus (HIV) infection in adults and adolescents from 12 years of age.
The demonstration of the benefit of the combination abacavir/lamivudine as a once daily regimen in antiretroviral therapy, is mainly based on results of one study performed in primarily asymptomatic treatment-naïve adult patients".

2. Part II: Chemical, pharmaceutical and biological aspects

Introduction

Kivexa is formulated as a film-coated tablet containing 600 mg of abacavir (corresponding to 702 mg of abacavir sulfate) and 300 mg of lamivudine, as active substances.

The other ingredients include microcrystalline cellulose, sodium starch glycolate type A, magnesium stearate and Opadry orange [hypromellose, titanium dioxide (E171), macrogol 400, polysorbate 80, sunset yellow aluminium lake (E110)].

It is presented either in opaque white polyvinyl chloride (PVC)/polyvinylidene chloride (PVdC)/ aluminium (alu) blisters or in high-density polyethylene (HPDE) bottles with a child-resistant closure.

Active Substance

No change has been made to abacavir and lamivudine active substances already approved through centralised procedures either as individual active substances (abacavir EU/1/99/112/001-003, lamivudine EU/1/96/15/001-003 and EU/1/99/114/001-003) or as part of fixed combinations (lamivudine/zidovudine EU/1/98/05/001-002 and lamivudine/abacavir/zidovudine EU/1/00/156/001-003).

Medicinal Product

- Pharmaceutical Development

This fixed combination with a once daily administration has been developed as a more convenient presentation to support patient adherence to treatment by reducing daily pill burden.

The pharmaceutical development was based on the already authorised formulations (see active substance). The formula and the direct compression manufacturing process are thus purposely similar to those of tablet formulations containing only abacavir or lamivudine as active substance. Compatibility of the active substances with the excipients is supported by forced degradation studies on the individual active substances, on the triple combination product and on abacavir-lamivudine tablets.
Formulation and process optimisation studies together with manufacturing experience indicated that acceptable blend uniformity and key finished product characteristics are obtained when using constituents having a particle size within normal range as procured by suppliers. Both active substances are soluble, and the physical characteristics are the same as those already authorised on an individual basis.

All the excipients selected are of PhEur quality except sunset yellow, which is adequately controlled according to a different standard. The colouring materials (sunset yellow and titanium dioxide) comply with the European directive relating to colouring matters that may be added to medicinal products and they conform with the purity criteria stipulated by the European directive concerning colours for use in foodstuff.

Regarding the TSE risk, the formulation does not include any components of ruminant origin.

Satisfactory specifications have been provided for the opaque PVC/PVdC/alu blister and for the HDPE bottle. Compliance with European regulation on plastic materials and articles intended to come into contact with foodstuffs has been confirmed.

The bioequivalence batch and clinical trial batches were manufactured using the commercial formulation and process (at both pilot scale and full-scale) at the commercial manufacturing site.

- Manufacture of the Product

The manufacturing process consists of a standard direct compression process comprising the following operations: weighing, sieving, blending, tablet compression, and aqueous film-coating.
The maximum holding time for the unpreserved film-coating suspension has been satisfactory validated based on microbiological data.
Process validation data provided for 4 production scale batches (including the biobatch) and one pilot scale batch manufactured at the commercial manufacturing site showed that the manufacturing process is robust and well controlled.

- Product Specification

The product specification includes tests controlled by validated methods for appearance, identity of abacavir and lamivudine (HPLC and TLC), identity of titanium dioxide and sunset yellow aluminium lake, assay (HPLC), uniformity of content (PhEur), impurity content, dissolution, microbial limit tests (PhEur non routine test).
As single-point dissolution test specification has been selected for abacavir/lamivudine tablets based on dissolution characteristics of the bioequivalence batch (see bioequivalence and bioavailability studies).
A low water activity has been shown for abacavir/lamivudine tablets. Therefore, microbiological contamination can be considered unlikely, and thus a routine microbial limit test not necessary.

Batch analysis data provided for 3 full-scale batches manufactured according to the proposed commercial process at the proposed commercial manufacturing site meet the specification at the time of release and confirm the robustness and reproducibility of the manufacturing process.

- Stability of the Product

24-month data under long-term conditions (30°C/60% RH - bottle and blister intended for commercialisation) and 6-month data under accelerated conditions (40ºC/75 % RH – bottle and blister intended for commercialisation) have been provided for 2 production scale batches and 1 pilot-scale batch. 12-month data under long-term conditions (30°C/60%RH - bottle and blister intended for commercialisation) and 6-month data under accelerated conditions (40ºC/75 %RH – bottle and blister intended for commercialisation) have been provided for 1 production scale batch. A photostability study has also been performed and shows that the product is not light-sensitive.
The results presented support the proposed shelf life and storage conditions defined in the Summary of Product Characteristics.

- Bioequivalence and bioavailability studies

Bioequivalence

A single bioequivalence study (CAL10001) was conducted to assess the bioequivalence between the fixed dose combination of abacavir/lamivudine (600 mg/300 mg) and the single entity products abacavir 2 x 300 mg and lamivudine 2 x 150 mg under fasted and fed conditions. The results indicate satisfactory bioequivalence (for further information see clinical section).

Dissolution and in vivo bioavailability

In the bioequivalence study, both abacavir and lamivudine were detected in the plasma of 100% of the subjects within 30 minutes post-oral administration. The same batch of abacavir/lamivudine tablets showed complete *in vitro* release after 30 minutes. Therefore, the dissolution method may be considered to be indicative of *in vivo* performance.

Discussion on chemical, pharmaceutical and biological aspects

No unauthorised change has been made to abacavir and lamivudine active substances already authorised via the centralised procedure. The pharmaceutical form selected is adequate taken into account the properties and the stability of the active substances and it is a well-accepted pharmaceutical form for oral administration. The excipients are commonly used for this kind of formulation and the packaging material is well documented. The manufacturing process allows obtaining reproducible finished product batches. Stability tests under ICH conditions indicate that the product is stable for the proposed shelf life.
At the time of the CHMP opinion there were no remaining quality issues.

3. Part III: Toxico-pharmacological aspects

Introduction

Abacavir and lamivudine are nucleoside reverse transcriptase inhibitors that have been shown to be have an antiviral activity against HIV. No specific preclinical studies have been performed with the fixed dose combination. The applicant has provided an overview of the comprehensive information on each active substance together with a summary of findings from a mitochondrial toxicity study with abacavir and lamivudine in CCRF-CEM cells that had not been previously submitted. Previous findings with the individual components in relation to pharmacology, pharmacokinetics and toxicology are summarised in the below sections.

Pharmacology

- Primary pharmacodynamics (*in vitro/in vivo*)

Abacavir, a guanosine analogue, and lamivudine, a cytosine analogue, are nucleoside reverse transcriptase inhibitors (NRTIs). Both agents are metabolised sequentially by intracellular kinases to the respective 5'-triphosphate (TP) active forms. Carbovir-TP (the active triphosphate form of abacavir) and lamivudine-TP inhibit the activity of the HIV-1-RT by competing with the natural nucleotide substrate and its incorporation into viral DNA. The lack of 3'-OH group in the incorporated nucleoside analogue prevents the formation of the 5' to 3' phosphodiester linkage essential for DNA chain elongation and therefore the viral DNA growth is terminated.
In vivo the intracellular half-life of carbovir-TP is 20.64 hours whereas the one for lamivudine-TP is 10 to 15.5 hours.

Antiviral activity

Abacavir
Abacavir has been shown to inhibit replication of laboratory strains and clinical isolates of HIV in transformed T cell lines, monocyte/macrophage derived lines and primary cultures of activated peripheral blood lymphocytes (PBLs) and monocytes/macrophages. IC_{50}s (the concentration inhibiting viral replication by 50%) ranged from 0.26 to 7.5 µM depending on virus strain and host cell type.

Lamivudine
Lamivudine has been shown to inhibit replication of several laboratory strains and clinical isolates of HIV-1 and HIV-2 in one of a number of different lymphocyte or monocyte cell lines or in fresh human PBLs. IC_{50}s were in the range 2 nM to 15 µM.

Combination
The *in vitro* activity of abacavir in combination with lamivudine was investigated in clinical virus isolates, along with abacavir in combination with various other anti-HIV agents (Daluge et al., 1997). Abacavir in combination with lamivudine exhibited additive anti-HIV activity, and all other combinations were additive or synergistic. None of the combinations were antagonistic.

Resistance

Viral resistance to abacavir develops relatively slowly *in vitro* and *in vivo* requiring multiple mutations to reach a 8-fold increase in IC_{50} over wild-type virus. Isolates resistant to abacavir may also show reduced sensitivity to lamivudine**,** zalcitabine, tenofovir, emtricitabine and/or didanosine but remain sensitive to stavudine and zidovudine. Abacavir-resistant isolates of HIV-1 selected in vitro are associated with specific genotypic changes in the RT codon region (M184V, K65R, L74V and Y115F). The first abacavir-resistance mutation detected is generally a change at codon 184, conferring a 2-3-fold decrease in HIV-1 susceptibility to abacavir.
Viral strains resistant to lamivudine also possess a mutation at codon 184 (M184I or V).
Cross-resistance studies with abacavir-associated mutations in HIV-1 strain HXB2 revealed reductions in sensitivity to didanosine and lamivudine. In clinical samples, lamivudine resistant HIV remained susceptible to zidovudine. Furthermore, the M184V mutation, in the context of several zidovudine-associated mutations, restores zidovudine sensitivity to some degree.

- Secondary pharmacodynamics

Lamivudine is also active against hepatitis B virus and has been approved for the treatment of HBV infection at the dose of 100 mg once daily. Abacavir has also shown anti-HBV activity.

- Safety pharmacology

Abacavir had no major effects on organ systems at doses up to 1000 mg/kg administered orally in mice and at doses up to 100 mg/kg administered intravenously in rats.

Lamivudine administered in mouse with oral doses up to 300 mg/kg did not have any effect on intestinal transport. There were no effects on respiratory system nor on cardiovascular system including blood pressure, heart rate and electrocardiogram with doses up to 100 mg/kg by intravenous route in anaesthetised cats and up 600 mg/kg by oral route in dogs.

- Pharmacodynamic interactions

No specific interaction studies have been carried out.

Pharmacokinetics

- Absorption- Bioavailability

Abacavir
After oral administration to rats, mice and monkeys abacavir was rapidly absorbed leading to an exposure proportional to the dose. The bioavailability in mice and monkeys was greater than 76% and the pharmacokinetic parameters after single or repeated administration were similar. Systemic exposure was similar after oral dosing in pregnant and non-pregnant rats, as well as in infant and mature rats.

Lamivudine
After oral administration, lamivudine was rapidly absorbed in rats and dogs with a bioavailability of 60 % and 80 % respectively. The limiting factor of bioavailability in dogs was metabolism while in the rat it was absorption from the gastrointestinal tract. After repeated doses in the rat, the relationship between dose and concentration of lamivudine in plasma was linear, and in general there was no change in systemic exposure over a dosing period of up to 6 months. Repeated administration of lamivudine to the dog for up to 12 months caused an increase in systemic exposure.

- Distribution

Abacavir
Abacavir distributed extensively to tissues. Measurable concentrations were found in cerebro-spinal fluid and brain in mice (CSF:blood ratios ranging from 0.36-0.51 and brain:blood ratios ranging from 0.09-0.11). In monkeys micromolar concentrations of abacavir were measured in both CSF and plasma after dosing. In pregnant rabbits and rats, abacavir-related material crossed the placenta and was excreted in maternal milk. The protein binding in mice, monkeys and humans is low to moderate (19-49 %). It binds extensively to melanin-containing tissues but ocular toxicity was not observed.

Lamivudine
Lamivudine distributed widely and rapidly through the rat tissues. It crossed the placenta in rats and rabbits and was excreted in maternal milk. There were no signs of accumulation. The protein binding was moderate to low (35-50 % to <10 %) and it did not bind to melanin in pigmented rats.

- Metabolism (*in vitro/in vivo*) and excretion

Abacavir
Abacavir is mainly cleared by hepatic route. Only 10-13 % of mice or monkeys dose and 2 % of the human dose undergo urinary excretion unchanged. Metabolism seems to occur mainly through alcohol/aldehyde dehydrogenase and glucoronidation pathways, with less involvement of CYP450 isoenzymes in humans and monkeys. The metabolic profile is qualitatively similar in mice, monkeys and humans. The two main metabolites in monkeys and humans are a 5'-glucoronide and a 5'-carboxylic acid. Minor metabolites were also identified carbovir and 139U91 representing less than 2.5 % of the abacavir concentrations.

Lamivudine

Lamivudine is almost entirely excreted via renal elimination in rats with an active tubular secretion, but without metabolism. Following oral administration, about 60 % of lamivudine was recovered in urine as unchanged. Two minor metabolites (< 5 %) were detected. The remaining was recovered in faeces indicating incomplete absorption. In dogs, lamivudine excretion involves in the same proportion both renal elimination without tubular secretion and metabolism. Quantitatively two metabolites have been identified: trans-sulphoxide metabolite of lamivudine and a cytosine metabolite representing 40 % of the intravenous dose and 52 % of the oral dose. The kinetics in humans is closer to that occurring in rats.

- Interaction

In vitro studies using human liver microsomal preparations showed no evidence for inhibition or induction of CYP450 activity at clinically relevant concentrations of abacavir and of lamivudine.

In vitro studies showed that abacavir metabolism was not altered by ethanol, but ethanol inhibited abacavir metabolism. In an in vitro human liver slice model, abacavir metabolism was not inhibited when co-incubated with amprenavir, which is a substrate of human microsomal CYP3A4. However in repeated dose studies in mice slight increases in the activity of some CYP450 isoenzymes were observed, suggesting a weak enzyme inducing potential.

Lamivudine transport across Caco-2 cell monolayers was not affected by zidovudine, zalcitabine, didanosine, acyclovir, probenecid, trimethoprim, sulfamethoxazole, ranitidine or cimetidine. In the same model, lamivudine did not affect the transport of didanosine, zalcitabine or zidovudine. In isolated perfused rat kidney the elimination of lamivudine was not affected by zidovudine but zalcitabine slightly reduced its secretion. The only interaction observed was with lamivudine and trimethoprim.

No interaction between abacavir and lamivudine at the level of the kinases for initial phosphorylation is expected, as the enzymes involved are different.

Toxicology

- Single dose toxicity

Abacavir

Abacavir had a low potential for toxicity in mice and rats. The median lethal doses were more than 100 times higher than the dose of 600 mg once daily (12 mg/kg/day for a 50 kg person).

Lamivudine

Single doses of lamivudine up to 2000 mg/kg i.v. in rats and mice or 2 x 2000 mg/kg orally in mice were well tolerated without signs of target organ toxicity.

- Repeat dose toxicity

Abacavir

Studies were conducted in mice with doses up to 708 mg/kg/day for 1 and 6 months, and in cynomolgus monkeys with doses up to 297 mg/kg/day for 1, 3 and 12 months. In addition, a 3-month study was performed in Wistar Han rats with doses up to 375 mg/kg/day. The majority of repeat-dose toxicity studies were performed using the succinate salt of abacavir; however, all doses are expressed in terms of the base.

The primary target organ for toxicity of abacavir is the liver in mice, rats and monkeys. There was an increase in liver weight at the dose of 234 mg/kg/day in mice and 200 mg/kg/day and above in rats. This was associated with mild hepatocellular hypertrophy, increased pigment deposits in the centrilobular hepatocytes and/or Kupffer-cells in both species at these dosages. All treatment-related findings reversed following the recovery period or showed evidence of regression within 4 weeks of

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the cessation of treatment. Slight increase in some CYP450 enzymes activity was observed after 6-month administration to rodents. In monkeys, there were minor changes in serum triglyceride concentrations and equivocal increases in alanine aminotransferase were seen at 297 mg/kg/day.

Abacavir caused changes in the haemapoietic system. In rats these changes, occasionally noted at all doses, included minimal decrease in red blood cell parameters and increased leucocytes count (especially lymphocytes). There was no evidence of an effect on bone marrow. These changes reversed in the recovery period. In monkeys, the haematological changes noted at all doses were mild (approximately 15 %) and corresponded to slight decrease in red blood cell counts occasionally accompanied by decreased haemoglobin concentrations and haematocrit.

In the 3-month study in rats, germ cell loss in the testis was seen in males with the highest dose of 452 mg/kg/day. The reversibility of the finding was not investigated, but the no effect level for this finding was 96 mg/kg/day, at which systemic exposure was 13 times higher than in humans following a once daily 600 mg dose.

Lamivudine

The toxicity of lamivudine was assessed in rats with doses up to 2000 mg/kg twice daily in studies of 1, 3 and 6 months duration, and in the dogs with doses up to 1500 mg/kg twice daily in studies of 14 days, 3 and 12 months duration. For all these studies, lamivudine was administered as a solution in acetate buffer (pH 3.7) by oral gavage.

Lamivudine caused changes to the haematopoietic system. In dogs, a decrease in red blood count, accompanied by increases in mean corpuscular volume and mean corpuscular haemoglobin was noted at all doses. The same changes were noted in rats but less pronounced (not exceeding 10%) than in dogs.

Changes in the caecum were observed in rats. In the 6-month study, these changes noted at the dose of 2000 mg/kg twice daily comprised slight to moderate, diffuse, mucosal hyperplasia, with local inflammatory cell infiltration and slight sub-epithelial eosinophilia. In recovery animals, some slight sub-epithelial eosinophilia was still present, but the other features had regressed. These changes could be considered as a result of low grade irritation to the caecum produced by very high oral doses of lamivudine.

- Reproductive and developmental studies

Abacavir

Abacavir did not cause any adverse effects on the mating performance or fertility of rats with doses up to 427 mg/kg/day. At this dose, which was maternally toxic, there was evidence of toxicity to the developing embryo and foetus (increased resorptions and decreased foetal body weights).

In rabbits no embryofoetal toxicity was observed even at materno-toxic doses. In an embryofoetal study in rats, there was evidence of toxicity corresponding to decreased body weight, foetal oedema, early intra-uterine deaths and skeletal malformations and variations at the maternally toxic dose of 648 mg/kg/day. The AUC_{0-24} at the lowest no effect level (seen in the rat fertility and embryofetal study) was 118 µg.h/ml, which is approximately 10 times the daily AUC in humans at the therapeutic dose of 600 mg once daily.

Abacavir at 500 mg/kg/day showed peri-post natal toxicity either maternal or to the progeny with reduced body weight in offspring F1 during lactation and throughout the remainder of post-natal life, through mating to birth of the F2 litters.

Lamivudine

Lamivudine did not impair the overall reproductive performance in rats. There was no evidence of teratogenic potential in rats (at doses up to 2000 mg/kg BID) or rabbits (at doses up to 500 mg/kg BID) and it did not induce peri-post natal toxicity in rats. The dams and offspring showed swollen/reddened anus/rectum during lactation period correlated with histological inflammatory changes at the ano-rectal junction. The findings were attributed to prolonged exposure of caecal region to large amounts of irritating agent. In the juvenile animals mild microcytic anaemia was observed,

similar to adult animals in repeat dose studies. Reduction of testis weights with histological changes corresponding to slight to moderate dilation of the seminiferous tubules was observed in high dosed males (2000 mg/kg/day). Testicular findings were not found in adult animals suggesting that the effect is related to testicular immaturity/developing status. The safety margin for this finding *versus* 300 mg daily human dose was higher than 80.

- Genotoxicity *in vitro* and *in vivo*

    Abacavir
Abacavir was not mutagenic in the presence or absence of metabolic activation at concentrations up to 3540 µg/plate in different *S. typhimurium* strains, or at concentrations up to 5086 µg/plate in several *E. coli* strains. Mutagenicity was observed in the mouse lymphoma assay with doses up to 177 µg/ml, which produced 6-fold increase in mutant frequency, compared to controls.

In human lymphocytes chromosomal aberrations were observed in the presence or absence of S9 metabolic activation after 3 hours exposure at doses of 2800 µg/ml and above (the result obtained in absence of S9 was not reproducible). Chromosomal aberrations were also observed in the absence of S9 after 50 hours exposure to concentrations of 100µg/ml or higher. This concentration corresponds to around 20 times the C_{max} expected in human with 600 mg at a once daily regimen. There was no effect using 27 hours treatment period. These results may be related to the overwhelming of the specificity to virally-encoded reverse transcriptase versus mammalian cell polymerase enzymes.

Abacavir was clastogenic *in vivo* in the mouse bone marrow micronucleus test assay. It induced a significant increase of micronucleated polychromatic erythrocytes in male mice at the dose of 708 mg/ml, corresponding to a systemic exposure of 104.9 µg/ml, which is around 8.5 times higher than the AUC expected in human after 600 mg dose once daily with the fixed combination. The corresponding C_{max} was 41.2µg/ml, which is around 10 times higher than the expected in humans.

    Lamivudine
Lamivudine was not mutagenic in the Ames test at concentrations up to 5000 µg/plate and fluctuation test using *E. coli* tester strains. In the mouse lymphoma assay, small increases in mutant frequency were observed with concentrations from 1000 µg/ml. In human peripheral lymphocytes, lamivudine showed clastogenicity at the highest concentrations of 300 µg/ml without S9 and 2292.5 µg/ml in the presence of S9. The concentration of 300 µg/ml is 150 times higher than the mean steady-state C_{max} at the 300 mg once daily clinical dose.

In mouse embryo cells lamivudine did not induce morphological transformation at concentrations up to 320 µg/ml without S9 or 5000µg/ml with S9.

In vivo, lamivudine was not clastogenic in the rat bone marrow metaphase analysis assay, the rat bone marrow micronucleus assay or the rat liver UDS assay following oral doses of up to 2000 mg/kg. Plasma levels in the bone marrow metaphase analysis assay were around 30 to 40 times higher than clinical levels.

- Carcinogenicity

The carcinogenic potential of abacavir and lamivudine was evaluated individually in life-span studies in rats and mice.

    Abacavir
An increased incidence of malignant and non-malignant tumours was noted, including in both species carcinoma in the preputial gland of males and in the clitoral gland of females. In female rats, carcinoma in the liver, urinary bladder, lymph nodes and subcutis hemangiosarcoma were observed. These neoplastic findings occurred at the highest doses tested: 330 mg/kg/day in mice and 600 mg/kg/day in rats, with the exception of preputial gland carcinoma in male mice which occurred

at 110 mg/kg/day. These doses gave a systemic exposure of respectively around 24 fold and 33 fold higher than the expected in humans treated with 600 mg/day. The non-effect dose levels were 55 mg/kg/day in mice which corresponds to 3 times the AUC in humans, and 120 mg/kg/day in rats, which corresponds to 7 times the AUC in humans.

Lamivudine

Lamivudine was neither carcinogenic in mice with doses up to 2000 mg/kg/day (corresponding to 17-fold the clinical exposure) nor in rats with doses up to 2000 mg/kg/day in males and 3000 mg/kg/day in females (corresponding to 60-90 fold the human exposure respectively).

- Local tolerance

Separate studies performed with lamivudine and abacavir did not reveal any skin/eye irritancy nor skin sensitising or antigenic potential.

- Other toxicity studies

Abacavir and lamivudine showed a very low cytotoxic potential.

The potential for mitochondrial toxicity of lamivudine, abacavir and other NRTIs, alone or in different associations, was studied. Abacavir and carbovir showed low potential for inhibition of human DNA polymerases. Abacavir did not change the mitochondrial content in a human leukaemic cell line. Lactate production, cell growth, glucose consumption and LDH leakage were not changed by up to 54.2 µM abacavir in CCRF-CEM cells for 4 days.

Lamivudine did not significantly induce damage to mitochondrial DNA in presence of normal functioning DNA repair mechanisms. Cell growth, lactate production, glucose consumption and LDH leakage were not affected by lamivudine in CCRF-CEM cells treated or 4 days with up to 32.5µM (3.6 times the expected human C_{max} following the fixed dose combination).

The *in vitro* mitochondrial toxicity of abacavir and lamivudine as single agents, both in combination and in combination with other NRTIs have been investigated 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.

No new impurities are present in the fixed combination compared to the individual formulations and therefore no further studies were necessary.

- Environmental risk assessment

Based on an analysis of the environmental risk posed by the use of lamivudine, abacavir individually and in the fixed combination, no significant risk to the environment related to the use of Kivexa is anticipated.

Discussion on non-clinical aspects

Abacavir and lamivudine are nucleoside reverse transcriptase inhibitors that have been shown to be potent selective inhibitors of HIV-1. No specific pharmacodynamic, pharmacokinetic and toxicological studies have been performed with the fixed dose combination but the applicant provided an overview of the comprehensive information on each active substance.

HIV-1 resistance to lamivudine involves the development of a M184V amino acid change close to the active site of the viral RT. For abacavir, the viral resistance involves the development of specific genotypic changes in the reverse transcriptase (RT) codon region (codons M184V, K65R, L74V and Y115F). With respect to safety pharmacology no related adverse effects were seen with either compound.

The pharmacokinetics studies showed both compounds are rapidly absorbed and that the bioavailability was for abacavir greater than 76% in monkeys and mice and for lamivudine 60% in rats and 80% in dogs respectively. The *in vitro* binding was low for both compounds. Abacavir is mainly excreted by hepatic clearance with the main routes of metabolism were alcohol/aldehyde dehydrogenase and the glucuronation pathways. Lamivudine is almost entirely excreted via renal elimination with an active tubular secretion, but without metabolism.

Both abacavir and lamivudine have low acute toxicity. In repeat-dose toxicity studies with abacavir and lamivudine, the most sensitive target organ was the haemopoietic system. The other target organs identified were the liver and testis for abacavir and the gastrointestinal tract for lamivudine. The clinical relevance of increased liver weights associated with abacavir is unknown and there is no evidence from clinical studies that abacavir is hepatotoxic. Lamivudine and abacavir crossed the placenta. In rats, abacavir demonstrated a potential toxicity to the developing of embryo and fœtus, however, no embryofoetal toxicity was observed in rabbits. Lamivudine was not teratogenic. In rats, abacavir and lamivudine had no effect on male or female fertility. Neither abacavir nor lamivudine were mutagenic in bacterial tests, but like many nucleoside analogues they show activity in the *in vitro* mammalian tests such as the mouse lymphoma assay. Lamivudine did not show any carcinogenic potential but abacavir showed an increase in the incidence of malignant and non-malignant tumours in mice and rats. With respect to the *in vitro* mitochondrial toxicity, no synergetic effects due to the combination have been observed in comparison with abacavir and lamivudine as single agents.

With respect to toxicokinetics, either the C_{max} or the AUC values of both abacavir or lamivudine reached in the toxicology studies were in excess to those expected in human with the fixed dose combination. Only in mice the C_{max} of abacavir at the end of 6 months repeat-dose studies presented similar magnitude to the human expected C_{max}, but in the carcinogenicity study in the same species an excess of 2 or more could be obtained at the end of the study. In this perspective, the individual studies can be considered as appropriate to support the individual non-clinical safety of abacavir and lamivudine at the doses included in the application. Interactions between abacavir and lamivudine are not expected on intracellular phosphorilation pathways, intestinal transport metabolism or excretion.

Clinical experience with the administration of lamivudine and abacavir, using the two substances in association as well as in the triple fixed dose combination of abacavir/lamivudine/zidovudine is available, although there are no extensive experience using abacavir as single 600 mg daily dose.

It was agreed that animal data with lamivudine and abacavir administered as fixed dose combination would not be expected to add any relevant information.

On this basis, and considering the extensive clinical experience with the association, the CHMP agreed that toxicological investigations with the combination were not necessary. This is also in line with the Note for Guidance on Fixed Combination Medicinal Products (CPMP/EWP/240/95).
A concern was raised however for potential increased genotoxicity with combination antiretroviral treatment with NRTIs. Indeed combination of zidovudine and didanosine have been reported to potentiate genetic damage in human cells *in vitro* [Meng, 2000] and in CD-1 mice *in vivo* [Bishop, 2004]. The applicant undertook therefore to conduct an oral rat micronucleus study to evaluate whether co-administration of abacavir with lamivudine has the potential to synergistically enhance the in vivo clastogenicity of abacavir, the results of which will be submitted as part of the follow-up measures to be fulfilled post-authorisation.
The information on the individual compounds relevant for the fixed combination have been mentioned in the Summary of Product Characteristics.

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4.   Part IV: Clinical aspects

Introduction

Since the two active substances of Kivexa have already been approved for the treatment of HIV in the EU, the applicant focused the clinical development programme on the demonstration of bioequivalence between the fixed dose combination of abacavir/lamivudine (600/300 mg) and the individual compounds, administered separately at the same dose (study CAL10001). The pharmacokinetic programme was also supported by a study of intracellular pharmacokinetics of the major abacavir active intracellular metabolite, carbovir-triphosphate (study CNA10905).

At the time of the submission of the application the 600 mg once daily regimen for abacavir was not yet approved. Therefore the clinical programme included a study which compared 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 naive patients (study CNA30021).
Subsequently, the applicant further substantiated the dossier by providing preliminary 24 weeks data of two new phase III studies in antiretroviral experienced patients using abacavir/lamivudine as the fixed dose combination: studies CAL 30001 and ESS 30008.
In terms of clinical efficacy, previous data had included an assessment of the efficacy of the two actives when administered concurrently as part of antiretroviral regimens since the original clinical development of abacavir was mainly supported by studies involving these two nucleoside analogues within multitherapies (e.g. studies CNAAB 3003 and CNAAB 3005).

Four clinical studies were submitted using the antiretroviral association with abacavir and lamivudine administered twice daily, however these were considered only as supportive considering that the fixed combination is only suitable for a once daily administration and therefore will not be summarised in this report (studies CNA30024, ESS40001, APV30001 and APV30002).

The applicant claimed that all studies were performed according to Good Clinical Practices.

Pharmacokinetics

The pharmacokinetics profile of abacavir and lamivudine as individual compounds have already been assessed. The pharmacokinetic programme for the fixed dose combination focused therefore on the demonstration of the bioequivalence between abacavir 600 mg/lamivudine 300 mg fixed dose combination formulation to the individual compounds administered at the same doses (study CAL10001). In addition a study aiming at characterising the intracellular pharmacokinetics of the major abacavir intracellular metabolite, carbovir triphosphate, was provided to support the once daily regimen of abacavir (study CNA1095).
A brief summary of the major pharmacokinetic parameters for each individual compound is presented for reference.

Abacavir

Following oral administration, abacavir is rapidly and well absorbed. The mean time (t_{max}) to maximal serum concentrations of abacavir is about 1-2 hours and the absolute bioavailability is about 83 %. At therapeutic dosages (300 mg twice daily) in patients, the mean (CV) steady state C_{max} and C_{min} of abacavir in plasma are approximately 3.0 µg/ml (30 %), and 0.01 µg/ml (99 %), respectively. The mean (CV) AUC over a dosing interval of 12 hours is 6 µg.h/ml (29 %). Food delays absorption and decreased C_{max} but does not affect overall plasma concentrations (AUC).

Following intravenous administration, the apparent volume of distribution is about 0.8 l/kg, indicating that abacavir penetrates freely into body tissues. *In vitro*, abacavir binds only low to moderately (~ 49 %) to human plasma proteins at therapeutic concentrations.

Abacavir is primarily metabolised by the liver with approximately 2 % of the administered dose being renally excreted as unchanged compound. The primary metabolism pathways are by alcohol dehydrogenase and by glucuronidation to produce the 5'-carboxylic acid and 5'-glucuronide which account for about 66 % of the dose. These metabolites are excreted in the urine. The mean half-life of abacavir is about 1.5 hours. Following multiple oral doses of 300 mg twice a day, there is no significant accumulation of abacavir. The metabolites and unchanged abacavir account for about 83% of the administered dose in the urine, the remaining being eliminated in the faeces.

An open-label single arm, pharmacokinetic study (study CNA10905) was conducted to characterise the pharmacokinetics profile of intracellular anabolite carbovir triphosphate following administration of an abacavir 300 mg BID containing regimen in HIV infected patients. This study demonstrated that *in vivo* carbovir-TP has a long half-life of 20.6 h.

Lamivudine

Lamivudine is well absorbed from the gastrointestinal tract, and the bioavailability of oral lamivudine in adults is normally between 80 and 85 %. Following oral administration, the mean time (t_{max}) to maximal serum concentrations (C_{max}) is about 1 hour. At therapeutic dose of 150 mg twice daily, mean (CV) steady-state C_{max} and C_{min} of lamivudine in plasma are 1.2 µg/ml (24%) and 0.09 µg/ml (27%), respectively. The mean (CV) AUC over a dosing interval of 12 hours is 4.7 h.µg/ml (18%). At a therapeutic dose of 300 mg once daily, the mean (CV) steady-state C_{max}, C_{min} and 24h AUC are 2.0 µg/ml (26%), 0.04 µg/ml (34%) and 8.9 h.µg/ml (21%), respectively. Food delays t_{max} and a lowered C_{max} (decreased by 47 %), but the extent (based on the AUC) of lamivudine absorbed is not influenced.

From intravenous studies, the mean volume of distribution is 1.3 l/kg.

Lamivudine exhibits linear pharmacokinetics over the therapeutic dose range and displays limited binding to the major plasma protein albumin (< 16 % - 36 % to serum albumin in *in vitro* studies).

The active moiety, intracellular lamivudine triphosphate, has a prolonged terminal half-life in the cell (16 to 19 hours) compared to the plasma lamivudine half-life (5 to 7 hours).

Metabolism is a minor route of elimination of lamivudine. It is predominately cleared by renal excretion as unchanged compound. The extent of hepatic metabolism is very low (5 - 10%). The observed lamivudine half-life of elimination is 5 to 7 hours. The mean systemic clearance is approximately 0.32 l/h/kg, with predominantly renal clearance (> 70 %) as unchanged compound via the organic cationic transport system.

Bioequivalence

Study CAL10001 was a single-center, open-label, randomised, single-dose, three-way crossover study aiming at evaluating the bioequivalence of the combined formulated tablet (600 mg/300 mg abacavir/lamivudine) compared to the individual formulations of abacavir (2 X 300 mg tablets) and lamivudine (2 X 150 mg tablets) administered concurrently. The effect of food on the absorption of the combined formulation compared to the individual formulations was also assessed.

Thirty healthy adults subjects were enrolled (males (87%) - females (13%)) and 25 completed the study. The reasons for premature discontinuation for 5 subjects are the following: 2 due to protocol violations, 2 withdrew consent, and 1 withdrawn at the investigator's discretion.

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Subjects received one of the three treatments, at each period in a randomised, balanced fashion, using a random code based on two 3 X 3 Latin squares. There was a washout period of 5 to 10 days between each dose.

- Treatment A = Fixed dose combination of abacavir/lamivudine (600 mg/300 mg) following an overnight fast
- Treatment B = abacavir 2 x 300 mg tablet and lamivudine 2 x 150 mg tablet sequentially following an overnight fast
- Treatment C = Fixed dose combination of abacavir/lamivudine (600 mg/300 mg) five minutes following a standardized breakfast

Bioequivalence and food effects were assessed from Geometric Least Squares (GLS) mean ratios and associated 90% confidence intervals (CI) of primary pharmacokinetic parameters (C_{max} and AUC) for treatment comparisons using standard bioequivalence criteria, where the 90 % CI of the GLS mean ratio is within the range of 0.80-1.25. The analytical methods used were adequate and validated.

Results

The results, displayed in table 1, demonstrated that in a fasted state, the fixed dose combination provides lamivudine and abacavir exposures equivalent to those provided with the individual formulations given sequentially (90% CI for the ratio of treatment A/treatment B of AUC and C_{max} comprised within the predefined hypothesis of bioequivalence (range of 0.80-1.25)).

Table 1: Abacavir and Lamivudine pharmacokinetic parameters following single oral administration of the fixed dose combination of abacavir/lamivudine (600 mg/300 mg) compared to administration of individual formulations

Geometric LS Mean[a]				
PK Parameter	Treatment A	Treatment B	Ratio of Geometric LS Mean A/B	90% CI
	N=25	N=25		
Abacavir				
AUClast (ug*h/ml)	14.12	14.12	1.000	0.955-1.048
AUC∞ (ug*h/ml)	14.15	14.15	1.000	0.954-1.048
Cmax (ug/ml)	4.68	4.94	0.946	0.855-1.048
Lamivudine				
AUClast (ug*h/ml)	12.36	13.00	0.951	0.910-0.995
AUC∞ (ug*h/ml)	12.60	13.23	0.952	0.912-0.994
Cmax (ug/ml)	2.64	2.84	0.930	0.865-0.999

[a] based on log transformed data

As it has been previously described for the individual formulations of lamivudine and abacavir, the co-administration of food resulted in a delayed T_{max} and a lower C_{max}, significant for abacavir (see Table 2). However, the abacavir and lamivudine exposures were not influenced by food: AUC_{last} and AUC_∞ remained unchanged whenever the fixed dose combination of abacavir/lamivudine (600 mg/300 mg) was administered at the fasted state or with breakfast (90% CI for the AUC ratio treatment A/treatment C comprised within the predefined hypothesis of bioequivalence (range of 0.80-1.25)).

The fixed combination can therefore be taken with or without food as highlighted in the Summary of Product Characteristics.

Table 2: Abacavir and Lamivudine pharmacokinetic parameters following single oral administration of the fixed dose combination of abacavir/lamivudine (600 mg/300 mg) fed compared to the administration of the fixed dose combination fasted

Geometric LS Mean[a]				
PK Parameter	Treatment A	Treatment C	Ratio A/C	90% CI

	N=25	N=25		
Abacavir				
AUClast (ug*h/ml)	14.12	12.74	0.902	0.861-0.945
AUC∞ (ug*h/ml)	14.15	12.79	0.903	0.862-0.947
Cmax (ug/ml)	4.68	3.54	0.757	**0.684**-0.838
Tmax (h)	1.26	2.37		
Lamivudine				
AUClast (ug*h/ml)	12.36	11.89	0.962	0.920-1.006
AUC∞ (ug*h/ml)	12.60	12.13	0.963	0.922-1.005
Cmax (ug/ml)	2.64	2.27	0.860	0.800-0.924
Tmax (h)	1.83	2.88		

[a] based on log transformed data

- Special populations

Renal impairment: Whilst no dosage adjustment of abacavir is necessary in patients with renal impairment, a dose reduction of lamivudine is required due to a decreased clearance. Therefore the fixed combination of abacavir/lamivudine is not recommended for use in patients with a creatinine clearance < 50 ml/min.

Hepatic impairment: The pharmacokinetic profile of lamivudine is not significantly affected in patients with moderate to severe hepatic impairment.
For abacavir, in patients with mild hepatic impairment (Child-Pugh score 5-6) receiving a single 600 mg dose, there was a mean increase of 1.89 fold [1.32; 2.70] in the abacavir AUC, and 1.58 [1.22; 2.04] fold in the elimination half-life. No recommendation on dosage reduction is possible in patients with mild hepatic impairment due to substantial variability of abacavir exposure. No data are available in patients with moderate hepatic impairment. In view of the above, the fixed combination of abacavir/lamivudine can be used in patients with mild hepatic impairment but is not recommended in patients with moderate hepatic impairment unless judged necessary. In both cases, as mentioned in the Summary of Product Characteristics, a close monitoring is required, and if feasible, a monitoring of abacavir plasma levels is recommended. The fixed combination is contraindicated in patients with severe hepatic impairment.

Children: The fixed combination of abacavir/lamivudine is not recommended for treatment of children less than 12 years of age as the necessary dose adjustment cannot be made.

- Interaction studies

No specific study has been performed with this fixed dose combination tablet, however no new interactions compared to the ones already known with the individual compounds are expected.

The information on the individual compounds relevant for the fixed combination has been mentioned in the Summary of Product Characteristics.

Pharmacodynamics

No data pertaining to the pharmacodynamics of the fixed combination of abacavir/lamivudine has been provided.

The antiviral activity and mutation pattern of the two individual compounds has been well identified *in vitro* and *in vivo.* No specific virological data have been provided except substantial genotyping and phenotyping analysis performed with antiretroviral naive patients receiving abacavir/lamivudine and efavirenz as a once daily in study CNA30021 (see section on clinical efficacy).

Clinical efficacy

At the submission of the application there was no specific clinical study performed to support the efficacy and safety of the fixed dose combination tablet.

In addition, the once daily dose of abacavir was not approved. The demonstration of the antiviral activity of the fixed combination abacavir with lamivudine as a once daily regimen was therefore mainly based on study CNA30021 which compared 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 naive patients.

Subsequently the applicant completed the clinical dossier by providing preliminary 24 weeks data of two new phase III studies in antiretroviral experienced patients using the fixed dose combination (studies CAL 30001 and ESS 30008).

- Main study(ies)

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 naive patients.

Methods

- **Study Participants**

Male or female adults ≥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. 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 authorised 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 Intent-To-Treat (ITT)-Exposed Population, which included patients exposed to at least one dose of study treatment. The evaluation of non-inferiority was based on 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 % CI adjusted for randomisation strata that excluded differences as large as 12 % in the direction of inferiority of the abacavir once daily group.

Results

- **Patient disposition**

The population enrolled had a median age of 36 years old mainly, was mostly White (54 %) and male (81%). The mean viral load at baseline was of 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 had symptomatic HIV-1 infection and only 7% (53/770) had AIDS.

The number of patients who discontinued and the reasons for discontinuation were overall balanced between the two groups as displayed in table 3.

Table 3: Patient disposition

	ABC OD n (%)	ABC 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 tables 4 and 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 both daily regimens (lower limit of the 95 % CI of the difference between ABC OD and BID in terms of proportion of patients with Plasma HIV-1 RNA <50 copies/ml at Week 48 greater than –12 %).
The distribution of patients in both arms in the subcategory of viral load <100 000 copies/ml (50-1000; 1000-10 000 and 10 000-100 000) was well balanced, which further substantiated the non-inferiority demonstration between abacavir once and twice daily regimen.

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

The virologic failure rate or failure due to lack of efficacy was low and comparable in both groups (abacavir OD group 10 % (38/384) compared with 8% (32/386) in the abacavir twice daily group). Genotype data at baseline and post-baseline were available for 31 patients with virological failure with viral loads > 500 copies/ml (16 in abacavir OD group and 15 in abacavir BID group).
There was a high proportion of patients with any treatment emergent 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 compared with the abacavir BID group (11/16 (69 %) versus 5/15 (33 %), p = 0.0076).
Among 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. Even if there is a trend in favour of a higher rate of emergence of resistance in the OD regimen, the sample size of the genotypic analysis warrants particular precaution in the interpretation of the data, the more so as similar virologic suppression was observed between abacavir once and twice daily regimen.

Although the results in term of percentage of patients with virological response were compatible with a non-inferiority margin, there was a 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 applicant was requested to discuss what represented the 8.4% in the ITT analysis in term 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 + efavirenz allowing direct evidence of the contribution of abacavir to a regimen containing abacavir, lamivudine, efavirenz, the applicant 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 term of adherence resulting from a simplified schedule regimen, especially when considering that in general non-adherence represents a critical cause of failure to anti-HIV treatment.

In terms of 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 the a Kaplan Meier estimate based on the TLOVR algorithm and on review of the proportions of patients with undetectable viral load at each timepoint.

Study CAL 30001

This is a randomised, open-label, parallel, multicenter study to evaluate treatment with fixed-dose combination of abacavir/lamivudine (600 mg/300 mg) once-daily versus abacavir (300 mg) 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 ($\geq$ 18 years) who are ART experienced but TDF naïve patients currently receiving a stable regimen containing 3 NRTIs, or 2 NRTIs + 1 PI or 2 NRTIs + 1 NNRTI for at least 3 months and having $\leq$ 3 NRTI-associated mutations (including M184V), but without K65R, L74V, 69S insertion, Q151M, M41L, L210W, OR $\geq$ 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 $\geq$ 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 ARV 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 authorised ARV agents. Patients who switched to the last option were considered as treatment failure at the time of change.

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- **Outcomes/endpoints**

The primary efficacy measure was to test the non-inferiority of abacavir in a fixed dose combination (FDC) 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 a 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

- **Patient disposition**

A total of 186 patients were enrolled and randomised. The demographic characteristics were 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 4th product was lopinavir/ritonavir and efavirenz.

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

	ABC/LAM FDC OD N (%)	ABC BID + LAM OD N (%)	Total N (%)
Total randomized (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

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 <u>at week 24</u> (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, <u>**0.37**</u>
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 TAMs mutation at baseline. Moreover, the patients enrolled were receiving a quadritherapy whereas, in clinical practice, the re-sort 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 term of baseline viral load (lower viral load in the OD arm).

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

Study ESS30008

This is a randomised, open-label, multicentre study comparing the safety and efficacy of the abacavir/lamivudine FDC tablet administered once a day versus abacavir + 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 ARV regimen containing abacavir 300 mg BID and lamivudine 150 mg BID in combination with either a PI or NNRTI for ≥ 24 weeks were eligible.
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 is 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 were enrolled and randomised. Patients were approximately 38 years old and the majority was male (82%). The population consisted mainly in asymptomatic well-controlled patients (80 %). The mean baseline HIV RNA was 1.73 log10 copies/ml (± 0.216) and the mean CD4 cell counts 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 inhibitor in both groups (20% and 16% in the abacavir + lamivudine arm, respectively, and 20 % and 18 % in the FDC OD arm, respectively).
Patients were well balanced in term 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 + lamivudine BID and FDC 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%)

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 $\geq$ 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 non inferiority (12%).

Clinical safety

The safety of both abacavir and lamivudine has been established in adults and children in multiple controlled clinical trials and corroborated by several years of post-marketing experience.
More than 36,700 subjects have been exposed to abacavir containing products in clinical trials and the worldwide estimated cumulative patient exposure to abacavir containing products, since first marketing approval is estimated to be approximately 508,958 patient-years of treatment up to the end of December 2003.
Approximately 2.64 million patient-years of post-marketing experience with lamivudine containing products authorised to treat HIV infection have been generated during the past 7 years.

The evaluation of the safety profile of abacavir/lamivudine as fixed dose combination tablet focused in assessing whether:
- the once daily dose of abacavir (600 mg) had a similar safety profile to twice daily dose (2 x 300 mg);

- the incidence and/or presentation of abacavir hypersensitivity was not altered by dosing it once daily instead of twice daily;
- abacavir and lamivudine provided an NRTI backbone with an acceptable safety profile when used with a variety of antiretrovirals from all three ART classes.

Therefore the safety data derived mainly from the study CNA30021 which provides a minimum of 48-week data on the safety of abacavir 600 mg OD or 300 mg BID with lamivudine 300 mg OD. In addition, data from five studies have been provided to support the safety and tolerability of abacavir and lamivudine used together as a backbone (CNA30024, EPV40001 using OD regimen, ESS40001, APV30001, and APV30002). Relevant safety data can also be found in historical studies CNAA2001, CNAB2002 and CNAB3001 where up to 600 mg of abacavir was administered twice or three times daily.
Finally, preliminary 24 weeks data have also been submitted from the two Phase III trials in antiretroviral experienced patients using the fixed dose combination.

Study CNA30021

The incidence of AES, related to treatment or not, was similar in both treatment groups (incidence of Grade 2 to 4 adverse events ABC OD 70% *vs* ABC BID 72%). Psychiatric disorders (ABC OD : 35 % *vs* ABC BID : 36%), nervous system disorders (ABC OD : 32% *vs* ABC BID : 28%) and gastrointestinal disorders (ABC OD : 30% *vs* ABC BID : 29%) were the most frequent treatment-related adverse events. Psychiatric and nervous system disorders were more likely due to efavirenz. No new safety concerns were therefore identified with abacavir once daily dose.

With regard to hypersensitivity reactions, which is the most significant adverse reaction associated with abacavir there was no sign of increased risk with ABC 600 mg administered once daily, although there was a trend for higher rate of hypersensitivity reaction in the OD group (36/384; 9%) versus BID group (28/386; 7 %).

Study CAL30001

The incidences of adverse reactions are generally comparable between treatment groups (47% of patients in the FDC OD group and 45 % in the ABC BID + LAM OD group) with the exception of fatigue and hypersensitivity reaction which were reported in a higher number of patients in the FDC OD group than in the ABC BID + LAM OD group, as shown in the table 10:

Table 10: Most Common (≥5 % Incidence) Adverse reactions

Adverse reactions	ABC/LAM FDC OAD N=93; n (%)	ABC BID + LAM OD N=89; n (%)
Subjects with ANY adverse reaction	44 (47)	40 (45)
Nausea	11(12)	12(13)
Diarrhoea	10(11)	7(8)
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 FDC OD group (11%) than in the ABC BID + LAM 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 ABC.

Serious adverse events, none fatal, were reported in 14% of subjects in the FDC OD group and 8% in the ABC BID + LAM OD group. This difference was driven mainly by hypersensitivity.
A total of nine patients (10%) in the FDC OD group experienced a serious adverse reaction compared with four (4%) in the ABC BID + LAM 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 FDC OD group.

Study ESS30008

The number of patients experiencing at least one adverse reaction was higher in the FDC OD group in comparison with the abacavir + 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 AEs in a treatment arm consisting in a new schedule regimen with a new fixed combination. There was no report of hypersensitivity reactions.

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 nevertheless by the CHMP as in the pivotal study CNA 30021, the incidence of cases of hypersensitivity reaction with abacavir once daily were higher (9%) 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).

A new abacavir hypersensitivity reaction case report form (HSR CRF) module was used. However 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 term of biological plausibility). No HSR was reported in ESS30008 which could be explained by the fact that the patients were treated 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.
The applicant addressed this 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 applicant provided 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 ABC OD was not a predictor of HSR. As a matter of fact, as underlined in published literature (Naisbitt and al; 2003) ABC HSR reaction has typical clinical features of an immune-mediated reaction considered as dose-independent. More recently, a strong association has been shown between ABC HSR and haplotype including HLA-B57.

Reference:
Naisbitt D, Pirohamed M, Park K. Immunopharmacology of hypersensitivity reactions to drugs. Current Allery and Asthma Reports 2003, 3:22-29

Discussion on clinical aspects

Pharmacokinetics

When developing the fixed dose combination of abacavir/lamivudine/zidovudine, the applicant conducted an interaction study to evaluate the pharmacokinetics of abacavir (600 mg), lamivudine (150 mg) and zidovudine (300 mg) when each compound was given alone and when any two or three compounds were given concurrently. The results of this study together with the clinical experience of abacavir in association with lamivudine showed that there is no clinically significant interaction between abacavir and lamivudine. In addition due the different mechanisms of elimination, there is no rationale for pharmacokinetic interaction.

There are no pharmacokinetics data with the fixed combination. The pharmacokinetic profile of abacavir and lamivudine, as individual compounds have already been assessed in the context of the development of the single agents.

As a prerequisite to support this fixed dose combination, study CAL10001 established the bioequivalence between the fixed dose combination tablet of abacavir/lamivudine (600 mg/300 mg) and the same doses of abacavir and lamivudine administered as separate formulations.

In view of these data, no further pharmacokinetic study with the fixed combination was considered necessary. The pharmacokinetics information on the individual components which are relevant for the fixed dose combination have been included in the SPC. However to further support the once daily regimen of ABC the applicant undertook to provide post-authorisation comparative pharmacokinetics data between abacavir OD and BID. 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).

Clinical efficacy and safety

The efficacy of lamivudine and abacavir as individual compounds have already been assessed and authorised, including data on their use in association together with other antiretroviral agents.

At the time of the submission of the application the once daily regimen for abacavir was not yet authorised and therefore clinical data were submitted to support this regimen since the fixed combination is intended for once daily dose only.

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 Lost 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 of 66% in the OD regimen versus 68 % in the BID regimen of abacavir [point estimate for treatment differences −1.7; 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 and the applicant presented confirmatory analyses demonstrating that the potential difference is sufficiently small to draw an overall conclusion of non-inferiority of abacavir OD over abacavir BID.

The fact that the clinical development of abacavir OD and thereby the fixed combination only targeted the population of antiretroviral naïve patients was also perceived as a concern by the CHMP.

The applicant subsequently submitted the preliminary data of two new phase III studies in antiretroviral experienced patients (CAL 30001 and ESS 30008) using the fixed dose combination.

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 + lamivudine OD group. However due to the limitations of the studies in terms of design, patients disposal as previously highlighted, results should be taken with caution. 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.

The applicant undertook to submit the final reports from these studies as part of the follow-up measures to be fulfilled post-authorisation.

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

The safety profile of abacavir and lamivudine as individual components have already been well defined. The 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 subjects exposed to abacavir in clinical trials according to cumulative data from the last PSUR of abacavir and in line with the current SPC). This trend was also seen in study CAL 30001 in antiretroviral experienced patients, where the rate of HSR was higher in the OD regimen (9 %) of abacavir than the BID regimen (4 %). This raised a concern over a potential deterioration of the safety profile associated with a once daily regimen of abacavir, which was especially critical since the benefit in terms of adherence was felt insufficiently substantiated. The applicant 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 applicant performed a retrospective analysis which supported that the strongest predictor for reporting an ABC HSR was the use of a new abacavir case report form module, as HSR is more readily identified by the study investigator. In addition the applicant provided complementary analysis showing that the difference observed is much more likely the result of an artificial finding in a small open label study since ABC dosing frequency (OD versus BID) is not risk factor for HSR.

A concern was raised in term of adherence. Data from all these studies suggest that ABC OD is no more sensitive to missed doses than ABC BID. In addition, there was a trend in CAL30001 to suggest that ABC/LAM FDC OD may improve adherence relative to ABC BID + LAM and that this trend may lead to some improvements in efficacy. Although it was poorly substantiated (not explored in study performed in antiretroviral naïve patients, conflicting results observed in other studies…), it has to be recognized 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 accumulated so far that a reduction of the pill burden and/or of frequency of intake could be translated into improved adherence.

5.   Overall conclusions, benefit/risk assessment and recommendation

Quality

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. There are no unresolved quality issues, which have a negative impact on the Benefit Risk balance of the product.

Non-clinical pharmacology and toxicology

Abacavir and lamivudine are nucleoside reverse transcriptase inhibitors that have been shown to be effective. No specific pharmacodynamic, pharmacokinetic and toxicological studies have been performed with the fixed dose combination. The safety of abacavir and lamivudine has been investigated separately during extensive preclinical programmes and the applicant provided an overview of the comprehensive information gathered on each active substance.

With respect to toxicokinetics, either the C_{max} or the AUC values reached in the toxicology studies of both abacavir or lamivudine were in excess to those expected in human with the fixed dose combination. Only in mice the C_{max} of abacavir at the end of 6 months repeat-dose studies presented similar magnitude to the human expected C_{max}, but in the carcinogenicity study in the same species an excess of 2 or more could be obtained at the end of the study. In this perspective, the individual studies can be considered as appropriate to support the individual non-clinical safety of abacavir and lamivudine at the doses included in the application. Interactions between abacavir and lamivudine are not expected on intracellular phosphorilation pathways, intestinal transport metabolism or excretion.

Clinical experience with the administration of lamivudine and abacavir, using the two substances in association as well as in the triple fixed dose combination of abacavir/lamivudine/zidovudine is available, although there are no extensive experience using abacavir as single 600 mg daily dose.

It was agreed that animal data with lamivudine and abacavir administered as fixed dose combination would not be expected to add any relevant information.

Overall the CHMP agreed that the toxicological data available were sufficient and that further toxicological investigations with the fixed combination were not warranted. This is in line with the CHMP Note for Guidance on Fixed Combination Medicinal Products (CHMP/EWP/240/95).

Because the combination of zidovudine and didanosine have been reported to potentiate genetic damage in human cells *in vitro* [Meng, 2000] and in CD-1 mice *in vivo* [Bishop, 2004], the applicant will conduct an oral rat micronucleus study. This study will evaluate whether co-administration of abacavir with lamivudine has the potential to synergistically enhance the in vivo clastogenicity of abacavir, the results will be submitted as part of the follow-up measures to be fulfilled post-authorisation.

The information on the individual compounds relevant for the fixed combination have been mentioned in the Summary of Product Characteristics.

Efficacy

Pharmacokinetics

The pharmacokinetics profile of the fixed combination has not been assessed however the pharmacokinetic profile of abacavir and lamivudine have already been assessed as individual compounds. There is no clinically significant interaction between abacavir and lamivudine.

As a prerequisite to support this fixed dose combination, study CAL10001 established the bioequivalence between the fixed dose combination tablet of abacavir/lamivudine (600 mg/300 mg) and same dose of abacavir and lamivudine administered as separate tablets.

In view of these data, no further pharmacokinetic study with the fixed combination was considered necessary. The pharmacokinetics information on the individual components which are relevant for the fixed dose combination has been included in the Summary of Product Characteristic.
However to further support the once daily regimen of abacavir the applicant undertook to provide post-authorisation comparative pharmacokinetics data between abacavir OD and BID.

Clinical efficacy

The efficacy of lamivudine and abacavir as individual compounds have already been assessed, including data on their use in association together with other antiretroviral agents.
At the time of the submission of the application however the once daily regimen for abacavir was not yet authorised and therefore clinical data were submitted to support this regimen as the fixed combination is intended for once daily dose only.
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 and the applicant presented confirmatory analyses demonstrating that the potential difference is sufficiently small to draw an overall conclusion of non-inferiority of abacavir OD over abacavir BID.

The fact that the clinical development of abacavir OD and thereby the fixed combination only targeted the population of antiretroviral naïve patients was also perceived as a concern. The applicant subsequently submitted 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. In study CAL3001, at 24 weeks the fixed combination abacavir/lamivudine once daily was non-inferior to the abacavir BID + 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 applicant undertook to submit the final reports from these studies as part of the follow-up measures to be fulfilled post-authorisation 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 as part of the follow-up measures to be fulfilled post-authorisation.

A concern was raised in term of adherence. Although it was poorly substantiated (not explored in study performed in antiretroviral naïve patients, conflicting results observed in other studies…), it has to be recognized 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 accumulated so far that a reduction of the pill burden and/or of frequency of intake could be translated into improved adherence.

Clinical safety

The safety profile of abacavir and lamivudine as individual components have already been well defined. The adverse reactions reported with Kivexa were consistent with the known safety profiles of abacavir and lamivudine given separately. Hypersensitivity reaction is a key safety concern associated with abacavir. In clinical studies, approximately 5 % of patients receiving abacavir developed a hypersensitivity reaction.Analyses showed that HSR risk is not linked to C_{max} or dose. 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 ABC 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. Moreover, when pooling the results of the available studies comparing abacavir OD and BID within multitherapies, the HSR incidences were comparable. The applicant is committed to pursue the educational programme initiated since the original marketing authorisation of abacavir to ensure a safe use of the abacavir containing products as well as to pursue to closely monitor of HSR post-authorisation.

Benefit/risk assessment

Given the prior approval of the two active substances and the fact that there is no evidence of a pharmacodynamic or pharmacokinetic interaction that might be detrimental for patients safety and efficacy, the combination tablet seems to represent a benefit in terms of convenience for selected patients. However, as a mandatory prerequisite to support this fixed combination, the applicant has performed a single dose bioequivalence study demonstrating that the fixed dose combination of abacavir/lamivudine (600/300 mg) provides an equivalent lamivudine and abacavir exposures as both substances administered separately.

Overall, considering that:
- There are no major concern raised on the quality and non clinical aspects of the dossier submitted to support the approval of this fixed combination,
- The bioequivalence has been demonstrated between both medicinal products used separately or in the fixed combination
- The pivotal study CNA 30021 has provided efficacy and safety data with abacavir and lamivudine as a once daily regimen in antiretroviral naïve patients,
- Preliminary data in antiretroviral experienced patients indicate non-inferiority of the fixed dose combination versus the abacavir BID plus lamivudine.

- There is no deterioration of the safety profile (increased risk of HSR) with a change in the dosing regimen of abacavir.
- The applicant is committed to pursue the educational programme initiated since the original Marketing Authorisation of abacavir to ensure a safe use of the abacavir containing products and to pursue its close monitoring of HSR post-authorisation (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/lamivudine encompassing not only the advantage of a fixed dose combination but also of a once daily regimen has the potential to simplify the daily life of patients.

The CHMP considered that the benefit/risk assessment of the fixed combination of abacavir/lamivudine is favourable.

Recommendation
Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the benefit/risk ratio of Kivexa in the treatment of HIV infection was favourable and therefore recommended the granting of the marketing authorisation in the following indication:
> "Kivexa is a fixed-dose combination of two nucleoside analogues (abacavir and lamivudine). It is indicated in antiretroviral combination therapy for the treatment of Human Immunodeficiency Virus (HIV) infection in adults and adolescents from 12 years of age. The demonstration of the benefit of the combination abacavir/lamivudine as a once daily regimen in antiretroviral therapy, is mainly based on results of one study performed in primarily asymptomatic treatment-naïve adult patients."