The study listed may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this Register, healthcare professionals should consult prescribing information for the product approved in their country.

**Study No:** CAL102120

**Title :** An open-label, two-period, crossover, pharmacokinetic study of abacavir and its intracellular anabolite carbovir triphosphate following once-daily and twice-daily administration of abacavir in HIV-infected subjects.

**Rationale:** Preclinical and clinical data showed that once daily (QD) administration of abacavir (ABC) 600 mg was possible in the treatment of human immunodeficiency virus type-1 (HIV-1) infection. However, there were no data on the intracellular pharmacokinetics of the ABC anabolite carbovir triphosphate (CBV-TP) for ABC 600 mg QD or ABC 300 mg twice daily (BID) administered in the same set of subjects. This study compared the multiple-dose steady-state pharmacokinetics of plasma ABC and intracellular CBV-TP using a crossover design in subjects who received ABC 600 mg QD and ABC 300 mg BID.

**Phase:** I.

**Study Period:** 05Sep2005 – 22May2006.

**Study Design:** Non-randomised, open-label, two-period, pharmacokinetic study.

**Centres:** This was a single centre study conducted at St. Stephen's Centre, Chelsea and Westminster Hospital, London, UK.

**Indication:** None.

**Treatment:** Subjects underwent screening between 30 and 8 days prior to Day 1. On Day -1, subjects underwent pre-pharmacokinetic sampling assessments in Period 1 and on Day 1 they underwent safety assessment and 24 h pharmacokinetic sampling in Period 1. The last 24-h pharmacokinetic sample was collected in the morning of Day 2, and the ABC dosing regimen was changed. From Days 2 – 11 interim safety assessments were conducted and a protocol compliance check took place. On Day 10, subjects underwent pre-pharmacokinetic sampling assessments in Period 2 and on Day 11 they underwent safety assessments and 24-h pharmacokinetic sampling in Period 2. The last 24-h pharmacokinetic sample was collected in the morning of Day 12 in Period 2. Subjects were discharged on Day 12 and attended a follow-up visit 7-10 days after Day 12. On the day of pharmacokinetic sampling when subjects received ABC BID-containing regimen, the evening dose of ABC was skipped.
Eligible subjects were assigned to the following treatment arms based on their ongoing regimen. Subjects currently on an ABC 300 mg BID (Treatment A)-containing regimen were assigned to Treatment Arm 1 and subjects currently on an ABC 600 mg QD (Treatment B)-containing regimen were assigned to Treatment Arm 2.

| Arm | Period 1 (Day –1 to Day 1) | Period 2 (Day 2 to Day 12) |
|---|---|---|
| 1 | Treatment A | Treatment B |
| 2 | Treatment B | Treatment A |

Treatment A = abacavir 300 mg BID-containing regimen = Treatment B: abacavir 600 mg QD-containing regimen

**Objectives:** To assess the pharmacokinetics of intracellular CBV-TP at steady state following administration of 600 mg QD and 300 mg BID ABC-containing regimens in HIV-infected adult subjects.

**Statistical Methods:** There was no formal analyses of HIV-1 viral genotype or of safety data. The following pharmacokinetic parameters were calculated for plasma ABC and intracellular CBV-TP in PBMC: AUC0-24, AUC0-$\tau$, Cmax, Cavg, and C$\tau$. Summary statistics were provided for these pharmacokinetic parameters by treatment and gender. Statistical analysis was performed to compare exposure difference in ABC and CBV-TP between ABC BID and ABC QD and assess gender effect.

**Study Population:** Healthy men and women, aged 18 – 65 years, with documented HIV-1 infection and undetectable viral load (<400 copies/mL) at screening who had been taking an ABC-containing regimen for at least 8 weeks were eligible for this study. Subjects were to have a CD4+ count $\geq$250 cells/mm$^3$ at screening and be willing to temporarily switch their ABC schedule from QD to BID, or vice verse, for 11 days. Subjects were to weigh 40 – 100 kg, inclusive, and have a body mass index within 19 to 29 kg/m$^2$ inclusive. Females were to be of non-child-bearing potential or were to agree to protocol-specified methods of contraception. All subjects provided written informed consent to participate in the study.

| Number of Subjects: | Total (N = 34) |
|---|---|
| Planned N | 30 |
| Randomised N | 34 |
| Dosed N | 33 |
| Completed n (%) | 29 (85) |
| Total Number Subjects Withdrawn N (%) | 5 (15) |

| | |
|---|---|
| Withdrawn due to Adverse Events n (%) | 0 |
| Withdrawn due to Protocol Violation n (%) | 1 (3) |
| Withdrawn for Other Reasons n (%) | 4 (12) |
| **Demographics** | |
| N (ITT) | 33 |
| Females: Males | 10 : 23 |
| Mean Age in Years (sd) | 45.1 (9.72) |
| Mean Weight in Kg (sd) | 70.8 (10.9) |
| Mean Height in cm (sd) | 173.4 (9.35) |
| Mean body mass index in $kg/m^2$ (sd) | 23.55 (3.12) |
| White – White/Caucasian/European Heritage n (%) | 25 (76) |
| African American/African Heritage n (%) | 6 (18) |
| American Indian or Alaskan Native n (%) | 1 (3) |

**Pharmacokinetics Endpoints: :** A summary (geometric mean [CV%]) of intracellular CBV-TP pharmacokinetics parameters by treatment and gender is presented in the following table:

| **Parameter** | **Geometric mean (CV%)** | | | | | |
|---|---|---|---|---|---|---|
| | **Treatment A** | | | **Treatment B** | | |
| | **All (n=27)** | **Female (n=9)** | **Male (n=18)** | **All (n=27)** | **Female (n=9)** | **Male (n=18)** |
| AUC(0-24); h.fmol/$10^6$cells | 814 (64) | 1138 (72) | 688 (53) | 1051 (71) | 1851 (69) | 792 (45) |
| Cmax; fmol/$10^6$ cells | 58.5 (54) | 82.5 (42) | 49.3 (49) | 114 (76) | 198 (83) | 86.5 (49) |
| Cavg; fmol/$10^6$ cells | 33.9 (64) | 47.4 (72) | 28.7 (53) | 43.8 (71) | 77.2 (69) | 33.0 (45) |
| $C\tau$; fmol/$10^6$ cells | 23.5 (102) | 37.2 (84) | 18.7 (98) | 27.1 (137) | 49.9 (148) | 20.0 (109) |

Treatment A = abacavir 300 mg BID-containing regimen; Treatment B = abacavir 600 mg QD-containing regimen
a. Data presented as median (range)

A summary (geometric mean [CV%]) of plasma ABC pharmacokinetics parameters by treatment and gender is presented in the following table:

| **Parameter** | **Geometric mean (CV%)** | | | | | |
|---|---|---|---|---|---|---|
| | **Treatment A** | | | **Treatment B** | | |
| | **All (n=27)** | **Female (n=9)** | **Male (n=18)** | **All (n=27)** | **Female (n=9)** | **Male (n=18)** |
| AUC(0-24); h.μg/mL | 7.90 (46) | 10.9 (35) | 6.74 (41) | 8.52 (43) | 11.7 (27) | 7.26 (40) |
| Cmax; μg/mL | 1.84 (40) | 2.48 (32) | 1.59 (34) | 3.85 (37) | 4.83 (11) | 3.43 (40) |
| Cavg; μg/mL | 0.329 (46) | 0.453 (35) | 0.281 (41) | 0.355 (43) | 0.489 (27) | 0.303 (40) |
| $C\tau$; μg/mL | 0.018 (105) | 0.026 (89) | 0.015 (106) | 0.009 (102) | 0.009 (117) | 0.008 (103) |

Treatment A = abacavir 300 mg BID-containing regimen; Treatment B = abacavir 600 mg QD-containing regimen
a. Data presented as median (range)

A summary of the results of intracellular CBV-TP pharmacokinetics parameter comparisons is presented in the following table:

| Parameter | Comparison | Ratio | 90% confidence interval |
|---|---|---|---|
| AUC(0-24); h.fmol/$10^6$cells | B versus A | 1.32 | 1.07, 1.63 |
| Cavg; fmol/$10^6$ cells | B versus A | 1.32 | 1.07, 1.63 |
| Cmax; fmol/$10^6$ cells | B versus A | 1.99 | 1.61, 2.45 |
| C$\tau$; fmol/$10^6$ cells | B versus A | 1.18 | 0.82, 1.71 |
| AUC(0-24); h.fmol/$10^6$cells | Female versus male | 2.09 | 1.69, 2.58 |
| Cavg; fmol/$10^6$ cells | Female versus male | 2.09 | 1.69, 2.58 |
| Treatment A = abacavir 300 mg BID-containing regimen; Treatment B = abacavir 600 mg QD-containing regimen | | | |
| A summary of the results of plasma ABC pharmacokinetics parameter comparisons is presented in the following table: | | | |
| **Parameter** | **Comparison** | **Ratio** | **90% confidence interval** |
| AUC(0-24); h.$\mu$g/mL | B versus A | 1.08 | 1.02, 1.15 |
| Cavg; $\mu$g/mL | B versus A | 1.08 | 1.02, 1.15 |
| Cmax; $\mu$g/mL | B versus A | 2.09 | 1.88, 2.32 |
| C$\tau$; $\mu$g/mL | B versus A | 0.374 | 0.28, 0.49 |
| AUC(0-24); h.$\mu$g/mL | Female versus male | 1.60 | 1.24, 2.05 |
| Cavg; $\mu$g/mL | Female versus male | 1.60 | 1.24, 2.05 |
| Treatment A = abacavir 300 mg BID-containing regimen; Treatment B = abacavir 600 mg QD-containing regimen | | | |
| **Safety results:** Adverse event data were collected from screening to follow-up. A summary of the most frequently reported AEs is presented in the following table: | | | |
| **Adverse Events:** | | **Treatment A** | **Treatment B** |
| N (safety population) | | 33 | 33 |
| No. subjects with AEs n (%) | | 4 (12) | 4 (12) |
| Most Frequent AEs | | | |
| Diarrhoea | | 2 (6) | 1 (3) |
| Nausea | | 1 (3) | 2 (6) |
| Abdominal distension | | 0 | 1 (3) |
| Abdominal pain upper | | 0 | 1 (3) |
| Flatulence | | 0 | 1 (3) |
| Vomiting | | 1 (3) | 0 |
| Headache | | 1 (3) | 2 (6) |
| Nasopharyngitis | | 1 (3) | 1 (3) |
| Back pain | | 0 | 1 (3) |
| Myalgia | | 0 | 1 (3) |
| Treatment A = abacavir 300 mg BID-containing regimen; Treatment B = abacavir 600 mg QD-containing regimen | | | |
| There were no AEs that led to discontinuation in the study. | | | |
| **Serious Adverse Events:** | | **Treatment A** | **Treatment B** |
| No. subjects with SAEs n (%) | | 0 | 0 |
| Treatment A = abacavir 300 mg BID-containing regimen; Treatment B = abacavir 600 mg QD-containing regimen | | | |

**Publications**: No publication

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