

# **PLASMA PHARMACOKINETIC STUDY OF ONCE VERSUS TWICE DAILY ABACAVIR AS PART OF COMBINATION ANTIRETROVIRAL THERAPY IN CHILDREN WITH HIV-1 INFECTION AGED 3 MONTHS TO <36 MONTHS - PENTA 15**

## **Summary**

Treatment of HIV-1 infection in children is complicated by several factors. One challenge is to reduce barriers to good adherence to medication in infants and children. Adherence is related to several factors, including volume and palatability of medication, complexity of medication schedules and interference with the child or caregiver's daily activities. Decreasing the frequency with which medication needs to be taken in a day is likely to increase convenience and to enhance adherence to antiretroviral therapy in HIV-1 infected children. Furthermore, for agents which need to be taken with food, parents have more flexibility in selecting the most appropriate time point during the day when a child takes medication with food.

A once daily dosing regimen of abacavir (ABC) and lamivudine (3TC) has been approved for adults and a pharmacokinetic study performed in HIV-1 infected children aged 2 to 12 years showed that ABC and 3TC taken once daily were well tolerated and non-inferior, in terms of pharmacokinetic profiles and continued HIV-1 RNA viral load suppression, compared to the corresponding twice daily regimen. However, only 3 children under 3 years of age were enrolled in this study.

This study will assess the pharmacokinetics, feasibility and acceptability of dosing ABC or ABC in combination with 3TC once daily in children aged 3 months to <36 months.

### **1.1 Trial design**

#### **1.1.1 Type of design**

A cross-over, open-label pharmacokinetic multi-centre study.

#### **1.1.2 Disease/patients studied**

Children with HIV-1 infection aged 3 months to <36 months of age who have been taking ABC *bid* with or without 3TC *bid* for at least 12 weeks as part of an antiretroviral regimen and who have stable or rising CD4% and HIV-1 RNA viral load below 20,000 copies/ml (if the viral load has not been <400 copies/ml on the last two measurements, it must be decreasing). Children should be expected to still be gaining benefit from the current regimen.

#### **1.1.3 Trial interventions**

At Week 0, while children enrolled in the study are on a twice daily ABC or ABC/3TC regimen, serial pharmacokinetic samples will be collected. Following collection of these samples, children will cross over and begin a regimen of ABC 16mg/kg once daily (and 3TC 8mg/kg once daily if applicable) for at least 12 weeks, with the second pharmacokinetic sampling at week 4. The same total daily dose will be maintained within 25% of dose (allowing for dose adjustment for growth as appropriate).

Eight blood levels (2.5 ml per sample) will be taken during each PK day at week 0 whilst on twice daily ABC or ABC/3TC:

at times 0h, 1h, 2h, 3h, 4h, 6h, 8h, and 12h (as a trough level before the second dose of the day)

four weeks after starting once daily ABC or ABC/3TC:

at times 0h, 1h, 2h, 3h, 4h, 6h, 8h and 24h

For those children taking 3TC, 3TC levels will be measured on the same sample required for ABC levels: i.e. additional quantification of 3TC levels in those children receiving it will not require additional blood to be drawn.

#### **1.1.4 Outcome measures**

##### **Primary objective**

- To compare plasma pharmacokinetic parameters of once versus twice daily dosing of ABC in HIV-1 infected infants and children aged 3 months to <36 months.

##### **Secondary objectives**

- To compare plasma pharmacokinetic parameters of once versus twice daily dosing of 3TC in HIV-1 infected infants and children aged 3 months to <36 months who are receiving 3TC in combination with ABC.
- To compare age-related differences in the pharmacokinetic parameters of once versus twice daily dosing of ABC and 3TC in infants and children in 3 age groups (ages  $\geq 3$  – <12 months,  $\geq 12$  – <24 months and  $\geq 24$  – <36 months)
- To describe child and family acceptability of and adherence to once daily compared to twice daily dosage regimens of ABC and 3TC

#### **1.1.5 Duration**

18 children will be recruited over 1 year and followed for 12 weeks. If any children recruited do not have evaluable ABC PK data at both time points, a further child from the appropriate strata will be recruited to replace them.

#### **1.1.6 Data recorded directly on CRFs**

Data will be recorded on case report forms (CRF)s, the top copy/original should be sent to the appropriate Trials Centre for data entry and a copy kept at the local centre. The type of data to be recorded is detailed in the Assessments and Procedures section (section 6).