Clinical Study Synopsis for Public Disclosure

This clinical study synopsis is provided in line with **Boehringer Ingelheim's *Policy on Transparency and Publication of Clinical Study Data***.

The synopsis - which is part of the clinical study report - had been prepared in accordance with best practice and applicable legal and regulatory requirements at the time of study completion.

The synopsis may include approved and non-approved uses, doses, formulations, treatment regimens and/or age groups; it has not necessarily been submitted to regulatory authorities.

A synopsis is not intended to provide a comprehensive analysis of all data currently available regarding a particular drug. More current information regarding a drug is available in the approved labeling information which may vary from country to country.

Additional information on this study and the drug concerned may be provided upon request based on **Boehringer Ingelheim's *Policy on Transparency and Publication of Clinical Study Data***.

Name of company: Boehringer Ingelheim		**Tabulated Study Report**		
Name of finished product: Alovudine				
Name of active ingredient: Alovudine		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:**		**Addendum No.:**
Report date: 24 May 2005	**Number:** U05-1667	**Study period (dates):** 01 APR 04 - 15 DEC 04		

Title of study:	Randomised, double blind, placebo-controlled dose ranging trial to determine the antiviral activity and safety of alovudine in nucleoside-experienced HIV-infected subjects experiencing virologic failure
Investigator:	[redacted]
Study centre(s):	Multicentre study (22 sites) (see Appendix 16.1.4)
Publication (reference):	Not applicable
Clinical phase:	II a
Objectives:	The primary objective was to determine the mean change in HIV viral load from baseline to Week 4 compared with placebo after 4 weeks of treatment in highly experienced HIV-infected patients. Secondary objectives were to determine (1) the tolerability, haematologic and hepatic safety of different doses of alovudine and (2) the effect of baseline nucleoside genotypic susceptibility on virologic response after 4 weeks of alovudine administration.
Methodology:	Trial 1211.1 was a randomised, double-blind, placebo-controlled, parallel group study in patients who were highly experienced with antiretroviral therapies. The four treatment groups were 0.5 mg, 1.0 mg and 2.0 mg per day of alovudine and placebo. After genotypic screening at baseline, qualified patients were randomised to one of the four blinded treatment groups. Blinded treatment was added to the patients' failing background regimens which consisted of three to six other antiretroviral agents for 1 month. After 1 month, study treatment was discontinued; and, after a follow-up visit patients were permitted to receive tipranavir through the tipranavir Expanded Access Program (EAP). This procedure was followed because enrolled patients had few remaining treatment options and alovudine was in an early phase of development.
No. of subjects: **planned:**	Enrolled : 120 patients entered: 84 patients

actual:	enrolled: 97 patients entered : 72 Treatment 1: alovudine 2.0 mg entered: 20 treated: 20 analysed (for primary endpoint): 20 Treatment 2: alovudine 1.0 mg entered: 18 treated: 18 analysed (for primary endpoint): 18 Treatment 3: alovudine 0.5 mg entered: 13 treated: 13 analysed (for primary endpoint): 13 Treatment 4: placebo entered: 21 treated: 21 analysed (for primary endpoint): 20
Diagnosis and main criteria for inclusion:	At study entry, patients were males or females of ≥ 18 years of age; HIV positive; experienced with nucleoside analogue reverse transcriptase inhibitors (NRTIs), non-nucleoside analogues reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs); and presented with at least two thymidine analogue resistance mutations (TAMs) on codons 41, 67, 70, 210, and 215 of the reverse transcriptase gene. At study entry, patients had to have a HIV viral load between >1,000 copies /mL and ≤75,000 copies/mL, a CD4+ cell count >50 cells/mm^3 and had to be on a stable antiretroviral regimen without stavudine or zidovudine for at least 6 weeks and stable regimen of medications for at least 12 weeks.
Test product:	Alovudine 0.5 mg (hard gelatine capsule) and matching placebo
dose:	0.5 mg, 1.0 mg, or 2.0 mg once a day
mode of admin.:	oral
batch no.:	B040101 and B040104
Duration of treatment:	1 month
Reference therapy:	Not applicable
dose:	
mode of admin.:	
batch no.:	

Name of company: Boehringer Ingelheim		**Tabulated Study Report**		
Name of finished product: Alovudine		**SUPPLEMENTARY SHEET**		
Name of active ingredient: Alovudine		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:**		**Addendum No.:**
Report date: 24 May 2005	**Number:** U05-1667	**Study period (dates):** 01 APR 04 – 15 DEC 04		

Criteria for evaluation:

Efficacy:

The primary objective was to determine the mean change in HIV viral load from baseline to Week 4 in three alovudine dose groups (0.5 mg, 1.0 mg and 2.0 mg) compared with a placebo group in highly experienced HIV-infected patients.

Secondary endpoints included the proportion of patients experiencing a drop in viral load of ≥ 1 $\log_{10}$ from baseline to Week 4, changes in viral load at each study visit, and the changes in CD4+ and CD8+ cell counts at each study visit.

Safety:

Safety endpoints were proportions of patients with adverse events, serious adverse events, discontinuations due to adverse events and DAIDS Grade 2 or greater laboratory test abnormalities at Week 4; and median changes from baseline to Week 4 in laboratory test values.

Statistical methods:

Continuous endpoints were analysed with an analysis of covariance, with baseline as a covariate. All analyses were repeated using Wilcoxon-rank-sum tests to ensure against violated normality assumptions. Binary endpoints were analysed with a Fisher exact test. Correlations were evaluated with Pearson's r and Kendall's tau. No adjustments for multiple pairwise comparison testing were made because this was an exploratory study.

SUMMARY – CONCLUSIONS:

Efficacy results:

Two major conclusions concerning efficacy can be drawn from this trial:

- Alovudine significantly decreased viral load after 4 weeks of treatment compared with placebo (e.g., 0.42 $\log_{10}$ copies/mL in the 2.0 mg group and 0.3 $\log_{10}$ copies/mL in the 1.0 mg group). Six patients obtained a 1 $\log_{10}$ copies/mL drop in viral load at least once during the study. These patients received 1.0 mg of alovudine (three patients), placebo (two patients) or 2.0 mg of alovudine (one patient).
- A significant difference in viral load reduction was observed between the 2.0 mg and 1.0 mg doses and the placebo group and between the 2.0 mg group and the 0.5 mg dose group of alovudine.

Safety results:

This study did not reveal any unexpected adverse events or serious adverse events. The most frequent adverse events were diarrhoea and headache. No changes in transaminases (increase), white blood cells or lymphocytes (decrease) were found. Minor decreases were observed for haemoglobin and reticulocyte cell counts.

Name of company: Boehringer Ingelheim		**Tabulated Study Report**		
Name of finished product: Alovudine		**SUPPLEMENTARY SHEET**		
Name of active ingredient: Alovudine		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:**		**Addendum No.:**
Report date: 24 May 2005	**Number:** U05-1667	**Study period (dates):** 01 APR 04 – 15 DEC 04		

Conclusions:

Alovudine significantly decreases HIV viral load after 1 month, with median decreases of 0.3 $\log_{10}$ copies/mL in the 1.0 mg group and 0.42 $\log_{10}$ copies/mL in the 2.0 mg group compared with placebo. Six patients obtained a 1.0 $\log_{10}$ copies/mL drop in viral load at least once during the study. These patients received 1.0 mg of alovudine (three patients), placebo (two patients) or 2.0 mg of alovudine (one patient).

It was not possible to exclude the decreases in reticulocyte and haemoglobin test values in the 1.0 mg and 2.0 mg groups as early signal of bone marrow toxicity.