Synopsis

Identifier: GM2005/00347/00 **Study Number:** CCR102881

Title: A Phase IIb, 96 week, randomised, partially double-blinded, multicentre, parallel group, repeat dose study to evaluate the safety, tolerability, pharmacokinetics and antiviral effect of GW873140 in combination with COMBIVIR (lamivudine and zidovudine) upon selected immunological and virological markers of HIV-1 infection in antiretroviral therapy naive adults

Investigators: Multicenter study

Study centers: The study was conducted at 24 centers in the European Union (EU) and 33 centers in the United States (US), and 4 centers in Canada.

Publications: None at the time of this report.

Study Period: Start Date: 14 January 2005 – Early Termination Date: 15 September 2005 - Completion Date: 30 January 2006.

Phase of Development: IIb

Objectives:

Primary: to select an aplaviroc (APL; GW873140) dose for further evaluation based on comparison of the short-term antiviral activity, safety, and tolerability of different oral doses of APL in combination with COMBIVIR™ (COM; lamivudine/[3TC]zidovudine [ZDV]) in human immunodeficiency virus type 1 (HIV-1) infected therapy-naïve subjects.

Secondary:

- to assess the HIV-1 RNA decay rate over the initial weeks of treatment;
- to assess the long-term safety and antiviral activity of APL in combination with COM in HIV-1 infected therapy-naïve subjects;
- to explore the longitudinal effects of a APL-containing or control regimen on plasma viral tropism;
- to assess the development of viral resistance to APL and other on-study drugs;
- to describe the pharmacokinetic (PK) parameters of APL in HIV-1 infected subjects receiving combination therapy;
- to assess the potential for pharmacokinetic interaction between APL and ZDV or 3TC;
- to explore exposure-response relationships (e.g., the relationship between PK parameters and HIV-1 RNA or occurrence of adverse events [AEs]) and to explore the effect of various demographic factors on PK parameters;

- to evaluate the effect of different doses of APL plus COM on selected virologic and immunological markers of HIV infection relative to a standard of care regimen;
- to explore how bothersome certain symptoms are for subjects taking COM plus APL or efavirenz (EFV), and how symptoms impact on health related quality of life.

Methodology: The study consisted of a 28-day screening period (which could have been extended to 35 days, e.g., to ensure availability of viral tropism test results), a 96-week treatment phase consisting of both a 48-week randomized phase and a 48-week non-randomized phase, and a 4-week post-treatment follow-up phase. After a safety signal, the protocol was amended to collect 12 weeks of post-treatment follow-up for those subjects receiving aplaviroc. The randomized period began on Day1/Baseline and was planned to continue through Week 48. At Day 1 (Baseline), subjects with R5-tropic virus were randomized 2:2:1 to one of the following three treatment groups: APL 600mg twice daily (BID) + placebo BID + COM BID (APL 600mg BID group) *or* APL 800mg BID + COM BID (APL 800mg BID group) *or* efavirenz (EFV) once daily (QD) + COM BID (COM+EFV group).

Number of subjects: The study was terminated due to treatment-emergent hepatotoxicity that occurred among some subjects receiving APL on this and the parallel study (CCR100136) of treatment naïve, HIV-1 infected subjects. A total of 147 subjects were randomized (2:2:1) to three treatments: APL 600mg BID, APL 800mg BID, and EFV, each in combination with COM. Of these, 145 subjects received at least one dose of study medication. Based on a study termination cutoff of 15 September 2005, three subjects were randomized and started treatment too late to have been able to complete 12 weeks on treatment. Of the remaining subjects, 115 (81%) completed the 12-week Treatment Phase and 112 subjects (77%) had additional data included in the Follow-up Phase. Twenty-seven subjects (19%) did not complete the 12-week Treatment Phase.

Diagnosis and main criteria for inclusion: HIV-1 infected male or female subjects aged 13 years or older (or ≥18 where required by local regulatory agencies) were allowed to participate in the study. Subjects had to have screening plasma HIV-1 RNA ≥10,000 copies/mL, CD4+ cell count of ≥100 cells/mm^3, and HIV-1 utilizing cellular chemokine receptor 5 (CCR5) (R5-tropic) based on viral tropism assessment, and be antiretroviral therapy (ART)-naive. In addition, subjects had to have no drug resistance mutations in the HIV-1 reverse transcriptase (RT) as determined by polymerase (*pol*) genotyping.

Treatment and administration: The dosing regimens for this study were:

- Treatment A = APL 600mg BID + 3TC 150mg BID/ZDV 300mg BID
- Treatment B = APL 800mg BID + 3TC 150mg BID/ZDV 300mg BID
- Treatment C = EFV 600mg QD + 3TC 150mg BID/ZDV 300mg BID

Batch numbers for APL 200mg tablets used in this study were 041045116, 041045118, 041040290, 041040724, 873140A-A-02P, and 873140A-A-01P.

Criteria for evaluation: Efficacy was assessed by monitoring of quantitative plasma HIV-1 RNA, lymphocyte subsets, and Centers for Diseases Control and Prevention (CDC)-defined HIV-associated conditions.

Safety was assessed by monitoring of clinical AEs and serious adverse events (SAEs), clinical laboratory tests, HIV-associated conditions, concomitant medications, electrocardiograms (ECGs) and vital signs during the treatment phase.

Analysis of viral tropism was carried out for all subjects with plasma HIV-1 RNA above the validated cut off of the Monogram PhenoSense Entry HIV Assay (≥1000 copies/ml). Further genotypic and phenotypic analyses were carried out for subjects with confirmed virologic failure.

Other evaluations included the PK parameters of APL, the potential for PK interaction between APL and ZDV or 3TC, and the impact of clinical symptoms on health-related quality of life.

Statistical methods: This study was not designed to evaluate formal statistical hypotheses. Rather, the design was based on an approach of estimation of early response in order to screen out ineffective regimens of APL. The planned sample size was 125 subjects (50 subjects in each of the two APL groups and 25 subjects in the COM+EFV group). The sample size was based upon ensuring that there was a high probability that a dosage regimen with truly poor response would not be selected for further study, while allowing for the formal consideration of other factors in dose selection should efficacy be similar across dosage regimens.

The primary analysis was to compare the proportion of responders with plasma HIV-1 RNA <400 copies/mL among subjects within each APL dosage regimen to the maximum observed response rate in these regimens. Dose selection was planned to be based on the observed response rates at Week 12, along with considerations for other outcomes.

Summary:

Safety:

- The study was terminated due to treatment-emergent hepatotoxicity that occurred among some subjects receiving APL. Specifically ALT and total bilirubin elevations were observed in some subjects, including one case of severe hepatic cytolysis.
- The reasons for the observed hepatotoxicity with APL are currently unknown; hepatotoxicity did not appear to be associated with APL dose. Genetic predictors of APL-associated hepatotoxicity are currently undergoing investigation, and will be the subject of a separate report.
- More subjects treated with APL experienced treatment emergent gastrointestinal (GI) AEs (all grades) than did subjects treated with COM+EFV. Specifically, diarrhea, nausea, and vomiting were each more than twice as likely to be observed in the APL treatment arms. No substantial differences were seen between the two APL dosing arms. These events were infrequently treatment-limiting although a trend toward a slightly higher discontinuation rate for GI events was noted among APL 800mg BID subjects.

- Two subjects each reported SAEs of anemia, depression, pyrexia, and drug abuse. Other than the hepatic events described above, these SAEs were not attributed to APL.
- One subject died during the study due to Burkitt's lymphoma. This event was not considered to be attributable to APL.
- The relative risk (95% confidence interval [CI]) of experiencing an 'Infections and Infestations SOC' AE in the APL containing groups relative to the COM+EFV arm was 1.257 (0.528, 2.994). There is no increased risk of infections and infestations on APL.

Efficacy:

- In general for the primary endpoint analysis, response rates were similar between the APL dosage regimens; however, a moderately diminished response relative to COM+EFV was noted overall, especially in the higher viral load stratum.
- Similar increases in CD4+ cell counts were observed across all treatment groups.

Pharmacokinetics:

- APL demonstrated nonlinear PK. The increase in APL AUC(0-τ), Cmax and Cτ parameters was more than proportional to the increase in dose. Inter-subject variability in APL PK parameters was high, especially for the 800mg BID group.
- The geometric mean plasma APL AUC(0-τ) values of 1184 and 2733ng.h/mL for the 600mg and 800mg BID dose groups, respectively, met or exceeded the antiviral target AUC based on the 10-day monotherapy study GSK813140/005 [GSK Document Number RM2004/00095/00].
- The geometric mean plasma ZDV and 3TC AUC(0-τ) values observed in this study were consistent with previously reported data.

Pharmacokinetics/Pharmacodynamics:

- No relationships between APL AUC(0-τ), Cmax or Cτ and measures of antiviral response were detected in the subset of subjects who participated in Week 12 Intensive PK.

Health Outcomes:

- APL subjects reported an increase in bothersome GI symptoms compared to baseline and the EFV arm, which was sustained over time. The Health Outcomes results therefore re-enforced the findings observed in the overall safety and tolerability profile of APL in this study.

Viral Genotyping, Phenotyping and Tropism Testing:

- Protocol defined virologic failure was infrequent in this study (8/145 subjects or 6%). Failures were limited to the APL-containing groups. Despite the similar response rates between the two APL-containing groups, the rate of protocol defined

virologic failure was higher in the 600mg APL BID group (10%) compared to the 800mg APL BID group (3%).

- Reduced susceptibility (>3 fold change IC_{50}) to APL at the population level was not observed in any subjects with virologic failure.
- Resistance to 3TC may have contributed to virologic failure in subjects receiving an APL-containing regimen.
- Tropism readouts were stable in the majority of subjects prior to and after the administration of randomized treatment. Tropism readout changes were observed in a minority of subjects prior to treatment, as well as in responders and virologic failures. The clinical utility of tropism testing remains to be determined.

Conclusions:

- The study was terminated due to treatment-emergent hepatotoxicity that occurred among some subjects receiving APL. Specifically ALT and total bilirubin elevations were observed in some subjects, including one case of severe hepatic cytolysis.
- More subjects treated with both APL regimens experienced treatment emergent GI AEs (all grades) than did subjects treated with COM+EFV. Had the program continued, close monitoring of GI toxicity would have been a priority in further studies.
- While target plasma concentrations of APL were achieved, the antiviral activity of APL as the third agent in a triple drug regimen did not appear to be comparable to COM+EFV.
- Protocol-defined virologic failure was infrequent in this study (6%) and was not associated with the development of resistance to APL or a change in tropism readout. Resistance to 3TC may have been a component of virologic failure for subjects receiving an APL-containing regimen.

Date of Report: 19 July 2006