Synopsis

Identifier: RM2005/00304/00 **Study Number:** CCR100136

Title: A Phase IIb, 96 week, randomized, open-label, multicenter, parallel-group, repeat-dose study to evaluate the safety, tolerability, pharmacokinetics and antiviral effect of different doses and regimens of GW873140 in combination with Kaletra (lopinavir and ritonavir) in HIV-1 infected antiretroviral therapy naive subjects

Investigators: Multicenter study

Study centers: The study was conducted at 36 centers in the United States (US), five centers in Canada and 38 sites in the European Union (EU).

Publications: None at the time of this report.

Study Period: Start Date: 13 December 2004 – Early Termination Date: 15 September 2005 - Completion Date: 27 March 2006.

Phase of Development: IIb

Objectives:

Primary: to select an aplaviroc (APL; GW873140) dose and dosage regimen for further evaluation based on comparison of the short-term antiviral activity, safety and tolerability of different oral doses of APL in combination with lopinavir (LPV)/ritonavir (r) in human immunodeficiency virus type 1 (HIV-1) infected therapy-naïve subjects.

Secondary:

- to assess the HIV-1 ribonucleic acid (RNA) decay rate over the initial weeks of treatment.
- to assess the long-term safety and antiviral activity of APL in combination with LPV/r 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 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 safety and antiviral activity of different doses and dosing regimens of APL plus LPV/r on selected virologic and immunologic markers of HIV-1 infection relative to a standard of care regimen.

Methodology: This 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 the Day 1 (Baseline) visit, subjects with R5- and/or R5X4-tropic virus and with screening plasma HIV-1 RNA ≥50,000 copies/mL and CD4+ >100 cells/mm^3 were randomized 2:2:2:1 to receive APL 200mg BID, 400mg BID, 800mg once daily (QD) or 3TC/ZDV (COMBIVIR; COM). All subjects received LPV/r 400mg/100mg BID.

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 (CCR102881) of treatment naïve, HIV infected subjects. A total of 193 subjects were randomized (2:2:2:1) to four treatments: APL 200mg BID, APL 400mg BID, APL 800mg QD, and COM BID, each in combination with Kaletra (LPV/r) BID. Of these, 191 subjects received at least one dose of study medication. A total of 141 subjects initiated treatment early enough to have been able to complete 12 weeks of treatment, while the remaining 50 could not have completed 12 weeks of treatment based on the date the study was terminated (15 September 2005). A total of 133 of the 141 eligible subjects (94%) completed the 12-week Treatment Phase and 174 subjects (91%) had additional data included in the Follow-up Phase.

Diagnosis and main criteria for inclusion: HIV-1 infected male and 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 ≥50,000 copies/mL, CD4+ cell count ≥100 cells/mm^3, R5-tropic or R5X4-tropic virus (not more than 20 subjects harboring R5X4-tropic virus at screening were to be randomized into the study), and be antiretroviral therapy (ART)-naïve. Subjects were not allowed to participate in the study if they had plasma X4-tropic virus only.

Treatment and administration: The dosing regimens used in this study were:

- Treatment A = APL 200mg BID + LPV/r 400mg/100mg BID
- Treatment B = APL 400mg BID +LPV/r 400mg/100mg BID
- Treatment C = APL 800mg QD + LPV/r 400mg/100mg BID
- Treatment D = 3TC 150mg/ZDV 300mg BID + LPV/r 400mg/100mg BID

Batch numbers for APL 200mg tablets used in this study were 051072212, 041045118, 041045116, 041040290, 041040724, 200088441A, 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 Disease 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 and for subjects enrolled with R5X4-tropic virus at screen.

Plasma samples for APL and ritonavir pharmacokinetic evaluation were collected for all subjects in each APL treatment group. LPV was also measured in plasma samples collected at the Week 12 visit in the intensive PK group.

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 175 subjects (50 subjects in each of the three APL groups and 25 subjects in the COM+LPV/r 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 with R5-only tropism (Intent-to-Treat; ITT-R5) in each APL dosage regimen to the maximum observed response rate in these regimens.

Summary:

Safety:

- The study was terminated due to treatment-emergent hepatotoxicity that occurred among some subjects receiving APL. Two subjects had a combined increase in alanine aminotransferase (ALT) and total bilirubin.
- 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 subjects in the control arm; an apparent dose response relationship was noted in the incidence of diarrhea, with subjects in the 400mg BID and 800mg QD arms demonstrating a higher incidence than those in the 200mg BID arm. However, these events were rarely treatment-limiting.
- SAEs were rarely reported in this study and none were attributed to APL. Approximately four months after discontinuing APL, one subject died as a result of end-stage liver failure (alcoholic cirrhosis, hepatitis C and portal hypertension with ascites, all of which predated treatment with APL). This event was thus not considered by the investigator 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+LPV/r arm was 1.727 (0.748, 3.987). The occurrence of Grade 3 and 4 infections was infrequent in both APL (2/165 subjects) and control (1/26 subjects) arms. These results indicate no statistically significant increase in the risk of developing an 'Infections and Infestations SOC' AE while receiving APL relative to the COM+LPV/r standard of care regimen over the short duration of follow-up in this study.

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 + LPV/r was noted overall.
- Similar increases in CD4+ cell counts were observed across all treatment groups.
- A limited number of subjects harboring R5X4-tropic virus were enrolled. These subjects did appear to respond to treatment but due to small numbers and the limited duration of follow up no meaningful conclusions could be drawn.

Pharmacokinetics:

- APL demonstrated nonlinear PK with high intersubject variability. The increase in APL area under the curve [AUC(0-τ)] and Cmax was more than proportional to the increase in dose.
- The 400mg BID and 800mg QD group had similar mean AUC(0-24) values. The 800mg QD treatment group had the highest geometric mean Cmax (approximately 9- and 2-fold higher than that of 400 and 200mg BID regimens), but the lowest Cτ (approximately 50% and 16% that of 200mg BID and 400mg BID regimens).
- The geometric mean plasma APL AUC(0-24) values of 2457, 7247 and 6584ng.h/mL for the 200mg BID, 400mg BID, and 800mg QD dose groups, respectively, met or exceeded the target AUC(0-24) of 1900ng.h/mL determined in the 10-day monotherapy Study ID 873140/002 [GSK Document Number RM2004/00215/00].
- LPV and RTV PK parameters were consistent with previously reported values.

Pharmacokinetics/Pharmacodynamics:

- No consistent 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.

Viral Genotyping, Phenotyping and Tropism Testing:

- Protocol defined virologic failure was infrequent in this study (11/191 subjects or 6%).
- No treatment emergent nonnucleoside reverse transcriptase inhibitor (NNRTI), major nucleoside reverse transcriptase inhibitor (NRTI) or major protease inhibitor (PI)

mutations were observed in any of the subjects with virologic failure across all treatment groups. Pre-existing NRTI or NNRTI mutations were detected in 3 subjects. None of the subjects with major PI mutations at baseline experienced virologic failure.

- Reduced susceptibility to APL (>3 fold change 50% inhibitory concentration [IC_{50}]) at the population level was observed at only a single visit in one subject prior to the time of virologic failure. No other subjects with virologic failure had evidence of reduced APL susceptibility at the population level.
- Tropism readout changes were detected in a minority of subjects in the absence of therapy as well as a minority of responders and virologic failures on randomized treatment, suggesting that 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. Two subjects had combined increased ALT and increased total bilirubin.
- More subjects treated with APL experienced treatment emergent GI AEs (all grades) than subjects in the control arm; an apparent dose response relationship was noted in the incidence of diarrhea, with subjects in the 400mg BID and 800mg QD arms demonstrating a higher incidence of diarrhea than the 200mg BID. However, these events were rarely treatment-limiting.
- While target plasma concentrations of APL were achieved, the antiviral activity of APL as part of a nucleoside-sparing two drug regimen did not appear to be comparable to COM+LPV/r.
- A limited number of subjects harboring R5X4-tropic virus were enrolled. These subjects did appear to respond to treatment but due to small numbers and the limited duration of follow up no meaningful conclusions could be drawn.
- 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.

Date of Report: 19 July 2006