1. TITLE

A Phase III, randomized, double-blind, placebo-controlled, multicenter, parallel group study to compare the efficacy and safety of GW873140 400mg twice daily (BID) in combination with a ritonavir (RTV)-containing optimized background therapy (OBT) regimen, versus placebo plus OBT over 48 weeks in human immunodeficiency virus type-1 (HIV-1) infected, treatment-experienced subjects with drug-resistant CCR5/CXCR4-tropic (R5X4) virus.

1.1. RATIONALE

Given the unmet medical need, the prevalence of R5-tropic and R5X4-tropic HIV-1, and the *in vivo* potency observed, APL appeared to be a promising new antiretroviral agent for treatment-experienced subjects infected with HIV-1.

However, due to the occurrence of treatment emergent idiosyncratic hepatotoxicity in some subjects receiving APL in the Phase IIB and III studies, all studies, including this one, were terminated by 24 October 2005. As this study was terminated prior to completing enrollment, there is insufficient data available to address the objectives of the study. Hence, this study data will be presented in the condensed study report format.

2. INVESTIGATOR(S)

CCR104458 was a global, multicenter study.

3. STUDY CENTER(S)

This study was conducted at 10 investigator sites in the US and at one site in Europe (Belgium). These statements reflect the sites that were actively enrolling patients at the time the APL development program was terminated.

4. PUBLICATION(S)

No publications at the time of this report.

5. STUDY PERIOD

The first subject was enrolled 5 August 2005. Early Termination Date: October 2005. Completion Date: 27 June 2007.

Given the urgent need for treatment-experienced subjects to access to new antiretrovirals, a small number of patients were allowed to remain on APL open-label compassionate use treatment after the premature termination of the program; at the time of this report one subject in this study remains on active therapy.

6. PHASE OF DEVELOPMENT

Phase III

7. OBJECTIVES

7.1. Primary Objective

The primary objective was to demonstrate the superiority of APL 400mg BID plus OBT compared to placebo plus OBT, as measured by the difference in plasma HIV-1 RNA average area under the curve minus baseline (AAUCMB) between the two treatment arms at 24 and 48 weeks. However, due to the premature termination of enrollment, the primary objectives will not be assessed formally as planned.

As secondary objectives were also not assessed formally as planned, they are not listed here, but can be found in Attachment 1, Section 2.2.

The original protocol was amended four times. The amendments are described briefly below; for details of the protocol and protocol amendments, please refer to Attachment 1.

In general, Amendment 1 made changes in the primary objective and primary endpoint with clarifications made to the statistical plan for the 24 and 48 week analyses, clarified wording regarding provision of tropism and resistance testing and results, added additional plasma samples for storage, clarified wording regarding analysis of APL sensitivity, revised statement regarding color of APL or placebo tablets, and changed frequency of fasting lipids testing. Amendment 2 outlined new toxicity information and prohibited enrollment of subjects with pre-existing liver disease and provided for closer safety monitoring for liver toxicities. After careful review of the available safety information Amendment 3 provided for termination of the Phase 3 studies and the open-label option for those patients who were responding to treatment. Lastly, Amendment 4 removed the protocol requirement for long-term follow-up; those patients who enrolled in the open-label option were still required to be followed for 12 weeks after discontinuing APL.

7.2. Endpoint(s)

7.2.1. Primary Endpoints

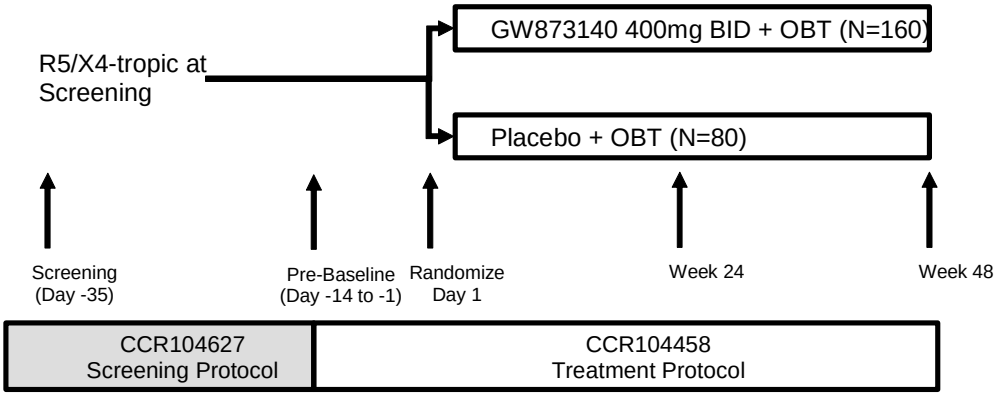
The primary endpoint of this study was the antiviral activity of APL 400mg BID plus OBT versus placebo plus OBT, following 24 and 48 weeks of treatment as measured by plasma HIV-1 RNA AAUCMB. Due to the premature termination of the study and the limited data available, this endpoint was not evaluated inferentially.

Secondary endpoints, as listed in Attachment 1, Section 3.2, were not evaluated formally and descriptive statistics only are provided.

8. METHODOLOGY

CCR104458 was a Phase III, randomized, multicenter, double-blind, placebo-controlled study in HIV-1 infected, treatment-experienced subjects with drug-resistant R5X4-tropic virus; subjects with R5-tropic only, X4-tropic only, or non-phenotypeable virus detected in the plasma were excluded. Screening assessments occurred as part of Study CCR104627 (Attachment 2). Study design details are included in the CCR104458 protocol and amendments (Attachment 1). Subjects with R5X4-tropic virus were randomized 2:1 to receive APL 400mg BID or placebo in combination with OBT (see Figure 1).

Figure 1 Study Design



The OBT regimen was chosen by the investigator prior to randomization, based on the subject's prior treatment history, screening genotypic and phenotypic resistance testing results, and any prior resistance testing results if available. The OBT regimen consisted of between three and six drugs, one of which must have been a RTV-boosted PI. More details on permitted OBT regiments are provided in Attachment 1.

There were three phases in this study: 1) an initial randomized phase, 2) a non-randomized phase following protocol-defined virologic failure where open-label APL was administered, and 3) an "off study drug/on study" phase to follow-up subjects who either experienced protocol-defined virologic failure in the randomized phase, but did not receive APL in their subsequent regimen, or who received and subsequently discontinued open-label APL.

The protocol was amended four times prior to study termination to clarify the objectives and statistical plan, to prohibit enrollment of subjects with pre-existing liver disease or liver function test abnormalities, to provide closer safety monitoring for emergent liver toxicities (and ultimately study termination) and to allow subjects who were receiving APL and who, in the opinion of the investigator, were receiving clinical benefit that outweighed the apparent risks of liver toxicity, to be switched to open-label APL (Attachment 1).

9. NUMBER OF SUBJECTS

It was estimated that approximately 240 HIV-1 infected, ART-experienced adults with R5X4-tropic virus at screening would be enrolled and randomized at a ratio of 2:1. At the time of study termination, 19 subjects had been randomized: 13 subjects received APL + OBT and six subjects received placebo + OBT.

10. DIAGNOSIS AND CRITERIA FOR INCLUSION

Screening assessments occurred as part of protocol CCR104627. A subject was eligible for inclusion in CCR104458 if all of the following criteria applied:

- HIV-1 infected subjects aged 18 years or older. All subjects were counselled on the practice of safe sex throughout the study. Females were either of non-childbearing potential, or were of childbearing potential with a negative pregnancy test result within 35 days of administration of investigational product, and using a proven double barrier method of contraception.
- Screening plasma HIV-1 RNA ≥5000copies/mL.
- Total prior ART experience of at least three months and documented genotypic or phenotypic resistance to at least one compound in each of the following classes of antiretrovirals: nucleoside reverse transcriptase inhibitors (NRTIs, includes the nucleotide reverse transcriptase inhibitor, tenofovir), non nucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs).
- R5X4-tropic virus according to viral tropism assessment.
- Current receipt of an unchanged "pre-study" ART regimen for at least four weeks prior to screening in CCR104627 protocol; this pre-study regimen may be no ART. Subjects must remain on this regimen until randomization (Day 1).
- Ability to receive a RTV-boosted PI as part of their OBT regimen.
- Ability to understand and comply with protocol requirements, instructions and protocol-stated restrictions.
- Signed and dated written informed consent prior to initiation of pre-baseline study procedures.

Subjects with plasma sample tests as R5-tropic only, X4-tropic only, or non-phenotypeable based on viral tropism assessment at screening were excluded. Subjects with any prior receipt of an investigational CCR5 or CXCR4 antagonist were also excluded.

11. TREATMENT AND ADMINISTRATION

APL, APL placebo, and open-label APL for the non-randomized phase were defined as investigational product. There was only one active batch of 200mg tablets used. The input 'bulk' batch number was R159473. Once it was bottled at Ware UK, it was given the batch number R170352.

APL tablets were round, brown film-coated tablets containing 200mg (based on free base) APL, and the inactive ingredients lactose, microcrystalline cellulose, povidone, low-substituted hydroxypropyl cellulose and magnesium stearate. APL placebo tablets matched the appearance of the APL tablets and contained lactose, microcrystalline cellulose, sodium starch glycolate, and magnesium stearate. The film coat for both active and placebo tablets contained polyvinyl alcohol, macrogol/PEG 3350, talc, titanium dioxide, yellow iron oxide, and red iron oxide.

APL tablets or placebo tablets were administered orally as 400mg BID. Each dose was to be administered with food.

12. CRITERIA FOR EVALUATION

Study assessments and procedures used in this study are presented in Attachment 1, Section 6.

The following assessments were made:

Demographic and baseline assessments included prior ART history, 12 lead ECG, CDC classification, review of HIV associated conditions, concomitant medication and concomitant ART assessment, current medical conditions, hepatitis B and C serology.

Laboratory evaluations (hematology, chemistry and fasting lipids) and clinical evaluations were performed according to time and events schedules. Adverse events (AEs) occurring during the study were evaluated by the investigator and graded according to the Division of AIDS (DAIDS) toxicity scales, 2004. Additional details on detecting, documenting and reporting AEs and serious adverse events (SAEs) are provided in Attachment 1, Section 10.

Efficacy evaluations included plasma for quantitative HIV-1 RNA and, lymphocyte subsets, and assessment of CDC-associated conditions collected according to time and events schedules.

Blood plasma and Peripheral blood mononuclear cells (PBMCs) were collected and stored for virologic evaluation (including exploratory analyses for resistance, tropism, and envelope genotyping/phenotyping).

Blood samples were also collected for plasma PK evaluation. Additionally, if a subject agreed and consented, a whole blood sample was collected for potential pharmacogenetic exploration.

The HIV Symptom Index Questionnaire was used for subjects to self-evaluate how bothersome certain symptoms were. This was complemented by the EuroQol questionnaire, a standardized instrument for the measure of health related quality of life.

13. STATISTICAL METHODS

The study was planned to evaluate the statistical hypothesis that treatment with APL + OBT was superior to OBT alone. Due to the premature termination of the study this hypothesis, as well as any interim analyses, were not tested as planned.

Sample size considerations no longer apply due to the premature termination of the study.

Initially, there were two primary populations for analysis:

- The All Subjects Population included all subjects who had data in the study covered by this reporting effort following the completion of the screening assessments in CCR104627. This population was only be used for certain summaries related to subject accountability.
- The Intent to Treat (ITT) Population: defined as all subjects randomized with evidence of receiving at least one dose of study medication. This was the primary population for all efficacy and safety analyses.

An additional population, the Open Label population, was to be used to describe the subjects who entered the compassionate use extension phase of the study. This population consists of the subjects who were allowed to enter this phase of the study following the termination of the study to enrollment.

No formal treatment comparisons were performed. Descriptive summary statistics only are provided.

For safety analyses, data were summarized for the 'Treatment Phase', which included data collected while on treatment (in the randomized phase or open label extension) and up to 30 days after study drug discontinuation, and for the 'Follow-up Phase', which includes data collected after the 30-day post-treatment period.

Data from the CCR104458 are presented here from a database freeze date of 28 June 2006: At this time, 4 subjects were ongoing in open-label, compassionate use, however, 3 of those patients have subsequently dropped, leaving 1 subject continuing in open-label compassionate use post the June cut-off. This subject was able to access an alternate CCR5 compound and on 27 June 2007 completed the 12 week follow-up. At that time the study CCR104458 was officially closed. Data subsequent to the May 2006 cut-off date for this one subject (i.e. between the data-cut date and final study closure date) are presented as a Patient Profile in Attachment 4 (Table 14.80).

14. SUMMARY

Study CCR104458 was terminated prior to completing full enrollment. Therefore, the available data are not able to address the study objectives and descriptive data only are provided.

14.1. Disposition of Subjects

Due to the early termination of this study, 25 subjects had been screened in study CCR104627, six of whom were screen failures. Of the 19 randomized subjects, 13 received APL + OBT and six received placebo + OBT. No subjects are currently receiving investigational product in the randomized phase of the study, and the majority of discontinuations were due to sponsor termination of the study (Table 1).

Table 1 Summary of Investigational Product Status (Randomized Phase, Study CCR104458)

	Number (%) Subjects	
	APL + OBT (N=13)	Placebo + OBT (N=6)
Completion status		
Completed	0	0
Prematurely withdrawn	13 (100)	6 (100)
Primary reason for withdrawal		
Adverse events	2 (15)	1 (17)
Subject decided to withdraw from study	1 (8)	0
Sponsor terminated study	8 (62)	5 (83)
Other	2 (15)	0

Source data: Table 14.34

In line with Protocol Amendment 3, four subjects who had no alternative ART options, and had been randomized to receive APL and who were considered to be deriving clinical benefit at the time of study termination were entered into a compassionate use, open-label extension to continue receiving APL (Source Table 14.13). [redacted]

14.2. Demographic and Baseline Characteristics

The demographic characteristics were generally well-balanced between the two treatment groups, despite the low subjects numbers (Table 2). The mean age of subjects was 45 years, and the majority were male (74%). All subjects were either White or of African American/African Heritage.

Table 2 Summary of Demographic Characteristics (Randomized Phase, Study CCR104458)

Demographic Characteristic	APL + OBT (N=13)	Placebo + OBT (N=6)	Total (N=19)
Age			
Median (range), years	43 (27-63)	44 (40-56)	43 (27-63)
Subjects <35, n (%)	1 (8)	0	1 (5)
Subjects ≥35, n (%)	12 (92)	6 (100)	18 (95)
Sex, n (%)			
Female	4 (31)	1 (17)	5 (26)
Male	9 (69)	5 (83)	14 (74)
Ethnicity, n (%)			
Hispanic or Latino	1 (8)	1 (17)	2 (11)
Not Hispanic or Latino	12 (92)	5 (83)	17 (89)
Race, n (%)			
African American/African Heritage	5 (38)	1 (17)	6 (32)
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific	0	0	0
White	8 (62)	5 (83)	13 (68)

Source data: Table 14.4 and Table 14.5

Baseline characteristics are summarized in Table 3. The majority of subjects recorded either homosexual contact or heterosexual contact as their primary HIV risk factor. Only two of the 19 subjects were co-infected with either Hepatitis B or Hepatitis C virus at Baseline. With the exception of CD4+ cell counts, baseline characteristics across treatment groups were generally well matched given the small number of patients who were enrolled prior to premature study termination.

Table 3 Summary of Baseline Characteristics (Randomized Phase, Study CCR104458)

Baseline Characteristic	APL + OBT (N=13)	Placebo + OBT (N=6)	Total (N=19)
HIV-1 RNA (log_{10} c/mL)			
Mean (SD)	4.51 (0.761)	4.89 (0.557)	4.63 (0.710)
Median (range)	4.55 (3.06-5.59)	4.67 (4.42-5.95)	4.62 (3.06-5.95)
CD4+ count (cells/mm^3)			
Mean (SD)	129 (113.93)	48 (39)	103 (102.82)
Median (range)	120 (19-326)	29 (19-110)	42 (19-326)
HIV risk factors, n (%)			
Homosexual contact	6 (46)	4 (67)	10 (53)
Heterosexual contact	6 (46)	2 (33)	8 (42)
Transfusion	1 (8)	0	1 (5)
CDC classification, n (%)			
A: Asymptomatic or lymphadeonopathy or acute HIV	4 (31)	1 (17)	5 (26)
B: Symptomatic, not AIDS	3 (23)	1 (17)	4 (21)
C: AIDS	6 (46)	4 (67)	10 (53)
Hepatitis B and C status, n (%)			
Hepatitis B non-reactive/reactive	12 (92)/1 (8)	6 (100)/0	18 (95)/1 (5)
Hepatitis C non-reactive/reactive	13 (100)/0	5 (83)/1 (17)	18 (95)/1 (5)

Source data: Table 14.7 and Table 14.8, Table 14.10, Table 14.11

Ninety-five percent of subjects had a current medical condition recorded at Baseline; the most common conditions were gastrointestinal disorders (37% of subjects) and skin and subcutaneous tissue disorders (37%), Table 14.9. All subjects were ART-experienced; the most common prior NRTIs, PIs and NNRTIs are summarized in Table 14.14. The majority of subjects (79%) had taken ≥3 NRTIs, 11% of subjects had taken ≥3 NNRTIs, and 58% of subjects had taken ≥3 PIs (Table 14.15).

All subjects received an NRTI and PI as part of their initial OBT regimen (Table 14.16). Enfuvirtide was included as part of the initial OBT for 31% of subjects in the APL + OBT group and for 100% of subjects in the placebo + OBT group (Table 14.16). The unique OBT regimen combinations for each subject are shown in Table 14.18.

All subjects were receiving a concomitant medication (including ART) at Baseline. The most commonly used non anti-infectives were loperamide hydrochloride (in five subjects and one subject in the APL + OBT and placebo + OBT groups, respectively), testosterone (in two and three subjects, respectively), and fluconazole (in three and two subjects, respectively) (Table 14.20).

14.3. Antiviral Response

Due to the premature termination of this study, no efficacy endpoints were evaluated inferentially. Descriptive summary statistics for the ITT population are provided.

A summary of the primary endpoint, plasma HIV-1 RNA AAUCMB, by treatment group over the entire treatment period is presented in Table 14.25. Median changes from Baseline in HIV-1 RNA by visit are presented in Table 14.24. The proportions of subjects with HIV-1 RNA levels <400copies/mL and <50copies/mL are presented by visit in Table 14.21 and Table 14.22, respectively. Changes in median CD4+ cell count are shown by visit in Table 14.28.

Only one subject reported an HIV-associated condition during treatment. [redacted]

Table 4 Summary of the Proportion of Subjects (n (%)) Responding Based on HIV-1 RNA <400copies/mL (ITT, Observed, Study CCR104558)

Visit	Response	APL +OBT (N=13)	Placebo + OBT (N=11)
Day 1	No	13 (100)	5 (100)
	Yes	0	0
Week 1	No	11 (92)	4 (80)
	Yes	1 (8)	1 (20)
Week 2	No	10 (83)	3 (75)
	Yes	2 (17)	1 (25)
Week 4	No	7 (70)	4 (80)
	Yes	3 (30)	1 (20)
Week 8	No	8 (89)	3 (75)
	Yes	1 (11)	1 (25)
Week 12	No	4 (67)	1 (100))
	Yes	2 (33)	0
Week 16	No	2 (50)	0
	Yes	2 (50)	0
Week 20	No	1 (33)	0
	Yes	2 (67)	0
Week 24	No	1 (50)	0
	Yes	1 50)	0
Week 32	No	1 (50)	0
	Yes	1 (50)	0
Week 40	No	0	0
	Yes	1 (100)	0

Source data: Table 14.21

14.4. Safety

14.4.1. Extent of Exposure

Median exposure to study drug was 58 days (range 22–330 days) for subjects receiving APL + OBT and 65 days (range 6–76 days) for subjects receiving placebo + OBT (Table 14.33).

14.4.2. Adverse Events

14.4.2.1. Adverse Events Regardless of Causality

Overall, 11/13 (85%) subjects receiving APL + OBT and 5/6 (83%) subjects receiving placebo + OBT reported at least one AE (all grades, all causality) during the Treatment Phase. The most frequent AEs were nausea and diarrhea (Table 5). No subjects reported AEs during the Follow-up Phase (Table 14.38).

Table 5 Summary of Adverse Events (Treatment Phase) by System Organ Class Reported in More than One Subject Overall

Adverse Event N(%)	APL + OBT (N=13)	Placebo + OBT (N=6)
Any Event	11 (85)	5 (83)
Gastrointestinal Disorders	7 (54)	3 (50)
Nausea	4 (31)	3 (50)
Diarrhea	6 (46)	0
Dry mouth	1 (8)	1 (17)
Vomiting	1 (8)	1 (17)
Infections and Infestations	5 (38)	2 (33)
Sinusitis	2 (15)	0
General Disorders and Administration Site Conditions	3 (23)	3 (50)
Fatigue	2 (15)	2 (33)
Psychiatric Disorders	2 (15)	1 (17)
Insomnia	1 (8)	1 (17)

Source data: Table 14.37

14.4.2.2. Drug-Related Adverse Events

The most common drug-related adverse events reported during the Treatment Phase were gastrointestinal disorders: 7/13 (54%) of subjects in the APL + OBT group and in 2/6 (33%) subjects in the placebo + OBT group. The majority of these events were diarrhea and nausea (Table 6).

Table 6 Summary of Drug-Related Adverse Events (Treatment Phase) by System Organ Class

Drug-Related Adverse Event N(%)	APL + OBT (N=13)	Placebo + OBT (N=6)
Any Event	7 (54)	2 (33)
Gastrointestinal Disorders	7 (54)	2 (33)
Diarrhea	6 (46)	0
Nausea	4 (31)	2 (33)
Dry mouth	1 (8)	1 (17)
Vomiting	1 (8)	1 (17)
Abdominal pain	0	1 (17)
Constipation	1 (8)	0
Gingival bleeding	0	1 (17)
General Disorders and Administration Site Conditions	1 (8)	2 (33)
Fatigue	1 (8)	1 (17)
Mass	0	1 (17)
Psychiatric Disorders	1 (8)	1 (17)
Insomnia	1 (8)	1 (17)
Investigations	1 (8)	0
ALT increased	1 (8)	0
AST increased	1 (8)	0

Source data: Table 14.39
ALT: alanine aminotransferase; AST: aspartate aminotransferase

14.4.3. Deaths

There were no deaths reported up to the cut-off date (Table 14.45), nor were there any deaths reported through the open-label compassionate use period.

14.4.4. Serious Adverse Events

Two subjects reported SAEs while on treatment (Table 14.41). Case narratives are provided in Section 18. No SAEs were reported during the open-label compassionate use period.

14.4.5. Adverse Events Leading to Discontinuation of Investigational Product

Three subjects discontinued study drug during the Treatment Phase due to AEs; two subjects in the APL + OBT group due to increases in alanine amino transferase (ALT), aspartate amino transferase (AST) and lipase; and one subject in the placebo + OBT group due to abdominal pain, nausea, vomiting and fatigue (Table 14.43).

14.4.6. Pregnancies

No subjects became pregnant up to the cut-off date (Table 14.46) or during the open-label compassionate use period.

14.4.7. Clinical Laboratory Evaluations

A summary of the clinical chemistry data by visit is provided in Table 14.47 for the Treatment Phase and in Table 14.48 for the Follow-up Phase. A summary of hematology data by visit is provided in Table 14.52 for the Treatment Phase and in Table 14.53 for the Follow-up Phase.

Treatment emergent laboratory abnormalities (all Grades) are summarized in Table 14.51. The following Grade 3/4 abnormalities were reported in subjects receiving APL + OBT: Grade 4 ALT (1 subject); Grade 4 AST (1 subject); Grade 4 lipase (1 subject); and Grade 4 total bilirubin (1 subject).

14.5. Health Outcomes

Data from the HIV Symptom Index questionnaire and the EuroQoL questionnaire are provided in Attachment 3 (Listing 14.59, Listing 14.60), respectively.

14.6. Pharmacokinetics/Pharmacodynamics

No clinical pharmacology data are reported. Blood samples for PK were collected from several subjects that reached Week 4 of dosing. APL (aplaviroc) plasma concentrations were measured by a validated LC/MS/MS assay [GlaxoSmithKline Document Number RD2004/00895/00] and the resulting concentration-nominal time data are stored according to study number in the GlaxoSmithKline SMS2000 database. Due to termination of the study, no pharmacokinetic or statistical analyses were performed on the plasma concentration data.

14.7. Pharmacogenetic Data Analyses

Pharmacogenetic (PGx) research was initiated on PGx samples collected in the APL Phase 3 clinical development program to investigate variation in subject response (e.g., PK, efficacy and adverse events). PGx samples collected in this study were included in this PGx experiment. The PGx research is ongoing and results of the PGx analyses will be summarized in a separate report.

Among the subjects randomized in the study, 17 subjects provided a blood sample for PGx research, however one subject later withdrew consent. Among those, 17 subjects had sufficient DNA for inclusion in the PGx experiment.

14.8. Viral Genotyping/Phenotyping

Descriptive genotypic and phenotypic results only are provided for virology data for the Intent to Treat and Virologic Failure populations, due to the premature termination of the study.

14.8.1. Intent to Treat (ITT) Population

Viral Tropism

Tropism test results were collected using the PhenoSense HIV Entry assay (Monogram BioSciences, Inc). This assay measures coreceptor usage by creating a population of pseudovirus containing the HIV-1 env gene from the sample and exposing that population on to a cell line engineered to express CD4+ and either CCR5 or CXCR4. The readout of the assay, relative light units (RLU), provides a qualitative measurement of HIV-1 coreceptor usage but can not distinguish a population of R5X4-tropic virus from a mixed population containing R5-tropic, R5X4-tropic, and/or X4-tropic virus. Therefore, in this section of results, the designation of DM-tropic (Dual or Mixed tropic) virus will be used rather than R5X4-tropic virus.

Screening for inclusion to CCR104458 took place in the context of Screening protocol CCR102627. Screening tropism results from this study and all available tropism data available for subjects is summarized below.

Tropism testing was performed at available timepoints during the randomized study. For the four subjects that re-consented to receive open label APL, tropism testing was performed at irregular intervals on samples with HIV-1 RNA levels >1000 copies/mL (validated cut-off for PhenoSense HIV Entry Assay).

Tropism Changes from Screen to Baseline

All 19 subjects in the ITT population had DM-tropic virus at the Screening visit. The Baseline visit was approximately 35 days post the Screening visit. [redacted]

Tropism Changes on Treatment

Seventeen of 18 subjects with Day 1 samples available (APL+OBT:12, placebo+OBT:5) had at least one sample post baseline for evaluation. Eight of 17 subjects (APL+OBT:7, placebo+OBT:1) did not have a change from DM-tropic virus while on study. Conversely, 9/17 subjects (APL+OBT:5, placebo+OBT:4) did have a change in tropism readout while on study. [redacted] Changes in tropism

readout are summarized below for the virologic responders (Table 7, Table 8, Table 9, Table 10, Table 11 and Table 12). The data for subjects with virologic failure are discussed in Section 14.8.2.

Table 7 HIV-1 RNA, CD4+ cell count, Tropism and APL Phenotype Results for Subject [redacted] (APL+OBT)

Source data: Table 14.74 and Table 14.77
a- "Visit" includes Calculated Visit, collection date and study day.
b- Not Available; due to low virus replication in the Monogram Biosciences assay.

[redacted] The HIV-1 RNA levels showed a steady increase throughout the course of study. Population tropism readouts changed to X4-tropic on Days 15 and 29 but CD4+ cell counts showed no change. No change in susceptibility to enfuvirtide (ENF) was detected on study. No treatment-emergent mutations in RT or PR were detected.

Table 8 HIV-1 RNA, CD4+ cell count, Tropism and APL Phenotype Results for Subject [redacted] (APL+OBT)

[redacted]

Source data: Table 14.74 and Table 14.77
a- "Visit" includes Calculated Visit, collection date and study day.
b- Not Available; due to low virus replication in the Monogram Biosciences assay.

[redacted] Virus from this subject was susceptible to APL and ENF throughout treatment. Treatment-emergent PR mutations L13V, L33F, M36M/V, M46L, F53L, Q58E, and G73S were detected at the Week 8 visit, consistent with the OBT the subject was receiving.

Table 9 HIV-1 RNA, CD4+ cell count, Tropism and APL Phenotype Results for Subject [redacted] (placebo + OBT)

Source data: Table 14.74 and Table 14.77
a- "Visit" includes Calculated Visit, collection date and study day.
b- Not Available; due to low virus replication in the Monogram Biosciences assay.

[redacted] No susceptibility information for APL was collected and virus from this subject had reduced susceptibility to ENF throughout treatment. No treatment emergent mutations in RT or PR were detected.

Table 10 HIV-1 RNA, CD4+ cell count, Tropism and APL Phenotype Results for Subject [redacted] (placebo + OBT) containing enfuvirtide

Source data: Table 14.74 and Table 14.77
a- "Visit" includes Calculated Visit, collection date and study day.

[redacted] Virus from this subject was susceptible to APL but had increasing reduced susceptibility to ENF while on treatment. Treatment-emergent, PR mutations A71T, and L90M were detected at the Week 8 visit.

Table 11 HIV-1 RNA, CD4+ cell count, Tropism and APL Phenotype Results for Subject [redacted] (placebo + OBT) containing enfuvirtide (ENF)

Source data: Table 14.74 and Table 14.77
a- "Visit" includes Calculated Visit, collection date and study day.

[redacted] Virus from this subject was susceptible to APL but had increasing reduced susceptibility to ENF while on treatment. No treatment-emergent mutations in RT or PR were detected.

Table 12 HIV-1 RNA, CD4+ cell count, Tropism and APL Phenotype Results for Subject [redacted] (placebo + OBT) containing enfuvirtide (ENF)

Source data: Table 14.74 and Table 14.77
a- "Visit" includes Calculated Visit, collection date and study day.

Virus from this subject was susceptible to APL but had increasing reduced susceptibility to ENF while on treatment. Treatment-emergent RT mutations, Y115F and PR mutation I54L, were detected at the Week 4 F/U visit.

Envelope Phenotypic Susceptibility to APL and Enfuvirtide (Population Level)

Phenotypic susceptibility for APL and ENF were determined using the PhenoSense HIV Entry assay (Monogram BioSciences, Inc). This assay measures susceptibility with a cell line engineered to express CD4 and only CCR5. As such, the susceptibility to APL of viruses that use solely CXCR4 for virus entry cannot be evaluated. As the clinically relevant phenotypic cut point for APL has not been determined, the biological cut point of 3 fold was used for R5- and DM-tropic samples. This cut point is based on the intrinsic assay variability. For ENF, susceptibility is determined in cells that express CD4+ and both CCR5 and CXCR4. Thus, for all virus samples, regardless of tropism readout, an ENF phenotype was attempted. A biological cut point of 6.8 fold was used to assess phenotypic susceptibility to ENF.

For the ITT population, APL phenotype testing was performed at Baseline and for available timepoints on drug. Testing was successful in 12 /17 subjects with baseline and at least one on-treatment sample. One subject had no APL susceptibility data due to low

viral replication in the R5 cell line of the PhenoSense HIV Entry assay. None of the 12 subjects had reduced APL.

Enfuvirtide was in the prior ART of 6/19 subjects (APL+OBT: 3, placebo+OBT:3). In CCR104458, subjects could use ENF as part of their OBT if deemed appropriate by the investigator. Subjects were stratified by ENF use in the OBT. Enfuvirtide was used in the OBT of 11/19 subjects, (APL+OBT: 5, placebo+OBT:6). Four of the 11 subjects (APL+OBT: 40971, placebo+OBT: 9013, 20020, and 40480) had prior ENF use.

Reverse Transcriptase and Protease Genotypic and Phenotypic Results

Genotypic ART mutations and phenotypic ART susceptibility results were determined using the PhenoSense GT assay (Monogram BioSciences, Inc.).

Screen sample genotypic summaries show the ITT population included in study to be treatment experienced. Most subjects have multi class drug-associated resistance mutations present.

Baseline genotypic and phenotypic data were available for 11 subjects in the APL + OBT and for three subjects in the placebo + OBT group (Table 14.69 and Table 14.74).

Of the 19 subjects, 11/19 subjects (APL+OBT: 7, placebo+OBT: 4) had paired samples to assess treatment-emergent RT/PR genotypic mutations. Four of these eleven subjects (APL+OBT: 2, placebo+OBT: 2) had no treatment-emergent genotypic mutations present. For the remaining 7/11 subjects, the following table summarizes the ART-associated mutations that emerged on treatment. Phenotypic reduced susceptibility was concordant for the 7 subjects with treatment-emergent ART –associated resistance mutations; none of these subjects were virologic failures.

Table 13 Summary of Subjects in CCR104458 with Treatment-emergent ART Resistance-associated Mutations

[redacted]

a. Source data: Table 14.69
b. "Visit" includes assessment and date of sample.
c. Study Day 104
d. Study Day 122

14.8.2. Virologic Failure Population

Criteria for protocol-defined virologic failure are included in the CCR104458 Protocol and Protocol Amendments (Attachment 1). [redacted] Listing of Tropism data for subjects with virologic failure can be found in Table 14.76. Listings of genotypic and phenotypic data by assessment period are provided in Attachment 3 (Listing 14.69, Listing 14.74), respectively. Each subject is summarized in an intext table.

Table 14 HIV-1 RNA, CD4+ cell count, Tropism and APL Phenotype Results for Subject [redacted] (APL+OBT)

[redacted]

Source data: Table 14.74 and Table 14.77
a- "Visit" includes Calculated Visit, collection date and study day.
b- Not Available; due to low virus replication in the Monogram Biosciences assay.
c-Confirmed protocol-defined virologic failure

[redacted] Population tropism readouts changed from DM-tropic to X4-tropic at Week 8 and CD4+ cell counts showed no change. Susceptibility to APL and ENF did not change throughout the course of study. No treatment-emergent mutations in RT or PR were detected.

Table 15 HIV-1 RNA, CD4+ cell count, Tropism and APL Phenotype Results for Subject [redacted] (APL+OBT) containing enfuvirtide (ENF)

a- "Visit" includes Calculated Visit, collection date and study day.
b- Not Available; due to low virus replication in the Monogram Biosciences assay.
c-Confirmed protocol-defined virologic failure

[redacted] Population tropism readouts changed from DM-tropic to X4-tropic at Week 2 and remained X4-tropic throughout the testing period; CD4+ cell counts showed no change. Susceptibility to APL did not change throughout the course of study but virus from this subject did develop a reduced susceptibility to ENF at Week 2 with a $FCIC_{50}$ of 32 which was retained throughout the study. No treatment-emergent mutations in RT or PR were detected.

Table 16 HIV-1 RNA, CD4+ cell count, Tropism and APL Phenotype Results for Subject [redacted] (APL+OBT)

Source data: Table 14.74 and Table 14.77
a- "Visit" includes Calculated Visit, collection date and study day.
b- Not Available; due to low virus replication in the Monogram Biosciences assay.
c-Confirmed protocol-defined virologic failure

Susceptibility to APL and ENF did not change throughout the course of study. No treatment-emergent mutations in RT or PR were detected.

Table 17 HIV-1 RNA, CD4+ cell count, Tropism and APL Phenotype Results for Subject [redacted] (APL+OBT)

Source data: Table 14.74 and Table 14.77
a- "Visit" includes Calculated Visit, collection date and study day.
b-Confirmed protocol-defined virologic failure

[redacted] Population tropism readouts were unchanged from DM-tropic and CD4+ cell counts showed no change. Virus from this subject remained susceptible to APL and ENF throughout the course of study. No treatment-emergent mutations in RT or PR were detected.

14.8.3. Summary Results for Open-Label Population

At the time of study termination, one subject was allowed to remain on study through open-label compassionate use treatment. HIV-1 RNA, CD4+ cell count, tropism and APL phenotype results for this subject are described in Table 18. Individual profile data displays for this subject can be found in Attachment 4 (Table 14.80).

Table 18 HIV-1 RNA, CD4+ cell count, Tropism and APL Phenotype Results for Subject [redacted] (APL+OBT)

[redacted]

Continued

[redacted]

a- "Visit" includes Calculated Visit, collection date and study day.
b- Confirmed protocol-defined virologic failure
c- No Result
d- Not available due to poor virus replication in the Monogram Biosciences assay

[redacted] Virus from this subject was sensitive to APL and ENF at study start. Only two on-study results of ENF susceptibility were available, Week 4 (Day 34) and Week 80 (Day 518), both were sensitive to ENF. No on-treatment results were available for RT/PR assessment of treatment-emergent mutations.

15. 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.

Given fewer than 10% of the subjects were enrolled prior to premature study termination no comparative conclusions are made due to the limited data available.

16. DATE OF REPORT

December 2007