1. TITLE

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

Two identical studies are combined and included in this report.

1.1. Rationale

CCR102709: A Phase III, randomized, double-blind, placebo-controlled, multicenter, parallel group study to compare the efficacy and safety of GW873140 (aplaviroc, APL) 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 (R5)-tropic virus.

CCR104456: A Phase III, randomized, double-blind, placebo-controlled, multicenter, parallel group study to compare the efficacy and safety of GW873140 (aplaviroc, APL) 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 (R5)-tropic virus.

Given the unmet medical need for new agents for patients with previous antiretroviral therapy (ART) experience, the prevalence of R5-tropic and R5/CXCR4 (X4)-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 both CCR102709 and CCR104456, were terminated on 24 October 2005. As these studies were terminated prior to the completion of enrollment, insufficient data were available to address the objectives of the study or to draw any conclusions. Hence, study data will be presented in the condensed study report format.

2. INVESTIGATOR(S)

CCR102709 and CCR104456 were both multicenter studies.

3. STUDY CENTER(S)

CCR102709 was conducted at 15 centers in the US and at one site in Canada.
CCR104456 was conducted at 1 center in Germany. 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

Start Date: the first subject was enrolled 2 August 2005. Early Termination Date: October 2005. Completion Date: 11 September 07.

Given the urgent need for treatment-experienced subjects to be able to access to new ARTs, a small number of subjects who had been randomized to APL were allowed to remain on open-label APL as compassionate use treatment after the premature termination of the program. Those subjects were allowed to remain on APL only if they had no evidence of liver toxicity and if they were deemed to be responding to treatment. At the time of study termination 11 subjects from CCR102709 and CCR104456 were all re-consented and allowed to continue on open-label APL. At the time of the database freeze for this report (28 June 2006), ten of those 11 subjects remained on active therapy. However, at the time this report (May 07) was written 7 subjects had subsequently dropped, leaving only 3 subjects remaining on open-label, compassionate use therapy (2 subjects in CCR102709 and 1 subject in CCR104456). The last subject in the open-label phase discontinued 11 September 2007; all data collected on subjects in the open-label population are included in the Patient Profile (Table 14.83 CCR102709, and Table 14.83 CCR104456 Patient Profiles).

6. PHASE OF DEVELOPMENT

Phase III.

7. OBJECTIVES

The primary objective of both studies was to demonstrate the superiority of APL 400mg BID plus OBT compared to placebo plus OBT, as measured by the proportion of responders with sustained plasma HIV-1 RNA <400copies/mL, defined by the outcomes of the time to loss of virological response (TLOVR) algorithm at 24 and 48 weeks. However, due to the premature termination of the study, the primary objectives were not assessed formally as planned.

Secondary objectives were also not assessed formally as planned and are not listed here, but can be found in Protocols and Protocol Amendments Attachment 1.

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.

7.1. Endpoint(s)

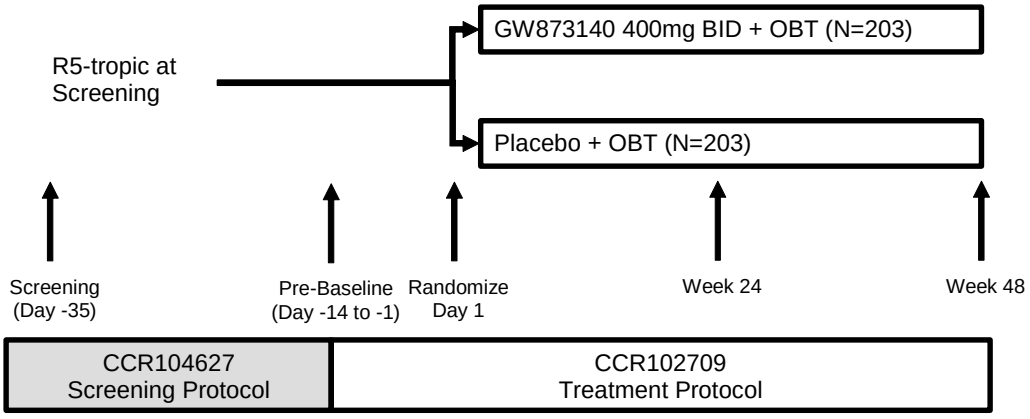
The primary endpoint of both studies was the proportion of subjects receiving APL 400mg BID plus OBT versus placebo plus OBT, with plasma HIV-1 RNA <400 copies/mL at Week 24 and 48 based on the outcomes from the TLOVR algorithm.

Secondary endpoints are not listed here, but can be found in Attachment 1.

8. METHODOLOGY

Both CCR102709 and CCR104456 were Phase III, randomized, multicenter, double-blind, placebo-controlled studies in HIV-1 infected, treatment-experienced subjects with drug-resistant R5-tropic virus; subjects with R5X4-tropic, X4-tropic only, or non-phenotypeable viruses detected in the plasma were excluded. Screening assessments occurred as part of Study CCR104627 [GlaxoSmithKline Document Number RM2006/00260/00]. Study design details are included in the CCR102709 and CCR104456 Protocols and Protocol Amendments (Attachment 1). Subjects with R5-tropic virus were randomized 1:1 to receive APL 400mg BID or placebo, in combination with OBT (Figure 1).

Figure 1 Study Design



The study design for CCR104456 was identical.

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 protease inhibitor (PI). More details on permitted OBT regimens are provided in Attachment 1.

There were three phases planned in these studies: 1) an initial Randomized Phase, 2) a Non-Randomized (Open-Label) 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 protocols were amended four times prior to study termination to clarify the objectives and statistical plan, to terminate the 'Off Study Drug/On Study' Phase, 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 406 HIV-1 infected, ART-experienced adults with R5-tropic virus at screening would be enrolled from multiple geographic regions and randomized at a ratio of 1:1 in each study. At the time of termination, 24 subjects had been randomized in CCR102709 and 1 subject has been randomized in CCR104456.

10. DIAGNOSIS AND CRITERIA FOR INCLUSION

Screening assessments occurred as part of protocol CCR104627. A subject was eligible for inclusion in either CCR102709 or CCR104456 if all of the following key criteria applied:

- HIV-1 infected subjects aged 18 years or older. All subjects were counseled 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 3 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 PIs.

- R5-tropic virus according to viral tropism assessment.
- Current receipt of an unchanged 'pre-study' ART regimen for at least 4 weeks prior to screening in CCR104627 protocol; this pre-study regimen may be no ART. Subjects must have remained on this regimen until randomization (Day 1).
- Ability to receive a ritonavir (RTV)-boosted protease inhibitor (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 testing as R5X4-tropic, X4-tropic only, or who were 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

For both studies, aplaviroc, 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 GSK Ware, UK, it was given the batch number R170352.

Aplaviroc 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. Aplaviroc 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.

Aplaviroc 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 both CCR102709 and CCR104456 are presented in Attachment 1, Section 6.

The following assessments were made:

Demographic and baseline assessments included prior ART history, 12 lead electrocardiogram (ECG), Centers for Disease Control and Prevention (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 pharmacokinetic (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 plan prior to study termination was to evaluate the statistical hypothesis that treatment with APL plus OBT was superior to OBT alone. The statistical methodology was identical in both CCR102709 and CCR104456; therefore any available data collected from both studies were combined and are presented in this report. Due to the premature termination of these studies, 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 studies covered by this reporting effort following the completion of the screening assessments in CCR104627. This population was only 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 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 Non-Randomized Phase [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 APL treatment period.

Data from the 2 studies are presented here from a database freeze date of 28 June 2006: at this time, 10 subjects were ongoing in open-label, compassionate use, however, seven of those patients have subsequently dropped, leaving two subjects in CCR102709 and 1 subject in CCR104456 continuing in open-label compassionate use post the June database freeze. On 11 September 2007 the last of these 3 subjects was able to access an alternate CCR5 compound and both studies were officially closed.

Additionally included in this statistical package are Patient Profiles ((Table 14.83 CCR102709 , and Table 14.83 CCR104456 Patient Profiles) -) for all randomized subjects (includes all data through 28 June 06) and Patient Profiles ((Table 14.83 CCR102709 , and Table 14.83 CCR104456 Patient Profiles)) for only those subjects that entered into the Open-Label phase (includes all open-label data through closure of the study [11 September 2007]).

14. SUMMARY

Studies CCR102709 and CCR104456 were terminated prior to completing full enrollment. Therefore, the available data are not able to address the study objectives and descriptive data only are provided. For the purposes of this report, data from study CCR104456 were pooled with data from Study CCR102709.

14.1. Disposition of Subjects

Due to the early termination of these studies, only 32 subjects were evaluated in the screening protocol CCR104627: 31 subjects in CCR102709 and one subject in CCR104456. Seven of these 32 subjects were screen failures (Table 14.1). The remaining 25 subjects were randomized: 24 subjects were enrolled in CCR102709 and 1 subject was enrolled in CCR104456. Of these 25 subjects, 13 were randomized to receive APL + OBT and 12 to receive placebo + OBT. One of these 12 subjects did not receive treatment with placebo + OBT; therefore the ITT Population for this analysis comprised 13 subjects in the APL + OBT group and 11 subjects in the placebo + OBT group (Table 14.2).

As of the cut-off date for this report no subjects are currently receiving investigational product in the Randomized Phase of either 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, ITT Population, Studies CCR102709 and CCR104456)

	Number (%) Subjects	
	APL + OBT (N=13)	Placebo + OBT (N=11)
Completion status		
Completed	0	0
Prematurely withdrawn	13 (100)	11 (100)
Primary reason for withdrawal		
Subject decided to withdraw from study	1 (8)	1 (9)
Sponsor terminated study	10 (77)	8 (73)
Other	2 (15)	2 (18)

Source data: Table 14.34

In line with Protocol Amendment 3, 11 subjects in CCR102709 and CCR104456 who had no alternative ART options, who had been randomized to receive APL and who were considered to be deriving clinical benefit at the time the studies were terminated, were entered into an open-label compassionate use extension to continue receiving APL (Table 14.36). One of these subjects discontinued study drug [virologic failure] prior to the database freeze date (28 June 2006) leaving 10 subjects ongoing. At the time of this report, seven of these subjects had subsequently discontinued study drug (due to insufficient viral load response [n=1], protocol-defined virological failure [n=3], availability of alternative ART options [n=2] and 'other' reasons [n=1]), leaving only two subjects in CCR102709 and one subject in CCR104456 still ongoing. Data for the subjects who entered the Open-Label compassionate use extension post the June database freeze date are provided as Patient Profiles ((Table 14.83 CCR102709 , and Table 14.83 CCR104456 Patient Profiles)).

14.2. Demographic and Baseline Characteristics

The demographic characteristics were generally well-balanced between the two treatment groups, despite the low subject numbers (Table 2). The majority of subjects were ≥35 years, and there were more males than females. All subjects were either White or African American/African Heritage.

Table 2 Summary of Demographic Characteristics (Randomized Phase, ITT Population, Studies CCR102709 and CCR104456)

Demographic Characteristic	APL + OBT (N=13)	Placebo + OBT (N=11)	Total (N=24)
Age			
Median (range), years	45 (37-59)	46 (32-51)	46 (32-59)
Subjects <35, n (%)	0	1 (9)	1 (4)
Subjects ≥35, n (%)	13 (100)	10 (91)	23 (96)
Sex, n (%)			
Female	2 (15)	2 (18)	4 (17)
Male	11 (85)	9 (82)	20 (83)
Ethnicity, n (%)			
Hispanic or Latino	0	3 (27)	3 (13)
Not Hispanic or Latino	13 (100)	8 (73)	21 (88)
Race, n (%)			
African American/African Heritage	3 (23)	3 (27)	6 (25)
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific	0	0	0
White	10 (77)	8 (73)	18 (75)

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. No subjects were known to be co-infected with Hepatitis B virus and only two subjects were known to be co-infected Hepatitis C virus at Baseline.

Table 3 Summary of Baseline Characteristics (Randomized Phase, ITT Population, Studies CCR102709 and CCR104456)

Baseline Characteristic	APL + OBT (N=13)	Placebo + OBT (N=11)	Total (N=24)
HIV-1 RNA (log_{10} c/mL)			
Mean (SD)	4.61 (0.746)	4.89 (0.428)	4.74 (0.625)
Median (range)	4.77 (3.32-5.76)	4.71 (4.32-5.66)	4.74 (3.32-5.76)
CD4+ count (cells/mm^3)			
Mean (SD)	169.5 (174.93)	156.4 (135.26)	163.5 (154.8)
Median (range)	125 (19-513)	134 (19-368)	129.5 (19-513)
HIV risk factors, n (%)			
Homosexual contact	9 (69)	7 (64)	16 (67)
Heterosexual contact	4 (31)	3 (27)	7 (29)
Injectable drug use	0	1 (9)	1 (4)
CDC classification, n (%)			
A: Asymptomatic or lymphadeonopathy or acute HIV	4 (31)	3 (27)	7 (29)
B: Symptomatic, not AIDS	0	2 (18)	2 (8)
C: AIDS	9 (69)	6 (55)	15 (63)
Hepatitis B and C status, n (%)			
Hepatitis B			
Non-reactive	12 (92)	9 (82)	21 (88)
Missing	1 (8)	2 (18)	3 (13)
Hepatitis C			
Non-reactive	11 (85)	8 (73)	19 (79)
Reactive	1 (8)	1 (9)	2 (8)
Missing	1 (8)	2 (18)	3 (13)

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

Ninety-six percent of subjects had a current medical condition recorded at Baseline; the most common conditions were psychiatric disorders (54% of subjects), nervous system disorders (42%) and gastrointestinal disorders (42%) (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, 13% of subjects had taken ≥3 NNRTIs, and 67% of subjects had taken ≥3 PIs (Table 14.15).

All subjects received an NRTI and PI, and 13% of subjects received an NNRTI as part of their initial OBT regimen (Table 14.16). Enfuvirtide (ENF) was included as part of the initial OBT for 62% of subjects in the APL + OBT group and for 73% 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 testosterone (in four subjects and three subjects in the APL + OBT and placebo + OBT groups, respectively) and acyclovir (in five and two subjects, respectively) (Table 14.20).

14.3. Antiviral Response

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

A summary of the primary endpoint, the proportion of subjects with HIV-1 RNA levels <400copies/mL, is presented by visit in Table 4. The proportion of subjects with HIV-1 RNA levels <50copies/ml is summarized by visit in Table 14.22. Median change from Baseline in HIV-1 RNA by visit is presented in Table 14.24. A summary of plasma HIV-1 RNA Average area under the curve minus baseline (AAUCMB) by treatment group for the entire study period is provided in Table 14.25. Changes from Baseline in median CD4+ cell count are shown by visit in Table 14.28.

No subjects reported any HIV-associated conditions emerging during treatment (Attachment 3 Listing 14.26).

Table 4 Summary of the Proportion of Subjects [n (%)] Responding Based on HIV-1 RNA <400copies/mL (ITT, Observed, Studies CCR102709 and CCR104456)

Visit	Response	APL +OBT (N=13)	Placebo + OBT (N=11)
Day 1	No	13 (100)	11 (100)
	Yes	0	0
Week 1	No	9 (90)	8 (100)
	Yes	1 (10)	0
Week 2	No	6 (46)	7 (88)
	Yes	7 (54)	1 (13)
Week 4	No	4 (31)	6 (67)
	Yes	9 (69)	3 (33)
Week 8	No	3 (25)	6 (67)
	Yes	9 (75)	3 (33)
Week 12	No	5 (45)	2 (67)
	Yes	6 (55)	1 (33)
Week 16	No	4 (40)	0
	Yes	6 (60)	0
Week 20	No	2 (25)	0
	Yes	6 (75)	0
Week 24	No	2 (29)	0
	Yes	5 (71)	0
Week 32	No	1 (17)	0
	Yes	5 (83)	0
Week 40	No	0	0
	Yes	3 (100)	0

Source data: Table 14.21

14.4. Safety

14.4.1. Extent of Exposure

At the time of the database freeze, median exposure to study drug was 182 days (range 72 to 325 days) for subjects receiving APL + OBT and 60 days (range 1 to 86 days) for subjects receiving placebo + OBT (Table 14.33). Of the 10 subjects on open-label, compassionate use, 3 subjects exposure to APL was greater than 1 year.

14.4.2. Adverse Events

14.4.2.1. Adverse Events Regardless of Causality

At the time of the database freeze, 11/13 (85%) subjects receiving APL + OBT and 5/11 (45%) subjects receiving placebo + OBT reported at least one AE (all grades, all causality) during the Treatment Phase. The most frequent AEs were gastrointestinal in nature (Table 5). One subject in each treatment group experienced at least one AE during the Follow-up Phase (Table 14.38); none of these AEs were considered by the investigator to drug related (Table 14.40).

Table 5 Summary of Adverse Events by System Organ Class Reported in More than One Subject Overall (Treatment Phase, ITT Population, Studies CCR102709 and CCR104456)

Adverse Event N(%)	APL + OBT (N=13)	Placebo + OBT (N=11)
Any Event	11 (85)	5 (45)
Gastrointestinal Disorders	9 (69)	3 (27)
Diarrhea	7 (54)	2 (18)
Nausea	3 (23)	1 (9)
Abdominal pain	1 (8)	1 (9)
General Disorders and Administration Site Conditions	3 (23)	2 (18)
Fatigue	2 (15)	0
Pyrexia	1 (8)	1 (9)
Infections and Infestations	2 (15)	3 (27)
Sinusitis	1 (8)	1 (9)
Nervous System Disorders	4 (31)	0
Headache	3 (23)	0

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 in 6/13 (46%) of subjects in the APL + OBT group and in 1/11 (9%) subjects in the placebo + OBT group. The majority of these events were diarrhea and nausea (Table 6).

Table 6 Summary of All Drug-Related Adverse Events by System Organ Class (Treatment Phase, ITT Population, Studies CCR102709 and CCR104456)

Drug-Related Adverse Event N(%)	APL + OBT (N=13)	Placebo + OBT (N=11)
Any Event	6 (46)	2 (18)
Gastrointestinal Disorders	6 (46)	1 (9)
Diarrhea	5 (38)	1 (9)
Nausea	3 (23)	0
Gastroesophageal reflux disease	1 (8)	0
Nervous System Disorders	2 (15)	0
Dysgeusia	1 (8)	0
Paresthesia	1 (8)	0
Skin and Subcutaneous Disorders	1 (8)	1 (9)
Lipodystrophy acquired	0	1 (9)
Rash generalized	1 (8)	0
General Disorders and Administration Site Conditions	1 (8)	0
Fatigue	1 (8)	0
Metabolism and Nutrition Disorders	0	1 (9)
Increased appetite	0	1 (9)
Muscoskeletal and Connective Tissue Disorders	1 (8)	0
Muscle spasms	1 (8)	0
Psychiatric Disorders	1 (8)	0
Depression	1 (8)	0
Restlessness	1 (8)	0

Source data: Table 14.39

There were no drug-related adverse events reported through the open-label compassionate use period.

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

There were no SAEs reported either during the Treatment Phase (Table 14.41) or the Follow-up Phase (Table 14.42). There were no SAEs reported through the open-label compassionate use period

14.4.5. Adverse Events Leading to Discontinuation of Investigational Product

No subjects discontinued due to AEs (Table 14.43, Table 14.44), nor were there any AEs leading to discontinuation reported through the open-label compassionate use period.
Pregnancies

No subjects became pregnant up to the cut-off date (Table 14.46), nor were there any pregnancies reported through the open-label compassionate use period.

14.4.6. 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 3 creatine kinase (two subjects), Grade 3 glucose, Grade 4 total bilirubin, and Grade 3 triglycerides (all in one subject each). Grade 4 elevated potassium was reported in one subject receiving placebo + OBT. Any Grade 3 or 4 lab abnormalities reported by subjects in the open-label compassionate use program are captured in the patient profiles. No Grade 3 or 4 lab abnormality was reported as an adverse event.

14.5. Health Outcomes

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

14.6. Pharmacokinetics/Pharmacodynamics

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.

Among the subjects randomized, 20 subjects in CCR102709 and 1 subject in CCR104456 provided a blood sample for PGx research, and among those, 20 subjects in CCR102709 and 1 subject in CCR104456 had sufficient DNA for inclusion in the PGx experiment. The PGx research is ongoing and results of the PGx analyses will be summarized in a separate report.

14.8. Viral Genotyping/Phenotyping

Descriptive genotypic and phenotypic results only are provided for virology data for the ITT and Virologic Failure populations, due to the premature termination of the study. Results for CCR102709 are presented here and a single case narrative for the 1 subject enrolled in CCR104456 is presented at the end of Section 14.8.

14.8.1. Intent to Treat Population (ITT) for CCR102709

14.8.1.1. 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 *env* gene from the sample and exposing that population 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 CCR102709 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 10 subjects in study CCR102709 that reconsented 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).

14.8.1.1.1. Tropism Changes from Screen to Baseline

All 24 subjects in the ITT population had R5-tropic virus at the Screening visit. The Baseline visit was approximately 35 days post Screening visit. [redacted]

14.8.1.1.2. Tropism Changes on Treatment

Of the 22 subjects in study and with Day 1 tropism data, 20/22 (APL+OBT: 11, placebo+OBT: 9) had at least one sample on treatment for evaluation of change in tropism readout. Fifteen of 20 subjects (APL+OBT: 7, placebo+OBT: 8) maintained R5-tropic virus throughout the study. Conversely, 5/20 subjects (APL+OBT: 4, placebo+OBT: 1) did have a change in tropism readout while on study. [redacted] Changes in tropism readout are summarized below for the virologic responders (Table 7 and Table 8). 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] (Placebo+OBT)

[redacted]

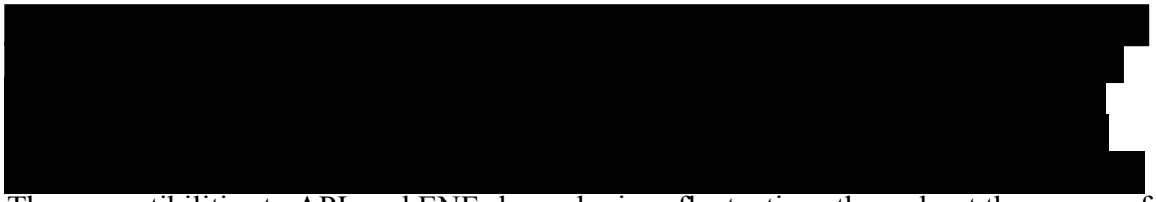
a. "Visit" includes Calculated Visit, collection date and study day.
b. No Result; HIV-1 RNA levels less than 1,000 copies/mL

[redacted]

Susceptibility to APL and enfuvirtide (ENF) showed minor variation through the course of the study.

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

Source data: Table 14.77 and Table 14.80
a. "Visit" includes Calculated Visit, collection date and study day.
b. Not Available; due to low virus replication in the Monogram Biosciences assay.



The susceptibilities to APL and ENF showed minor fluctuations throughout the course of study.

14.8.1.2. Envelope Phenotypic Susceptibility to APL and Enfuvirtide (Population Level)

Phenotypic susceptibility for APL and ENF was 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+ cell count 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 all 21 subjects (APL+OBT: 11, placebo+OBT: 10) with baseline and at least one timepoint on study for testing. None of the 21 subjects had reduced APL susceptibility (>3 $FCIC_{50}$).

Enfuvirtide was in the Prior ART of 11/24 subjects (APL+OBT: 6, placebo+OBT: 5). In all Phase 3 studies, 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 15/24 subjects, (APL+OBT: 7, placebo+OBT: 8).

Table 9 HIV-1 RNA, CD4+ cell count, Tropism and APL Phenotype Results for Subject (Placebo+OBT containing enfuvirtide)

Source data: Table 14.77 and Table 14.80
a. "Visit" includes Calculated Visit, collection date and study day.

No treatment emergent mutations in RT or PRO were observed.

14.8.1.3. 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.).

Baseline genotypic and phenotypic data were available for 12 subjects in the APL + OBT and for 11 subjects in the placebo + OBT group. A listing of genotypic and phenotypic data for the entire ITT population can be found in Table 14.71 and Table.14.77.

Screening sample genotypic summaries show the ITT population included in study to be treatment experienced. Most subjects had multi class drug-associated resistance mutations present. In general, phenotypic data was concordant with genotypic findings.

Of the 24 subjects, 12/24 subjects (APL+OBT:4, placebo+OBT:8) have paired samples to assess treatment-emergent RT/PR genotypic mutations. Seven of these twelve subjects (APL+OBT:2, placebo+OBT:5) had no treatment-emergent genotypic mutations present.

For the remaining 5 subjects (APL+OBT:2, placebo+OBT:3), the Table 10 summarizes the ART-associated mutations that emerged on treatment. In general, phenotypic data was concordant with genotypic findings.

Table 10 Summary of Subjects in CCR102709 with Treatment-emergent ART Resistance-associated Mutations

[redacted]

Source data: Table 14.71
a. "Visit" includes assessment and date of sample.

14.8.2. Virologic Failure Population for CCR102709

Criteria for protocol-defined virologic failure are included in the CCR102709 and CCR104456 Protocols and Protocol Amendments (Attachment 1). Four of the 24 subjects (17%) met the criteria for protocol-defined virologic failure (Table 14.32). [redacted] A listing of Tropism data for subjects is in Table 14.80. Listings of genotypic and phenotypic data by assessment period are provided in Table 14.71 and Table 14.77, respectively. Each subject will be summarized in an in text Table 11.

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

[redacted]

Source data: Table 14.77 and Table 14.80

a. "Visit" includes Calculated Visit, collection date and study day.
b. Confirmed protocol-defined virologic failure

[redacted] Population tropism readouts remained R5-tropic and CD4+ cell counts showed no change. Similarly, susceptibility to APL and ENF had minor fluctuations throughout the course of study. 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] (APL+OBT)

[redacted]

Source data: Table 14.77 and Table 14.80

a. "Visit" includes Calculated Visit, collection date and study day.
b. Confirmed protocol-defined virologic failure

[redacted]

Population tropism readouts changed from R5-tropic to DM-tropic at Week 4 (Day 15) and beyond. CD4+ cell counts remained similar throughout the course of study. Susceptibility to APL remained below an $FCIC_{50}$=1 with little fluctuation over time. Similarly, susceptibility to ENF remained relatively stable, despite being above the biological cutoff for reduced susceptibility. Treatment emergent mutations in RT (M184M/V) and PR (I54I/L) were detected at Week 12 (Day 87).

Table 13 HIV-1 RNA, CD4+ cell count, Tropism and APL Phenotype Results for Subject [redacted] (APL+OBT)

Source data: Table 14.77 and Table 14.80
a. "Visit" includes Calculated Visit, collection date and study day.
b. Confirmed protocol-defined virologic failure

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

[redacted]

Source data: Table 14.77 and Table 14.80

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] No on-treatment results were available for RT/PR assessment of treatment-emergent mutations.

14.8.3. Subject [redacted] from CCR104456

[redacted] This subject reconsented to go on to open-label APL. [redacted] Virus from this subject was sensitive to APL but resistant to ENF at both timepoints tested. 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

March 2008