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## Abstract

**Background:** Amlaviroc (APL; 873140), a CCR5 antagonist in clinical development as an HIV entry inhibitor, is a CYP3A substrate. This study evaluated the effect of efavirenz (EFV), a CYP3A inducer, on APL PK.

**Methods:** 25 subjects were enrolled into this 2-period, single sequence, inpatient study; with APL dosed 600mg BID for 7 days followed by a 6 day washout period, and then APL 600mg BID + EFV 600mg QD for 10 days. All doses were administered 3h after a 30% fat meal; EFV was administered with the PM APL dose. Plasma PK samples were collected following the AM and PM APL doses on the last day of each treatment period and analyzed for APL and EFV by HPLC/MS. PK parameters were calculated by non-compartmental methods and compared by treatment using ANOVA. Safety was assessed throughout the study.

**Results:** Repeated dosing of EFV decreased APL exposures by 57%. APL had no effect on EFV exposures compared with historical data. APL PK parameters following the AM and PM doses were similar. The combination of APL and EFV was generally well tolerated. All adverse events were mild to moderate, with self-limiting gastrointestinal complaints being the most common. 5/25 subjects prematurely discontinued (1 rash, 3 loose stools, 1 concomitant medication use).

APL PK Parameter (AM Dose)	Geometric Mean (95% CI); N=20		Ratio of GLS Means [90% CI]
	APL Alone	APL + EFV	APL + EFV vs APL Alone
AUC(0-∞) (ng·h/mL)	1342 (971, 1855)	574 (463, 712)	0.43 [0.37, 0.49]
C <sub>max</sub> (ng/mL)	563 (392, 810)	233 (182, 298)	0.41 [0.35, 0.49]
C <sub>τ</sub> (ng/mL)	6.65 (4.94, 8.95)	2.62 (2.02, 3.40)	0.39 [0.30, 0.52]

**Conclusion:** Co-administration of APL and EFV resulted in significantly reduced APL plasma concentrations due to EFV induction of GI and hepatic enzymes.

## Introduction

Amlaviroc (873140, APL) is an entry inhibitor that targets CCR5 that is in clinical development. In vitro human liver microsomal studies have demonstrated that APL is metabolized by CYP450 3A enzymes.

The HIV non-nucleoside reverse transcriptase inhibitor, efavirenz (EFV) is a potent inducer of CYP450 3A4. This study explored the potential for a drug-drug interaction between APL and EFV. The specific objectives were as follows:

### Primary

- To compare steady-state APL PK parameters with and without EFV

### Secondary

- To describe steady-state EFV PK when co-administered with APL
- To assess the safety and tolerability of repeat dose co-administration

## Methods

The study was a Phase 1, single center, open label, 2-period, single sequence, inpatient study in healthy male and female adult subjects (≥18 and ≤55 years of age). The treatment periods were as follows:

Period 1 Treatment A	6-day washout	Period 2 Treatment B
APL 600mg q12h x 7 days		APL 600mg q12h + EFV 600mg q24h x 11 days

EFV was administered simultaneously with the evening dose of APL. All APL and EFV doses were administered 2.5h after completion of a moderate fat/calorie meal. A 6-day washout period was included to monitor CCR5 receptor occupancy during the off-drug period.

### Pharmacokinetics Assessments

Serial blood samples for APL PK were obtained at 0 (pre-dose), 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12 h following both the morning and evening doses on Day 7 of Period 1 and following the evening dose on Day 10 and the morning dose on Day 11 of Period 2. Serial blood samples for EFV PK were obtained at 0 (pre-dose), 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16 and 24 h after the evening dose on Day 10 of Period 2.

Plasma APL concentrations were measured by a validated LC/MS/MS method with a calibration range of 0.5 to 500ng/mL. Plasma EFV concentrations were determined with a validated LC/UV assay with a lower limit of quantitation of 0.1µg/mL. Plasma PK parameters for APL and EFV were estimated by standard non-compartmental methods using WinNonlin Professional v4.1 (Pharsight; Mountain View, CA).

### Safety Assessments

Vital sign measurements, clinical laboratory tests and ECGs were conducted at various times throughout the treatment periods and at follow-up 7 to 10 days after the last dose. Adverse events (AEs) were monitored throughout the study.

### Statistical Comparisons

Comparisons of interest were assessed by ANOVA using SAS (Cary, NC) PROC MIXED to construct the ratio of treatments of test versus reference and 90% confidence interval (CI), where the model included Treatment as fixed effect and Subject as random effect.

## Results

Table 1. Summary of Demographic Data

N (Started/Completed)	25/20
Age (yrs)	30 (19 - 54)
Sex (M/F)	24/1
Race/Ethnicity (W/B/H)	19/1/5
Weight (kg)	76 (62 - 102)
Body Mass Index	24.6 (21.3 - 28.9)

Data reported as median (range)  
Abbreviations: W, Caucasian; B, African-American; H, American Hispanic

### Pharmacokinetics

A total of 20 subjects provided PK parameters for both Period 1 and 2 and were included in the PK population. APL plasma concentrations and PK parameters are shown in Figure 1 and Table 2, respectively. Repeated co-administration of EFV with APL resulted in decreased APL exposures. Following the morning dose, the geometric mean AUC(0-∞), C<sub>max</sub>, and C<sub>τ</sub>, were 57%, 59%, and 61% lower than that observed for APL alone. Following the evening dose, the geometric mean AUC(0-∞), C<sub>max</sub>, and C<sub>τ</sub>, were 63%, 65%, and 59% lower, respectively, than that observed for APL alone (Table 2).

EFV PK parameters are shown in Table 3. EFV exposures were similar to those reported in the SUSTIVA™ Package Insert: AUC(0-24)=59.1±23.0µg·h/mL, C<sub>max</sub>=4.1±1.2µg/mL, C<sub>τ</sub>=1.8 ±1.0µg/mL.

Table 2. Steady-State PK Parameters and Treatment Comparisons for Amlaviroc Following AM and PM Doses

APL PK Parameter (AM Dose)	Geometric Mean (95% CI) <sup>a</sup> ; n=20		Ratio of GLS Means [90%CI]
	Treatment A APL Alone	Treatment B APL + EFV	B/A APL + EFV vs APL
AUC(0-∞) (ng·h/mL)	1342 (971, 1855)	574 (463, 712)	0.43 [0.36, 0.43]
C <sub>max</sub> (ng/mL)	563 (392, 810)	233 (182, 298)	0.41 [0.32, 0.50]
C <sub>τ</sub> (ng/mL)	6.65 (4.94, 8.95)	2.62 (2.02, 3.40)	0.39 [0.26, 0.53]
T <sub>max</sub> (h)	2.0 (1.0-3.0)	1.8 (1.0-3.0)	NA

APL PK Parameter (PM Dose)	Geometric Mean (95% CI) <sup>a</sup> ; n=20		Ratio of GLS Means [90% CI]
	Treatment A APL Alone	Treatment B APL + EFV	B/A APL + EFV vs APL
AUC(0-∞) (ng·h/mL)	1744 (1255, 2423)	650 (545, 776)	0.37 [0.31, 0.44]
C <sub>max</sub> (ng/mL)	634 (428, 941)	223 (180, 276)	0.35 [0.28, 0.42]
C <sub>τ</sub> (ng/mL)	11.10 (8.10, 15.21)	4.49 (3.52, 5.73)	0.40 [0.30, 0.50]
T <sub>max</sub> (h)	2.5 (1.0-8.0)	2.0 (0.0-6.0)	NA

Treatment A: APL 600 mg, q 12h for 7 days  
Treatment B: APL 600mg, q 12h + EFV 600 mg, q 24h for 11 days  
<sup>a</sup>Geometric mean (95% CI) for all parameters except T<sub>max</sub> (median, range).

Figure 1. Median APL Plasma Concentration-Time Profiles

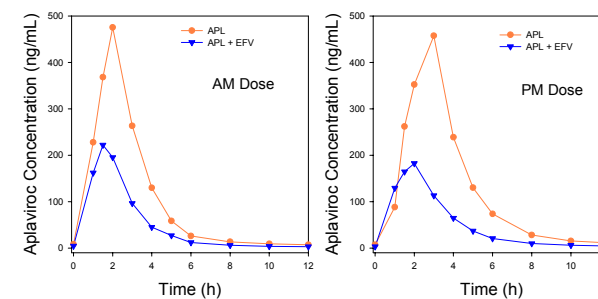


Figure 2. Amlaviroc Individual PK Parameter Comparison

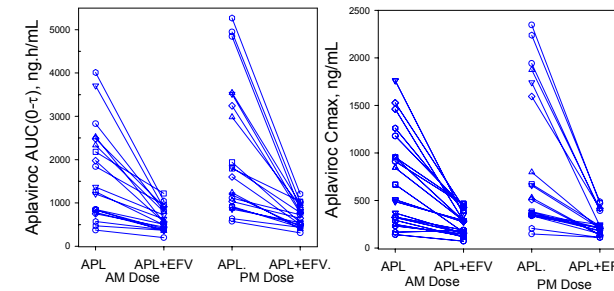


Table 3. Efavirenz PK Parameters

EFV PK Parameter	Geometric Mean (95% CI) <sup>a</sup> ; n=20 Treatment B APL + EFV
AUC(0-∞) (µg·h/mL)	65.75 (57.16, 75.65)
C <sub>max</sub> (µg/mL)	4.66 (4.07, 5.32)
C <sub>τ</sub> (µg/mL)	1.97 (1.66, 2.34)
T <sub>max</sub> (h)	3.02 (1.52, 6.04)

Treatment B: APL 600mg, q 12h + EFV 600 mg, q 24h  
<sup>a</sup>Geometric mean (95% CI) for all parameters except T<sub>max</sub> (median, range).

### Receptor Occupancy

Prolonged CCR5 receptor occupancy with an estimated half-life of approximately 127 h was previously reported [Sparks, et al.; CROI, 2005]

### Safety & Tolerability

Overall, 20 (20/25, 80%) subjects during Period 1 and 21 (21/23, 91%) subjects during Period 2 experienced at least 1 adverse event (AE) during the study. Four (4/25, 16%) subjects prematurely discontinued due to adverse events: 1 (1/25, 4%) due to drug-related rash and 3 (3/25, 12%) due to loose stools. Loose stools were the most common AE reported by subjects with 18/25 (72%) reporting loose stools during APL alone and 14/23 (61%) reporting loose stools during APL + EFV. All GI-related events were of mild or moderate intensity and generally resolved on therapy within 5 days of onset. The most common drug-related AEs are shown in Table 4. In general, the frequencies of these events were similar between the treatment groups, with the exception of dizziness and abnormal dreams, which were only reported by subjects who received APL + EFV. No pregnancies, serious AEs, Grade 4 events, or deaths were reported. No significant effects on ECG or viral signs were observed. One Grade 3 event (severe upper abdominal pain [stomach cramps]) was reported during the study, which was determined by the investigator not to be drug-related and resolved.

Table 4. Summary of Most Frequently Reported Drug-related Clinical Adverse Events (>10% subjects)

	APL Alone N=25	APL + EFV N=23
Any Event	20 (80%)	21 (91%)
Gastrointestinal:		
Loose stools	19 (76%)	16 (70%)
Nausea	13 (52%)	10 (43%)
Abdominal pain, upper	4 (16%)	1 (4%)
Abdominal distention	0	3 (13%)
Flatulence	3 (12%)	2 (9%)
Nervous system disorders:		
Dizziness	6 (24%)	16 (70%)
Headache	0	13 (57%)
Headache	6 (24%)	4 (17%)
Psychiatric disorders		
Abnormal dreams	0	9 (39%)
Restlessness	0	5 (22%)
General disorders		
Feeling hot	2 (8%)	8 (35%)
Feeling hot	0	3 (13%)

## Discussion

- Repeated co-administration of amlaviroc (600mg q12h) with efavirenz (600mg q24h) resulted in significant reduction in the geometric mean amlaviroc AUC(0-∞), C<sub>max</sub>, and C<sub>τ</sub>, by 57, 59, and 61%, respectively, following the morning dose and 63, 65, and 60%, respectively, for the PM dose.
- The results are consistent with in vitro and clinical study data which indicate that amlaviroc is a CYP3A substrate and that efavirenz is a CYP3A inducer.
- Amlaviroc did not appear to affect efavirenz exposures, which were similar to those reported in the SUSTIVA™ Package Insert.
- The most common adverse events were gastrointestinal (GI) in nature and primarily included loose stools. All GI-related events were of mild or moderate intensity and generally resolved on therapy within 5 days of onset.

## Conclusion

- Amlaviroc exposures following both the AM and PM doses were reduced when co-administered with efavirenz, most likely due to induction of amlaviroc metabolism.
- A subsequent study evaluated the combination of amlaviroc and efavirenz with a ritonavir-boosted PI and it was shown that the efavirenz induction effect could be attenuated by co-administration of a potent CYP3A inhibitor [see Poster A-1194; 45<sup>th</sup> ICAAC].

## References

S Sparks, K Adkison, A Shachoy-Clark, S Piscitelli, and James Demarest. Prolonged Duration of CCR5 Occupancy by 873140 in HIV-negative and HIV-positive Subjects. 12th Conference on Retroviruses and Opportunistic Infections. Feb, 2005, Boston, MA  
SUSTIVA™ Package Insert

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<sup>†</sup>USAN approved only