

Final 48 Week Safety, Tolerability and Efficacy of Capravirine (CPV) + Lopinavir/ritonavir (LPV/r) and 2 NRTIs in Treatment Experienced Patients

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ABSTRACT

Background: CPV is a next-generation NNRTI that exhibits potent antiviral activity against wild type and NNRTI-resistant strains of HIV *in vitro*. In a Ph 2 study evaluating CPV 700 or 1400 mg as add-on therapy to nevirapine (NFV) + 2 NRTIs in NNRTI-experienced, PI-naïve patients, neither of the CPV-containing arms demonstrated a significant difference in efficacy versus background therapy.

Methods: Study 1006 is a Ph 2, prospective, randomized (1:1:1:1), multi-center, double blind, dose ranging study of CPV (200, 400 or 700 mg) or placebo (PBO) + LPV/r and ≥2 PhenoSenseGT selected NRTIs. Patients must have previously failed ≥1 NNRTI, ≥2 NRTIs, and 1-3 PIs and demonstrate <40-fold change (FC) in susceptibility to LPV at baseline (BL). Patients assigned to the PBO, CPV 200 or CPV 400 treatment groups received 400/100 mg LPV/r BID while patients assigned to CPV 700 mg received 533/133 mg LPV/r BID to account for dose-dependent drug interaction.

Results: Study arms were similar at BL in overall mean age (42.2 yr), gender (78% male), race (54% white, 20% black, 15% hispanic) and percent with ≥1 NNRTI resistance mutations (81%). 44.6% and 69.6% of patients had <2.5-FC and <10-FC in CPV susceptibility at BL, respectively. 73.7% and 86.4% of patients had <2.5-FC and <10-FC in LPV susceptibility at BL, respectively. Key data (ITT, non-completers = failures or †ast observation carried forward) are presented in the following table:

Endpoints through week 48	Placebo (N=80)	CPV 200 mg (N=77)	CPV 400 mg (N=79)	CPV 700 mg (N=80)
% Discontinuations	36	27	25	45
Mean days to virologic failure	207	221	245	187
Mean log ₁₀ VL reduction from BL*	1.06	0.92	1.30	0.87
% <400 c/mL	55	60	65	49
% <50 c/mL	40	52	58	40

The primary (time to virologic failure) and most secondary efficacy endpoints were statistically insignificant (p>0.05) for all active arms vs. PBO. However, a greater proportion of patients receiving CPV 400 mg achieved <50 copies/mL at week 48 compared to PBO (p<0.05). The most frequently reported AEs (>10% in any CPV arm) were diarrhea, nausea, headache and influenza. Most AEs were mild in severity. There were non-significant trends towards more gastrointestinal AEs, more AEs leading to treatment interruption or discontinuation, and more shifts in laboratory results of at least 2 toxicity grades with CPV 700 mg relative to the other treatments (p>0.05).

Conclusions: Through 48 weeks of therapy, CPV was generally safe and well tolerated, but showed little or no added efficacy over LPV/r + 2 NRTIs.

INTRODUCTION

Capravirine (CPV) is a novel, next generation NNRTI that exhibits potent *in vitro* antiviral activity against HIV-1 strains that contain mutations in RT that confer resistance to the currently available NNRTIs.¹

A CPV monotherapy study in HIV infected, antiretroviral naïve patients demonstrated that 10 days of CPV (1400 and 2100 mg BID) monotherapy reduced mean HIV RNA levels by 1.59 to 1.69 log₁₀, an amount similar to a standard 3 drug regimen (nevirapine + 3TC + AZT; 1.65 log reduction).² A Phase 2 study evaluating CPV 700 or 1400 mg BID as add-on therapy to a standard three-drug regimen, nevirapine (NFV) + 2 NRTIs, in NNRTI-experienced, PI-naïve patients (Study 1002)³, further established the safety and tolerability of CPV at doses of 700 and 1400 mg, but failed to demonstrate a significant improvement in efficacy.

CPV is predominantly metabolized by CYP3A4 and the co-administration of CPV with 400/100 mg lopinavir/ritonavir (LPV/r) boosts the AUC and C_{trough} of CPV approximately 5- and 20-fold, respectively.⁴ Thus the co-administration of CPV with LPV/r enables the use of lower doses of CPV, which may offer the advantage of fewer gastrointestinal adverse events and improved adherence, while maintaining trough values in excess of the *in vitro* IC₅₀ for NNRTI-H strains. While CPV 200 or 400 mg BID does not significantly alter the PK of LPV or RTV administered as 400/100 mg BID, CPV 700 mg BID reduces the AUC of LPV and RTV administered as 400/100 mg BID by 38% and 12%, respectively. Administration of LPV/r as 533/133 mg in the presence of CPV 700 mg provides LPV and RTV concentrations similar to those achieved with 400/100 mg LPV/r alone.⁵

Study 1006 is a dose-ranging, Phase 2 study designed to determine whether CPV at doses of 200, 400 or 700 mg BID added to a regimen of LPV/r + 2 NRTIs in NRTI-, NNRTI- and PI-experienced patients improves virologic response over 48 weeks vs LPV/r + 2 NRTIs alone. LPV/r was dosed at 400/100 mg BID with CPV 200 and 400 mg, and at 533/133 mg BID with CPV 700 mg.

METHODS

Population

- HIV-infected men or women at least 18 years of age who had failed (i.e., required a change in antiretroviral therapy due to an increase in HIV RNA level) antiretroviral regimens containing PIs, NNRTIs and NRTIs. Each patient's combined prior regimens must have included 1-3 PIs, ≥1 NNRTI and ≥2 NRTIs.
- HIV-1 RNA >1,000 copies/mL
- The study was conducted in Argentina, Brazil, Canada, France, Mexico, the Netherlands, South Africa, Spain, the United Kingdom and the United States.

Study Design

- Dose-ranging, 48-week, 1:1:1:1, randomized, double-blind, placebo-controlled, parallel-group, multicenter study.
- During a 7-day run-in period (Days -7 to -1), all patients received 3 capsules of open-label LPV/r (400/100 mg BID) and the PhenoSenseGT™ informed, investigator-selected NRTIs. On Day 1, blinded CPV or placebo was added, and LPV/r was administered as 3 unblinded LPV/r capsules (133/33 mg) and a fourth blinded LPV/r or placebo capsule.

Study Treatments

- Patients were randomly assigned to one of three doses of CPV (200, 400 or 700 mg BID) or CPV placebo.
- Use of enfuvirtide was prohibited.

Key Exclusion Criteria

- LPV IC₅₀ >40-fold relative to wild type HIV.
- Patients could not have been off their last failing antiretroviral regimen for more than 6 months at run-in (Day -7).

Endpoints

- The primary efficacy endpoint was time to virologic failure (loss of virologic response) at 48 weeks (failure criteria based on 400 copies/mL).
- Secondary endpoints included change from baseline in viral load, time to virologic failure at 24 and 48 weeks (failure criteria based on 50 copies/mL), proportion of patients achieving <400 and <50 copies/mL at 24 and 48 weeks, proportion of patients achieving ≥1.0 log reduction in viral RNA at 24 and 48 weeks, and change in CD4 counts at 24 and 48 weeks.

RESULTS

Table 1. Baseline demographics and disease characteristics

	Placebo (N=80)	CPV 200 mg (N=77)	CPV 400 mg (N=79)	CPV 700 mg (N=80)
Male (%)	75	70	82	84
Age at screening (years, median)	41	42	41	41
Race (%)				
White	56	49	63	49
Black	23	21	15	20
Asian	1	0	3	1
Hispanic	15	13	13	20
Native American	0	0	1	0
Other	5	17	5	10
Median viral load (log ₁₀ copies/mL)	3.46	3.37	3.56	3.42
Median CD4+ cell count (cells/mm ³)	227	265	285	286
Fold-change in LPV IC ₅₀ relative to wild type (median)	2.6	3.0	4.2	4.3
Fold-change in LPV IC ₅₀ relative to wild type (median)	1.0	1.1	1.1	1.2
Number of resistance associated mutations (median) ^a				
NNRTI	1	2	1	2
NRTI	3	4	4	3
PI	3	3	3	2

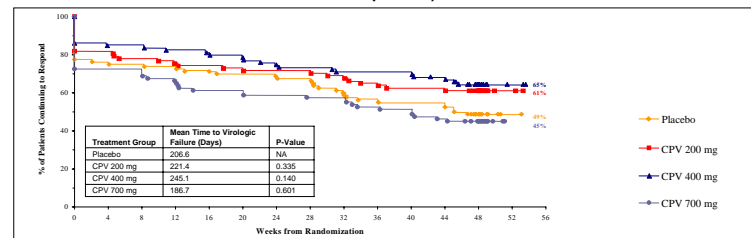
- The study arms were well balanced with respect to baseline demographics; disease characteristics; LPV and CPV susceptibility; and NRTI, NNRTI and PI resistance associated mutations.

Table 2. Subject disposition through week 48

	Placebo (N=80)	CPV 200 mg (N=77)	CPV 400 mg (N=79)	CPV 700 mg (N=80)
Completed 48 weeks, N (%)	51 (64)	56 (73)	59 (75)	44 (55)
Early termination before 48 weeks, N (%)	29 (36)	21 (27)	20 (25)	36 (45)
Reason for early termination, N (%)				
Protocol-defined treatment failure	16 (20)	12 (16)	9 (11)	13 (16)
Adverse event	6 (8)	2 (3)	5 (6)	13 (16)
Death	0	1 (1)	1 (1)	0
Protocol violation	2 (3)	0	1 (1)	0
Lost to follow-up	1 (1)	0	0	2 (3)
Withdrew consent	0	3 (4)	2 (3)	4 (5)
Noncompliance	2 (3)	2 (3)	1 (1)	2 (3)
Investigator discretion	1 (1)	1 (1)	1 (1)	0
Other	1 (1)	0	0	2 (3)

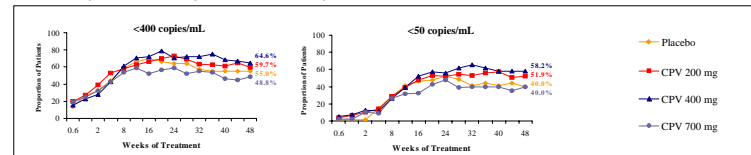
- The most common reasons for early termination were treatment failure (50 patients, 16%) and AEs (26 patients, 8%). Although there were no statistically significant differences in rate of discontinuation between any CPV dose group and the placebo group, the rate of discontinuations due to treatment failure was lowest in the CPV 400 mg group (11%). The rate of discontinuations due to AEs was highest in the CPV 700 mg group (16%; also see Tables 4 and 5).

Figure 1. Kaplan-Meier estimates of time to virologic failure (failure criteria based on two consecutive HIV-1 RNA levels ≥ 400 copies/mL)



- None of the differences observed for the primary endpoint (time to virologic failure based on HIV-1 RNA >400 c/mL) between placebo and CPV dose groups were statistically significant (p>0.05).

Figure 2. Patients (%) achieving HIV RNA <400 and <50 copies/mL over time (ITT, Non-Completers = Failures)



- There were no statistically significant differences (p>0.05) between any CPV dose group and placebo at 24 or 48 weeks. However, a greater proportion of patients receiving CPV 400 mg achieved a viral load <50 c/mL at week 48 compared to placebo (p<0.05).

Table 3. Summary of week 48 primary and secondary efficacy endpoints

Endpoint	Placebo (N=80)	CPV 200 mg (N=77)	CPV 400 mg (N=79)	CPV 700 mg (N=80)
Mean time (days) to virologic failure (400 c/mL failure criteria)	206.6	221.4	245.1	186.7
Mean time (days) to virologic failure (50 c/mL failure criteria)	158.5	193.6	225.3 ^a	147.7
HIV-1 RNA <400 copies/mL (% of patients) ^b	55.0	59.7	64.6	48.8
HIV-1 RNA <50 copies/mL (% of patients) ^b	40.0	51.9	58.2 ^a	40.0
Mean log ₁₀ copies/mL change from baseline in HIV-1 RNA (range) ^c	-1.06 (-4.0, 1.8)	-0.91 (-3.5, 2.2)	-1.30 (-4.2, 1.7)	-0.87 (-3.0, 2.1)
≥1.0-log decrease in HIV-1 RNA from baseline (% of patients) ^d	48.8	51.9	59.5	42.5
Median change from baseline in CD4+ cells (cells/mL) (range) ^e	82.0 (-105, 324)	53.5 (-333, 479)	80.0 (-143, 417)	82.0 (-199, 353)

- a. p<0.05. All other comparisons of placebo versus CPV dose groups were >0.05.
- b. Non-completers = Failures; ITT
- c. On-treatment. LOCF= Last observation carried forward.

Table 4. Virologic response at week 48 in patients whose virus contained multiple protease-inhibitor resistance mutations at baseline*

Endpoint	Placebo (N=13)	CPV 200 mg (N=13)	CPV 400 mg (N=20)	CPV 700 mg (N=17)
Mean time (days) to virologic failure (400 c/mL failure criteria)	128.2	140.3 ^a	210.1 ^a	200.0 ^a
HIV-1 RNA <400 copies/mL (% of patients) ^b	15.4	46.2	45.0 ^a	58.8 ^a
HIV-1 RNA <50 copies/mL (% of patients) ^b	7.7	46.2 ^a	40.0 ^a	41.2 ^a
Mean log ₁₀ copies/mL change from baseline in HIV-1 RNA ^c	-0.25 (-1.05, 0.24)	-0.73 (-3.33, 4.79)	-0.89 (-1.41, 0.63)	-1.41 ^a
≥1.0-log decrease in HIV-1 RNA from baseline (% of patients) ^d	15.4	46.2	35.0	47.1 ^a

- a. p<0.05. All other values are insignificant (p>0.05)
- b. Non-completers = Failures; ITT
- c. On-treatment. LOCF= Last observation carried forward.

*Patients whose baseline genotype indicated the presence in the protease gene of at least one substitution at amino acid position 32, 47, 48, 50, 82 or 84, and at least three substitutions at positions 10, 20, 24, 30, 32, 33, 36, 46, 47, 48, 50, 53, 54, 71, 73, 77, 82, 84, or 90.

- In an unplanned subgroup analysis of patients whose virus contained multiple protease-inhibitor resistance mutations at baseline, trends favoring the addition of CPV were consistently observed and in some cases were statistically significant. However, it is important to note that this represents a small, non-randomized group of patients.

Table 5. Treatment-emergent adverse events (Grade 1-4) occurring in ≥10% of patients in any arm

Adverse Event (%)	Placebo (N=80)	CPV 200 mg (N=77)	CPV 400 mg (N=79)	CPV 700 mg (N=80)
Diarrhea	40	30	43	50
Nausea	15	22	19	26
Headache	19	18	24	19
Influenza	25	19	20	13
Nasopharyngitis	10	12	14	9
Vomiting	8	10	10	16
Insomnia	13	8	6	18
Herpes simplex	10	3	14	13
Cough	9	13	10	4
Upper respiratory tract infection	8	3	13	13
Abdominal pain	6	12	8	8
Depression	8	3	8	10
Arthralgia	4	10	8	4
Dysgeusia	0	3	4	18
Rash	6	10	4	1

- Most AEs were mild in severity. There were no statistically significant differences between placebo and any of the CPV dose groups, however, there were non-significant trends towards more gastrointestinal AEs (diarrhea, nausea and vomiting) with CPV 700 mg relative to other dose groups (p>0.05). Whether this is related to the higher dose of CPV or the higher dose of LPV/r is unclear. However, systemic exposures of LPV were similar between the 700 mg dose group and other treatment groups.

- Treatment-emergent AEs led to temporary interruption of blinded study treatment in 14%, 10%, 14% and 18% of patients who received placebo, CPV 200 mg, CPV 400 mg and CPV 700 mg, respectively. There were no statistically significant differences between the placebo group and any of the CPV dose groups.

Table 6. Percent of patients with Grade 3 or 4 abnormalities in laboratory test results: incidence >5% of patients in any treatment group

Laboratory Test	Placebo (N=80)	CPV 200 mg (N=77)	CPV 400 mg (N=79)	CPV 700 mg (N=80)
Amylase	8	14	14	14
Triglycerides	8	13	20	17
Creatine kinase	22	4	5	19
AST	4	0	4	9
ALT	4	0	3	5
LDH	4	0	0	5

- As with AEs, there were no statistically significant differences in % of patients with Grade 3 or 4 laboratory abnormalities between placebo and any of the CPV dose groups, however, there were non-significant trends towards more shifts in laboratory abnormalities of at least 2 toxicity grades with the CPV 700 mg group (p>0.05).

SUMMARY

- The addition of CPV to LPV/r + ≥2 PhenoSenseGT™ selected NRTIs in NRTI-, NNRTI- and PI-experienced patients failed to produce statistically or clinically significant improvements in virologic outcome after 48 weeks of treatment.
 - However, a greater proportion of patients receiving CPV 400 mg achieved a viral load <50 c/mL at week 48 compared to placebo (p<0.05). There was also a 66.8-day difference in mean time to virologic failure (based on HIV-1 RNA >50 c/mL) between the CPV 400 mg and placebo groups (p<0.05).
- In an unplanned subgroup analysis of patients whose virus contained multiple protease-inhibitor resistance mutations, trends favoring the addition of CPV were consistently observed. However, this represents a small, non-randomized group of patients.
- The most frequently reported AEs (>10% in any CPV arm) were diarrhea, nausea, headache and influenza. Most AEs were mild in severity. There were non-significant trends towards more gastrointestinal AEs, more AEs leading to treatment interruption or discontinuation, and more shifts in laboratory abnormalities of at least 2 toxicity grades with the CPV 700 mg group relative to the other dose groups (p>0.05).
- Based on the failure of CPV to meet its primary outcome in two Phase 2 clinical trials and potentially problematic drug-drug interactions, no further development of CPV is planned.

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