

24 and 48 Week Safety, Tolerability and Efficacy of Capravirine (CPV), as Add-on Therapy to Nelfinavir (NFV) and 2 Nucleoside Reverse Transcriptase Inhibitors (NRTIs) in Patients Failing a Non-nucleoside Reverse Transcriptase Inhibitor (NNRTI)-Based Regimen

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Introduction

Capravirine (CPV) is a novel, next generation non-nucleoside reverse transcriptase inhibitor (NNRTI) that exhibits potent *in vitro* activity against HIV-1 strains that contain mutations in the reverse transcriptase (RT) enzyme that convey resistance to all approved NNRTIs.^{1,2} In *in vitro* serial passage studies, high-level resistance to CPV was slow to emerge and was associated with multiple amino acid substitutions in RT.³ These data suggest a high genetic barrier to resistance, and that CPV may provide antiviral activity in patients who have failed NNRTIs.

The safety and tolerability of CPV has been demonstrated in over 429 patient years of therapy in Phase 1 and 2 clinical trials (healthy volunteers and HIV+ patients). When dosed with (nelfinavir) NFV + 2 nucleoside reverse transcriptase inhibitors (NRTIs), the most common side effects reported more frequently by patients receiving CPV than placebo were nausea, diarrhea and vomiting.⁴

CPV monotherapy studies in HIV+, antiretroviral-naïve patients have shown that 10 days of CPV (1400 and 2100 mg BID) monotherapy reduces mean HIV RNA levels by similar amounts to those with a standard 3-drug regimen, NFV + Combivir (CBV).⁵ Previous studies⁶ have demonstrated that NFV boosts plasma concentrations of CPV by 2-fold, which enables the use of lower doses of CPV with the advantage of fewer gastrointestinal (GI) adverse events and greater study compliance. Study 1002 was designed to determine whether the addition of one of two doses of CPV to a regimen of NFV + 2 NRTIs would provide a higher virologic response rate over 48 weeks than NFV + 2 NRTIs. At the time of abstract submission in October, only the week 24 interim data were available. The study has since completed and both the 24- and 48-week efficacy and safety data are presented here.

Methods

1002 is a 1:1:1 randomized, double-blind, placebo controlled, multicenter, Phase 2 trial conducted in the USA, France, Germany, Italy, Spain, and Republic of South Africa. HIV+ patients that had failed a prior NNRTI-containing regimen, were PI naïve and met all study selection criteria (see Table 1) were eligible for this study. Patients were randomly assigned to CPV 700 mg BID, CPV 1400 mg BID or CPV placebo, and all were dosed with NFV (1250 mg BID) and 2 new NRTIs selected by the investigators based on prior treatment history and resistance testing (Pharmacia/CPI ViroLogic, Inc., South San Francisco, CA). Randomization was stratified by plasma HIV RNA <20,000 versus ≥20,000 c/mL and geographic region.

The primary efficacy endpoint, time to virologic failure, was defined in the protocol as:

- Failure to achieve at least a 0.5-log decrease from the log-transformed calculated baseline plasma HIV RNA level by week 4 on study
- An increase of at least 3 times the calculated baseline plasma HIV RNA level by week 4 on study
- Achieving at least a 0.5-log decrease from the log-transformed calculated baseline plasma HIV RNA level by week 4 on study followed at any time thereafter by an increase of at least 3 times the on-study plasma HIV RNA level nadir, or a plasma HIV RNA level of at least 2000 c/mL.
- Plasma samples were drawn at screening, baseline, day 3, and weeks 1, 2, and 4, and every 4 weeks thereafter through week 48. HIV RNA levels were determined by a centralized laboratory (Covance CLS, Geneva, Cape Town or Indianapolis) using the Roche Amplicor v1.5 RT-PCR assay. CD4 and CD8 lymphocyte counts were determined at screening and baseline, and every 4 weeks through week 48. Plasma samples for viral resistance tests were collected at screening, weeks 24 and 48, and time of early termination. Safety labs, CBC, chemistry and urinalysis were collected at screening, baseline, and weeks 1, 2, and 4, and every 4 weeks through week 48. Fasted chemistry samples were collected at baseline and week 24 and 48.
- Sample size calculation: Fifty patients per arm providing approximately 80% power to detect a 25% increase in response rate between any of the CPV arms and the placebo arm using log-rank test for time to virologic failure through 48 weeks, assuming exponential distributions, an accrual time of 6 months, and a response rate for the placebo arm of 55% at week 48. A slightly lower power is achieved when using Chi-square test to compare two proportions. Each CPV arm was compared with the placebo arm using Fisher's exact test. All patients who received at least one dose of CPV or placebo were included in the safety and efficacy analysis.

Table 1. Selection criteria: Patients were eligible for this study if they met all inclusion criteria and no exclusion criteria listed below

Inclusion criteria	Exclusion criteria
• Male or female, ≥18 years of age	• Any active uncontrolled infection or other unstable or severe concurrent medical condition
• Currently taking an NNRTI (delavirdine, efavirenz, or nevirapine) + 2 NRTIs for ≥20 days and failing that regimen (HIV RNA >1000 c/mL X 2-7 days apart). Patients that had previously received antiretroviral therapy with NRTIs alone, and then received an NNRTI + 2 NRTIs were also eligible.	• Is receiving or expected to require the use of: amiodarone, quinidine, cisapride, midazolam, triazolam, ergot alkaloids, rifampin, lovastatin, simvastatin, cyclosporin, tacrolimus, pimozide, H ₁ -receptor antagonists, proton pump inhibitors, garlic supplements, phenytoin, phenobarbital, carbamazepine, methadone, or St. John's wort.
• CD4 cell count >50 cells/mm ³ at the screening visit	• Has received treatment with an investigational agent, cytotoxic chemotherapy, immunomodulators or radiation therapy within 28 days prior to the first dose of CPV.
• Absolute neutrophil count >1000/mm ³	• Has a history of systemic vasculitis
• Platelets ≥75,000	• Is pregnant or lactating
• Hemoglobin ≥90 g/L	• Has a psychological or sociological condition or an addictive disorder that would preclude compliance with the protocol
• Serum creatinine ≤1.5 X ULN	
• AST, ALT and bilirubin ≤2.5 X ULN (regardless of Hep B or C serology)	
• Negative anti-nuclear antibody (ANCA)	
• Willing and able to comply with the protocol, and to sign an informed consent in accordance with institutional and regulatory guidelines	
• Willing and able to continue using a barrier method of contraception during the study period. Women of child-bearing potential had to agree to use an additional method of contraception such as an injectable, implantable, or non-ethinyl-estradiol-containing oral contraceptive; spermicide; or abstinence.	

Results

Table 2. Baseline demographics and disease characteristics

	Placebo (n=59)	CPV 700 mg (n=60)	CPV 1400 mg (n=60)
Male (%)	66	65	67
Race (%)			
White	32	38	50
Black	51	50	47
Hispanic	10	7	3
Other	7	5	0
Age (yr)	38.2	39.9	37.6
Mean HIV RNA (log ₁₀ c/mL)	4.45	4.39	4.39
(range)	(2.93-5.88)	(2.85-5.71)	(2.92-5.67)
Median CD4 count (cells/mm ³)	208	248	249
(range)	(15-792)	(15-1285)	(33-905)

• The study arms were well balanced in terms of baseline demographics and disease characteristics. Other baseline characteristics, such as CD8 cell count, prior antiretroviral use, NRTI-genotype and NNRTI-genotype were similar across the three treatment groups. NNRTI resistance mutations (L100I, K101E, K103N, V106A, V108I, Y181C/L, Y188C/H/L, G190A/E/S, P225H and/or P236L) were detected in viral isolates from 84% of the study population at baseline.

Table 3. Summary of NRTI use by treatment arm (all treated patients)

	Placebo (n=59)	CPV 700 mg (n=60)	CPV 1400 mg (n=60)
Didanosine (ddI)	27 (46)	18 (30)	28 (47)
Tenofovir (TDF)	20 (34)	20 (33)	23 (38)
Stavudine (d4T)	15 (25)	24 (40)	23 (38)
Abacavir (ABC)	16 (27)	17 (28)	13 (22)
Zidovudine (ZDV)	14 (24)	15 (25)	12 (20)
Lamivudine (3TC)	10 (17)	13 (22)	13 (22)
Combivir (ZDV/3TC)	14 (24)	13 (22)	8 (13)
Zalcitabine (ddC)	0 (0)	3 (5)	0 (0)
Entricitabine (FTC)	0 (0)	0 (0)	1 (2)
Trizivir (ZDV/3TC/ABC)	0 (0)	0 (0)	1 (2)

No statistically significant differences between CPV and placebo arms

- The proportion of patients using the various NRTIs was similar in each arm.

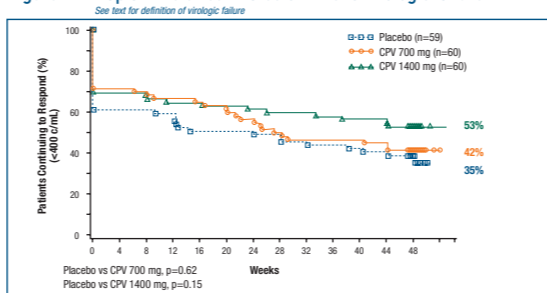
Table 4. Subject disposition through week 48 by predefined category

	NFV + 2 NRTIs +		
	Placebo (n=59)	CPV 700 mg (n=60)	CPV 1400 mg (n=60)
Protocol-defined treatment failure	14 (24)	9 (15)	8 (13)
Adverse event	5 (8)	9 (15)	4 (7)
Death	1 (2)	1 (2)	1 (2)
Pregnancy	1 (2)	0 (0)	0 (0)
Lost to follow-up	3 (5)	1 (2)	2 (3)
Withdraw consent	1 (2)	2 (3)	2 (3)
Non-compliance	1 (2)	3 (5)	1 (2)
Total	26 (44)	25 (42)	18 (30)

No statistically significant differences between CPV and placebo arms

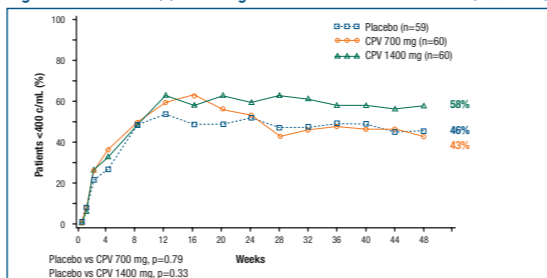
- Discontinuation rates through week 48 due to adverse events were 8% in the placebo arm, 15% in the CPV 700 mg arm, and 7% in the CPV 1400 mg arm (placebo vs CPV 700 mg, p=0.40 and placebo vs CPV 1400 mg, p=0.74).
- Overall discontinuation rates were somewhat lower in the CPV 1400 mg arm (30%) vs the placebo (44%) and CPV 700 mg (42%) arms. The majority of these non-statistically significant differences in discontinuation rates were driven by patients failing treatment in the placebo arm (24%) and discontinuations due to adverse events in the CPV 700 mg arm (15%), as compared to rates in the CPV 1400 mg arm. It is unclear why CPV 1400 mg BID would have better tolerability than CPV 700 mg BID when dosed with NFV + 2 NRTIs.

Figure 1. Kaplan-Meier estimates of time to virologic failure



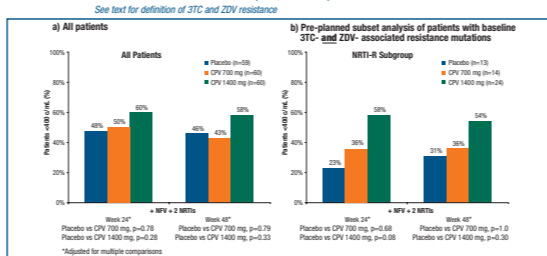
- Fifty-three percent (53%) of patients in the CPV 1400 mg arm achieved and maintained HIV RNA <400 c/mL through week 48 compared to 42% in the CPV 700 mg and 35% in the placebo arms. However, the differences between treatment arms were not statistically significant.

Figure 2. Patients (%) achieving HIV RNA <400 c/mL over time (ITT, NC=F)



- A higher, but not statistically significant, proportion of patients in the CPV 1400 mg arm achieved HIV RNA <400 and <50 c/mL at week 48 compared to the placebo arm (Table 5).

Figure 3. Proportion of patients achieving HIV RNA <400 c/mL at the week 24 and 48 visits (ITT, NC=F)



- In a planned subgroup analysis of patients with 3TC and ZDV resistance, the proportion of patients achieving HIV RNA <400 c/mL at weeks 24 and 48 in the CPV 1400 mg arm was numerically higher than with the same population in the placebo arm. However, the differences between the treatment arms do not reach statistical significance, and it is important to note that this represents a small, non-randomized group of patients. 3TC resistance was defined as the presence of the M184V mutation, while ZDV resistance was defined as the presence of any of the following thymidine associated resistance mutations: M41L, D67N, K70R, L210W, T215Y/E, or K191E/N/Q. Similar results were observed for the proportion of patients achieving HIV RNA <50 c/mL (data not shown).

Table 5. Summary of week 24 and 48 efficacy endpoints

Endpoint	Study week	P-value vs placebo		
		Placebo n=59	CPV 700 mg n=60	CPV 1400 mg n=60
Time to protocol-defined virologic failure (days)	24	NA	NA	NA
HIV-1 RNA <400 c/mL (% of patients)	48	168	179	194
HIV-1 RNA <50 c/mL (% of patients)	48	46	43	58
Mean log ₁₀ c/mL change from baseline in HIV-1 RNA (min, max)	24	-2.0 (-4, 1)	-2.3 (-4, 0)	-2.4 (-4, 0)
Median CD4 count change from baseline (cells/mm ³) (min, max)	48	108 (-111, 483)	124 (-162, 454)	105 (-229, 716)
LOOC ^a	48	82 (-143, 483)	69 (-943, 454)	97 (-229, 716)

a NC=F, ITT

b On-treatment, LOOC=Last observation carried forward

c P-values determined testing mean change from baseline

- No statistically significant difference in any of the efficacy endpoints was observed at weeks 24 or 48 between either of the CPV treatment arms and placebo.

Table 6. Adverse events Grade 1 through 4 regardless of causality through week 48 occurring in >10% in any arm

MEDRA	Placebo n (%) (n=59)	CPV 700 mg n (%) (n=60)	CPV 1400 mg n (%) (n=60)
Diarrhea	29 (49)	32 (53)	39 (65)
Nausea	12 (20)	16 (27)	21 (35)
Loose stools	13 (22)	9 (15)	15 (25)
Headache	8 (14)	10 (17)	14 (23)
URTI	19 (32)	9 (15)	14 (23)
Vomiting	5 (8)	13 (22)	8 (13)
Lymphadenopathy	4 (7)	6 (10)	7 (12)
Abdominal pain	9 (15)	2 (3)	6 (10)
Herpes	6 (10)	6 (10)	4 (7)
Bronchitis	7 (12)	4 (7)	4 (7)
Fatigue	6 (10)	6 (10)	3 (5)
Gastroenteritis	5 (8)	4 (7)	6 (10)
Depression	6 (10)	4 (7)	4 (7)
Dyspepsia	3 (5)	4 (7)	6 (10)
Oral candidiasis	7 (12)	4 (7)	2 (3)
Dyspnea	2 (3)	3 (5)	6 (10)
Dizziness	3 (5)	2 (3)	6 (10)
Insomnia	3 (5)	3 (5)	6 (10)

- The most frequently reported adverse events occurring in at least 10% of patients in any arm, regardless of causality, are presented. There were no statistically significant differences between either of the CPV treatment arms and the placebo arm.

Table 7. Grade 3 or 4 laboratory abnormalities through week 48 in ≥3% of patients in any arm

	Placebo n (%) (n=59)	CPV 700 mg n (%) (n=60)	CPV 1400 mg n (%) (n=60)
ALT	5 (9)	2 (3)	2 (3)
AST	4 (7)	1 (2)	0 (0)
Amylase	8 (14)	8 (13)	11 (18)
CK	2 (3)	3 (5)	4 (7)
Hemoglobin	0 (0)	0 (0)	0 (0)
LDH	1 (2)	2 (3)	4 (7)
Triglycerides*	0 (0)	2 (4)	1 (2)
Neutropenia	1 (2)	2 (3)	4 (7)
Uric Acid	2 (3)	1 (2)	2 (3)

*Lipid values are reported without regard to fasting. N for triglycerides are 53, 54, and 54, respectively.

There were no reports of Grade 3 or 4 laboratory abnormalities reported for serum creatinine or alkaline phosphatase.

- The Grade 3 or 4 laboratory abnormalities were similar for all treatment groups. Only one subject experienced a serious study drug related adverse event: Grade 4 AST/ALT in the 700 mg CPV arm.

Discussion

CPV at doses of 700 and 1400 mg BID dosed with NFV + 2 NRTIs failed to reach statistical significance for the primary endpoints of this study. Whether this represents the difficulty in demonstrating a benefit of 3 vs 4 active drugs is unclear. In a preplanned subgroup analysis evaluating a small, non-randomized subgroup of patients who entered the study with genotypic evidence of 3TC and ZDV resistance, there may be a suggestion of better efficacy with CPV vs placebo. However, additional studies are required to prove this. Another study, 1006, to examine the effect of CPV vs placebo in patients who have failed NRTIs, NNRTIs, and PIs is underway.

The high proportion of patients with HIV RNA >400 c/mL at week 48 (42-57%) warrants further evaluation, given that even in the placebo arm, the NRTIs were selected based on resistance testing and patient treatment history. Additional analyses of response by baseline NNRTI genotype and the evolution of NNRTI resistance in patients who initially responded to therapy and then failed are also underway.

CPV appeared to be well tolerated with only 1% more patients in the 4-drug CPV 1400 mg arm discontinuing study due to an adverse event through week 48 compared with the 3-drug plus placebo arm. The most common side effects appeared to be GI in nature (diarrhea, nausea, and vomiting, consistent with earlier studies), with low rates of neuro-psychological side effects or rash. Interestingly, there were low rates of dyslipidemia reported in all arms of this study, which is not entirely consistent with prior studies evaluating NFV + 2 NRTIs.

Conclusions

- CPV was safe and well tolerated as part of a 4-drug regimen for 48 weeks of therapy with few discontinuations due to adverse events.

- Neither of the 4-drug CPV-containing arms demonstrated a statistically significant difference in efficacy vs the standard 3-drug background regimen (NFV + 2 NRTIs) during this 48-week trial in NNRTI-experienced, PI-naïve patients.

- A preplanned, subgroup analysis of a small, non-randomized group of patients with baseline 3TC and ZDV resistance suggests that CPV may offer clinical benefit to HIV+ patients with a greater degree of resistance than the overall patient population in this study. Additional studies would be required to prove this.

- A second Phase 2 study (1006) pairing CPV or placebo with lopinavir/ritonavir + 2 NRTIs in patients failing PIs, NRTIs and NNRTIs is currently underway.

References

1. Fujitani T et al. Antimicrob Agents Chemother 1998; 42(6):1340-5.
2. Potts KE et al. 6th CROI 1999, Chicago, USA. Abstract 12.
3. Blau WS et al. 14th ICAR 2001, Seattle, USA. Abstract 45.
4. Wolfe P et al. 8th CROI 2001, Chicago, USA. Abstract 323.
5. Raber S et al. 4th International Workshop on Clinical Pharmacology of HIV Therapy 2003, Cannes, France. Abstract 8.8.

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