

A dose-ranging study to evaluate the safety and efficacy of abacavir alone or in combination with zidovudine and lamivudine in antiretroviral treatment-naive subjects

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Objective: To compare antiretroviral efficacy, safety and tolerance of three dosing regimens of the novel nucleoside reverse transcriptase inhibitor, abacavir (1592U89) over 24 weeks and its efficacy in open-label combination with zidovudine and lamivudine.

Design: Sixty HIV-1-infected antiretroviral therapy naive subjects (entry criteria; CD4+ cell count ≥ 100 cells/mm³, plasma HIV-1 RNA $\geq 30\,000$ copies/ml), randomized into 20 subjects per cohort received 100, 300 or 600 mg abacavir twice daily. Subjects successfully completing 24 weeks' randomized therapy could switch to open label therapy (abacavir, zidovudine, lamivudine at 300, 300 and 150 mg twice daily, respectively) for a further 24 weeks of study, as could subjects meeting one or more switch criteria.

Methods: Subjects were assessed for antiretroviral activity by measuring changes in plasma HIV-1 RNA load and CD4+ cell counts. Evaluation of safety and tolerance was based on clinical adverse events and laboratory analyses.

Results: At week 4, subjects receiving 300 or 600 mg abacavir twice daily had greater reductions in plasma HIV-1 RNA (median changes -1.55 and -1.61 log₁₀ copies/ml, respectively); differences ($P = 0.007$ and $P \leq 0.001$, respectively) than subjects receiving 100 mg abacavir twice daily (median change, -0.63 log₁₀ copies/ml). Differences between the 300 and 600 mg twice daily groups were not clinically or statistically significant. At 24 weeks, analysis showed a median change in plasma HIV-1 RNA of -0.70 and -1.30 log₁₀ copies/ml in the 300 and 600 mg twice daily groups, respectively. During the open label phase in which zidovudine/lamivudine was added to 300 mg abacavir twice daily, a further median reduction in plasma HIV-1 RNA of 1.74 log₁₀ copies/ml was seen. At 48 weeks pooled data from all abacavir-treated subjects showed a sustained reduction in plasma HIV-1 RNA of 2.8 log₁₀ copies/ml; 65% and 43% of subjects had ≤ 400 and ≤ 50 HIV-1 RNA copies/ml, respectively, and a further median increase of

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111 CD4+ cells/mm³ were seen. Abacavir was generally well tolerated with few clinically significant adverse events. Two subjects (3.3%) developed hypersensitivity reactions to abacavir. There were no differences between the groups with regard to serious adverse events.

Conclusions: In terms of antiretroviral therapy naive subjects, treatment with 300 or 600 mg abacavir twice daily was statistically superior to a 100 mg twice daily dose at 4 weeks. Combinations therapy containing abacavir–zidovudine–lamivudine was a highly effective antiretroviral regimen, resulting in substantial reductions in plasma HIV-1 RNA which may be comparable to combinations containing protease inhibitors. Abacavir was generally tolerated. © 1998 Lippincott Williams & Wilkins

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Introduction

New, potent, well-tolerated antiretroviral agents continue to be needed for use in combination with clinically proven anti-HIV drugs. Abacavir (1592U89), currently in phase III clinical trials, is a novel carbocyclic nucleoside analogue with potent anti-HIV activity *in vitro* [1]. *In vitro*, several point mutations in reverse transcriptase are required to confer high level reduction in susceptibility of HIV to abacavir [2]. The observations that abacavir and zidovudine act synergistically *in vitro* [1], and that virus strains resistant to zidovudine were not cross-resistant to abacavir, suggest that a combination of zidovudine and abacavir may be clinically beneficial.

A dose escalation study (CNAA2001) with four treatment regimens (200, 400, or 600 mg three times daily, or 300 mg twice daily), has evaluated the safety, tolerance and pharmacokinetics of the drug over 12 weeks and demonstrated clinical changes greater than the *in vitro* data predicted [3]. However, this study did not distinguish clear differences amongst abacavir dosing regimens, suggesting that lower doses of abacavir should be evaluated.

The current study (CNAB2002) was designed with three aims: (i) to compare the antiviral activity of three different dosing regimens (100, 300 and 600 mg twice daily) of abacavir over 24 weeks, (ii) to assess preliminarily the antiviral efficacy of abacavir in combination with zidovudine and lamivudine, and (iii) to assess the drug's safety and tolerance.

Methods

Study design and subject population

The study was a phase II, randomized, double-blind, dose-ranging, multicentre study conducted in France and Germany evaluating three treatment regimens of

abacavir in antiretroviral therapy-naive, HIV-1-infected subjects. Subjects (male or female) were aged ≥ 18 years and had CD4+ cell count $\geq 100 \times 10^6/l$ and plasma HIV-1 RNA load $\geq 30\,000$ copies/ml, less than 14 days before administration of the drug.

Subjects were randomized on entry into one of three cohorts receiving 100, 300 or 600 mg abacavir twice daily. All subjects completing 24 weeks of randomized therapy, or who met the protocol-defined switch criteria earlier, could switch to open-label treatment (300, 300 and 150 mg twice daily of abacavir, zidovudine and lamivudine, respectively). The switch criteria were as follows: plasma HIV-1 RNA reduction from baseline below $0.7 \log_{10}$ copies/ml at week 4, plasma HIV-1 RNA above 5000 copies/ml after week 12, CD4+ cell count returning to baseline, or a new Centers for Disease Control and Prevention AIDS-defining event after 4 weeks.

Evaluation of treatment

Subjects were assessed (generally every 4 weeks) for abacavir antiretroviral activity, safety and tolerance. Antiretroviral activity was assessed by measuring changes in plasma HIV-1 RNA (Roche Amplicor Assay and Roche Ultradirect Assay; Roche Molecular System, Alameda, California, USA, detection limits, 400 and 50 HIV RNA copies/ml, respectively) and CD4+ cell counts. Safety evaluations were based on clinical adverse events and laboratory analyses. Subjects' samples were screened for the emergence of HIV with phenotypic or genotypic resistance to abacavir [4,5], which will be the subject of a further report.

Statistical analysis

Using estimates from earlier studies with abacavir, we calculated that 20 patients per arm of the study would provide 80% power to detect treatment differences in the average area under the curve minus baseline (AAUCMB) of 45% (approximately $0.45 \log_{10}$ copies/ml). Differences of this magnitude would be considered meaningful. Data from subjects including

those who switched treatments early, because of meeting switch criteria, were summarized by AAUCMB. Treatment group analyses were performed by non-parametric analysis of covariance with baseline plasma HIV-1 RNA as a covariate. To ensure that all subjects contributed data to the AAUCMB at week 24, analysis was by last observation carried forward (LOCF) and intention-to-treat methods. Analysis of the randomized and open-label phase was also by the ‘as treated’ method.

Results

Sixty HIV-1-infected, antiretroviral-naive subjects without an active AIDS-defining condition were enrolled and randomized into three cohorts of 20 subjects each. Although no formal statistical testing was performed treatment groups were considered well balanced with regard to demographic and baseline characteristics (Table 1). Median baseline CD4+ cell count was $360 \times 10^6/l$ (range, $140\text{--}720 \times 10^6/l$) and the median baseline plasma HIV-1 RNA was $5.0 \log_{10}$ copies/ml (range, $3.77\text{--}6.13 \log_{10}$ copies/ml).

Randomized phase

By week 4, subjects receiving 300 or 600 mg abacavir twice daily had greater reductions in plasma HIV-1 RNA [median changes, $-1.55 \log_{10}$ copies/ml (range, -2.36 to $-0.01 \log_{10}$ copies/ml) and $-1.61 \log_{10}$ copies/ml (range, -2.32 to $0.52 \log_{10}$ copies/ml), respectively] than subjects receiving 100 mg abacavir twice daily (median change, $-0.63 \log_{10}$ copies/ml; range, -1.54 to $0.52 \log_{10}$ copies/ml). The AAUCMB differences between the 100 mg twice daily group and the 300 and 600 mg twice daily groups were statistically significant ($P = 0.008$ and ≤ 0.001 , respectively). Median plasma HIV-1 RNA over time profiles demonstrated rapid decreases in plasma viral load in the 300 and 600 mg twice daily groups (Fig. 1a) There were no statistically significant differences between the 300 and 600 mg twice daily groups at 4, 12 or 24 weeks.

Table 1. Baseline characteristics of study population.

	Abacavir twice daily dose			Total
	100 mg	300 mg	600 mg	
No. subjects	20	20	20	60
CDC classification [n (%)]				
Class A (asymptomatic)	15 (75)	12 (60)	14 (70)	41 (68)
Class B (symptomatic, not AIDS)	4 (20)	7 (35)	6 (30)	17 (28)
Class C (AIDS)	1 (5)	1 (5)	0 (0)	2 (3)
Median time from HIV-1 diagnosis (months)*	24	30	19	26
Median (range) CD4+ cell count ($\times 10^6/l$)	365 (140–720)	347 (142–641)	396 (176–648)	360 (140–720)
Baseline median (range) plasma HIV-1 RNA load (\log_{10} copies/ml)	4.89 (3.77–5.56)	4.94 (4.22–6.13)	5.04 (4.34–5.60)	5.00 (3.77–6.13)

*Data for 18 subjects in each group (total, 54 subjects). Median age, 36 years (range, 21–61 years); gender, 51 male, nine female; race, 59 Caucasian, one mixed race. CDC, Centers for Disease Control and Prevention.

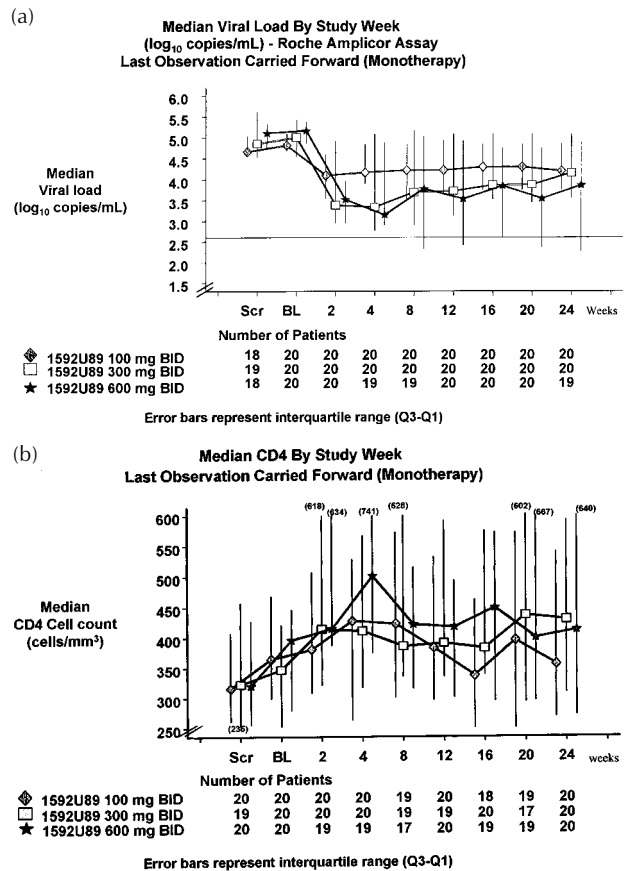


Fig. 1. Randomized phase. (a) Median viral load by study week (Amplacor assay), by last observation carried forward (LOCF) analysis. (b) Median CD4+ cell counts by study week, by LOCF analysis. Scr, Pretreatment screen; BL, baseline.

Because of the modest changes in plasma HIV-1 RNA load in the 100 mg twice daily group at 4 weeks, a protocol amendment was introduced to offer these subjects open-label therapy. Therefore, by week 24 (Fig. 1a), comparisons between the 100 mg twice daily group and the other two groups were not meaningful because 17 out of 20 of the 100 mg twice daily cohort had entered the open-label phase.

At 24 weeks, LOCF analysis showed a median reduction in plasma HIV-1 RNA of $-0.7 \log_{10}$ copies/ml (range, -2.29 to $-0.10 \log_{10}$ copies/ml) and $-1.30 \log_{10}$ copies/ml (range, -2.41 to $0.3 \log_{10}$ copies/ml) for the 300 and 600 mg twice daily groups, respectively. The AAUCMB differences between the 300 and 600 mg twice daily doses over 24 weeks were not statistically significant ($P = 0.187$). The as-treated analysis showed median decreases in plasma HIV-1 RNA of $-1.01 \log_{10}$ copies/ml (range, -2.29 to $-0.10 \log_{10}$ copies/ml) and $-2.11 \log_{10}$ copies/ml (range, -2.41 to $-1.30 \log_{10}$ copies/ml) for the 300 mg twice daily ($n = 8$) and 600 mg twice daily ($n = 7$) groups, respectively.

By week 4, median CD4+ cell counts had increased in all three treatment groups by $27 \times 10^6/l$ (range, -147 to $387 \times 10^6/l$), $89 \times 10^6/l$ (range, -104 to $244 \times 10^6/l$) and $134 \times 10^6/l$ (range, -50 to $370 \times 10^6/l$) among subjects in the 100, 300 and 600 mg twice daily groups, respectively (Fig. 1b). Differences between the 100 and 300 mg twice daily and the 100 and 600 mg twice daily treatment groups were statistically significant at $P = 0.001$. These increases were sustained throughout the randomized phase for subjects on 300 and 600 mg twice daily abacavir, with the LOCF analysis showing median increases in CD4+ cell counts of $26 \times 10^6/l$ (range, -180 to $387 \times 10^6/l$), $97 \times 10^6/l$ (range, -63 to $283 \times 10^6/l$) and $40 \times 10^6/l$ (range, -150 to $389 \times 10^6/l$) for the 100, 300 and 600 mg twice daily doses, respectively. As-treated analysis showed data with changes of $95 \times 10^6/l$ (range, -61 to $170 \times 10^6/l$) and $68 \times 10^6/l$ (range, -150 to $390 \times 10^6/l$) among subjects in the 300 and 600 mg twice daily groups, respectively.

Open-label phase

Prior to 24 weeks, 40 subjects met a switch criterion (16 in the 100 mg twice daily group and 12 in each of the other two groups) and were offered 300 mg twice daily zidovudine and 150 mg twice daily lamivudine in addition to 300 mg twice daily abacavir. During the open-label phase, subjects had sustained reductions in plasma HIV-1 RNA with further median reductions from the combined baseline of $1.74 \log_{10}$ copies/ml (range, -2.75 to $-1.15 \log_{10}$ copies/ml; Fig. 2a) and sustained increases in CD4+ cell counts with further median increases of $118 \times 10^6/l$ (range, $62-186 \times 10^6/l$; Fig. 2b).

Intention-to-treat analysis

Data from all abacavir-treated subjects were pooled. Subjects had sustained reductions in plasma HIV-1 RNA with reductions of $2.8 \log_{10}$ copies/ml at 48 weeks (Fig. 2c), when 65 and 43% of subjects had plasma HIV-1 RNA levels of ≤ 400 and ≤ 50 copies/ml, respectively (Fig. 3).

Safety and tolerance of abacavir

During the randomized phase, four subjects withdrew

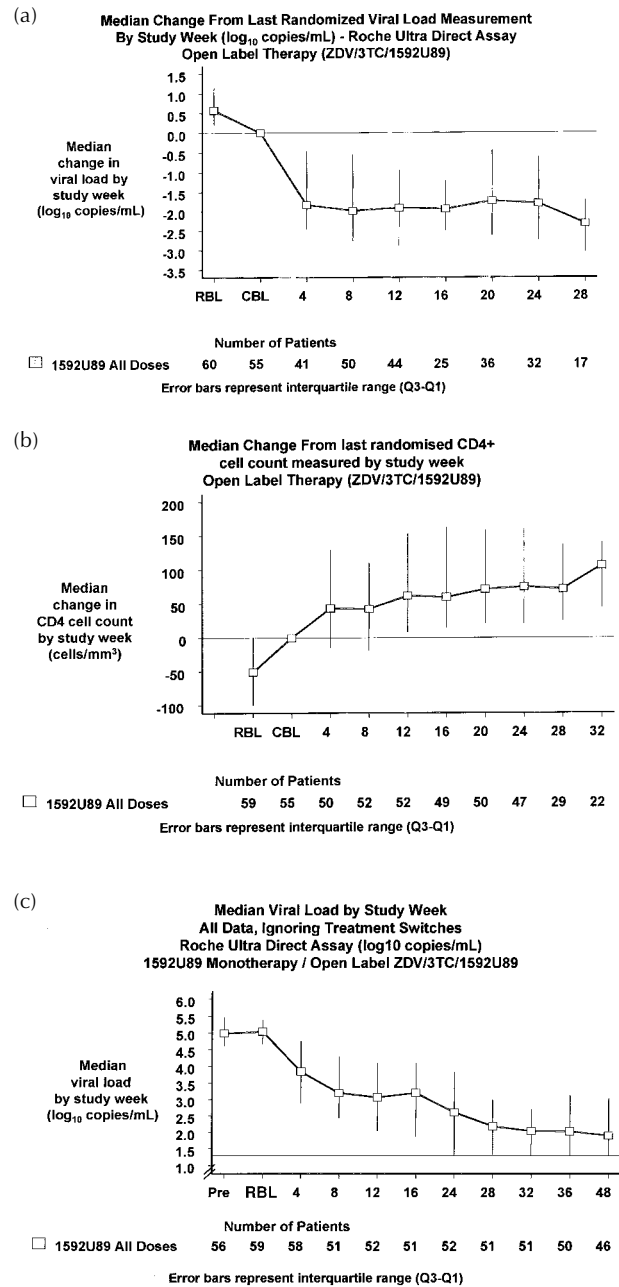


Fig. 2. Open-label phase. (a) Median change from last randomized plasma HIV-1 RNA load measurement by study week (Ultra Direct assay). (b) Median change from last randomized CD4+ cell count measurement by study week. (c) Intention-to-treat analysis; median plasma HIV-1 RNA by study week. RBL, Randomized baseline at time 0; CBL, combination baseline; Pre, pretreatment plasma HIV-1 RNA load.

due to adverse events, one subject because of myocardial infarction (100 mg twice daily), although not thought to be associated with treatment, and one with rhabdomyolysis (300 mg twice daily). Two subjects developed an abacavir hypersensitivity reaction (300 and 600 mg twice daily), one within 20 days (300 mg

twice daily), and the other within 14–28 days; rechallenged with abacavir resulted in a more severe hypersensitivity reaction in these patients.

The frequency and nature of reported adverse events were similar in all groups (Table 2), although there was a trend of increased nausea and malaise with increased dose. The majority of reported adverse events were of mild or moderate intensity, transient in duration and not leading to dose modification or withdrawal.

There were few (n = 6) reports of grade 3 or 4 treatment-emergent clinical chemistry or haematological abnormalities or unexpected laboratory findings during the randomized phase. The most frequently reported grade 3/4 toxicity was elevated triglycerides (non-fasting) in six subjects, which was thought not to be of clinical significance. All but one of these subjects subsequently returned to grade 1 or 2, and none required dose adjustment.

During the open-label phase, the only withdrawals (n = 2) were due to nausea/vomiting and depression/skin rash. There were no hypersensitivity reactions during the open-label phase.

Emergence of virus resistant to abacavir

Following therapy many patients’ viral load was so low that it was difficult to isolate virus for analysis and therefore trends in dose dependence of resistant virus could not be deduced.

Discussion

This study confirms that amongst antiretroviral therapy-naive subjects there was not a significant difference in antiviral efficacy between treatment with the 300 and 600 mg twice daily doses of abacavir. After 4 weeks of treatment, abacavir monotherapy elicited a sustained median reduction in plasma HIV-1 RNA load of 1.55 and 1.61 log₁₀ copies/ml at 300 and 600 mg twice daily, respectively, whereas subjects

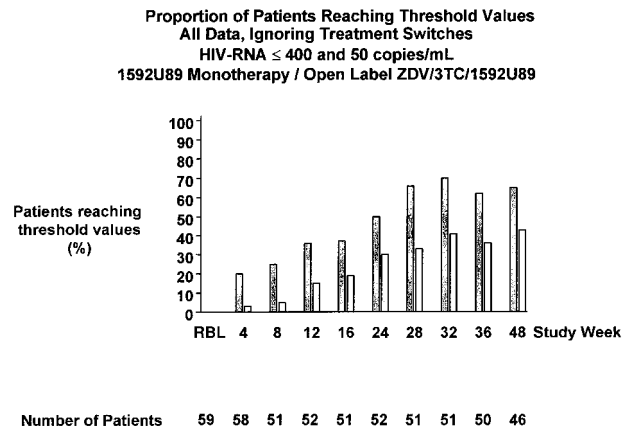


Fig. 3. Proportion of patients reaching threshold values. Intention-to-treat analysis. RBL, Randomized baseline.

treated with 100 mg twice daily had significantly lower plasma HIV-1 RNA decreases than subjects on the other two doses. The 100 mg twice daily dose was considered suboptimal and will not be studied further. These data support 300 mg twice daily as an appropriate clinical dose.

In addition, during the open-label treatment phase, subjects receiving 300 mg twice daily abacavir and zidovudine–lamivudine had plasma HIV-1 RNA load decreases comparable to those previously reported with other combinations of antiretroviral drugs, including those containing protease inhibitors, where plasma HIV RNA reductions of 1.8–2.0 log₁₀ copies/ml have been reported [6–8].

The drug was well tolerated with few clinically significant adverse effects. The hypersensitivity reaction to abacavir seen in two subjects (3.3%) has also been reported from other studies (unpublished data). Subjects developing this reaction should not be rechallenged with abacavir. The trend of increasing nausea and malaise at higher doses also supports 300 mg twice daily as the clinical dose.

Table 2. Number of patients reporting adverse events.

	Abacavir twice daily dose			Total (n = 60)
	100 mg (n = 20)	300 mg (n = 20)	600 mg (n = 20)	
Most frequent events [n (%)]				
Nausea, vomiting	6 (30)	7 (35)	10 (50)	23 (38)
Malaise, fatigue	2 (10)	4 (20)	11 (55)	17 (28)
Diarrhoea	7 (35)	5 (25)	2 (10)	14 (23)
Headache	5 (25)	7 (35)	4 (20)	16 (27)
Viral ear, nose and throat infection	2 (10)	4 (20)	3 (15)	9 (15)
Sleep disorders	3 (15)	4 (20)	1 (5)	8 (13)
Fever, chills	3 (15)	1 (5)	4 (20)	8 (13)
Dizziness	1 (5)	1 (5)	4 (20)	6 (10)
Gastrointestinal discomfort and pain	0 (0)	1 (5)	5 (25)	6 (10)

Because of the inability to recover virus from treated subjects, few resistance data were obtained at this time-point and no conclusions could be made about dose-related effects. However, a further study discussing the genotypic and phenotypic data obtained from the patients in this study will be presented in due course.

Data on the triple combination abacavir–zidovudine–lamivudine is preliminary, but may be indicative of the combination's efficacy. These data suggest that abacavir–zidovudine–lamivudine may be a highly efficacious therapy for HIV-1-infected subjects. Further studies are underway to evaluate additional abacavir-containing combinations.

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