

The study listed may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this Register, healthcare professionals should consult prescribing information for the product approved in their country.

<b>Study No.:</b> CNAF3007-Ecureuil
<b>Title:</b> An open label, randomised study, to evaluate the safety and efficacy of <i>Combivir</i> <sup>TM</sup> plus abacavir ( <i>Ziagen</i> <sup>TM</sup> ) versus <i>Combivir</i> <sup>TM</sup> plus <i>Viracept</i> <sup>TM</sup> , in HIV-1 infected antiretroviral therapy naive adults with a plasma HIV-1 RNA between 1000 and 500,000 copies /mL.
<b>Rationale:</b> Zidovudine [ZDV] 300mg and lamivudine [3TC] 150mg and abacavir [ABC] could offer a good alternative to the use of a protease inhibitor (PI) containing regimen when initiating treatment in antiretroviral naive subjects.
<b>Phase:</b> III
<b>Study Period:</b> 6 Nov 1998 to 7 Jul 2000
<b>Study Design:</b> Open-label, randomised study
<b>Centres:</b> 61 centres in France
<b>Indication:</b> HIV-1 infection in antiretroviral ART -naive subjects
<b>Treatment:</b> Subjects were randomised to receive either: 3TC 150mg / ZDV 300mg (COMB: 1 tablet twice daily, ( <i>bis in die</i> , bid) plus ABC 300mg (1 tablet bid) 3TC 150mg / ZDV 300mg (COMB: 1 tablet bid) plus nelfinavir (NFV) 750mg (3 capsules every 8 hours)
<b>Objectives</b> To compare the efficacy and safety of the triple nucleoside analogue regimen with the PI containing regimen over 48 weeks, in order to further evaluate the concept of a PI saving regimen when initiating treatment in ART-naive subjects.
<b>Primary Outcome/Efficacy Variable:</b> The proportion of subjects achieving plasma HIV-1 RNA concentrations <50 copies/mL at 48 weeks'
<b>Secondary Outcome/Efficacy Variable(s):</b> <ul style="list-style-type: none"> <li>• Proportion of subjects with plasma HIV-1 RNA &lt; 50 copies/mL after 24 weeks of treatment.</li> <li>• Changes from baseline in plasma HIV-1 RNA over 48 weeks</li> <li>• Changes from baseline in CD4+ cell count over 48 weeks</li> <li>• Clinical progression : measured by clinical events</li> </ul>
<b>Statistical Methods:</b> Percentages were compared by a Chi-square test at week 48. Given that similar antiretroviral activity was observed in the Week 24 report, a retrospective analysis was conducted to further evaluate the non inferiority of the two treatments regimens. Mean and median viral load changes, mean and median CD4 and CD8 changes, from Day 0 to Week 24 and to Week 48 were compared by a Wilcoxon test. Multivariate analysis was used for the relationship between virological response at week 48 and baseline genotype using a logistic regression, baseline viral load, CD4 count and treatment were also included in the model. Populations analysed are as follows: Intent to Treat (ITT)- population <ul style="list-style-type: none"> <li>• All randomised: In addition to the population defined in the protocol, this method of analysis was used in order to ensure consistency across this project and within this therapeutic area for regulatory submission. All subjects randomised were included in this population.</li> <li>• ITT with switch/missing=failure: Subjects who discontinued or switched antiretroviral treatment are included as failures beyond the last dose of randomised study drug for calculations of proportions. All missing data were replaced by failure.</li> <li>• ITT with switch included: Subjects who discontinued randomised treatment and added or switched randomised antiretroviral treatment were included in this analysis irrespective of treatment outcome. All observed efficacy data were used even after treatment discontinuation. All missing data were replaced by failure.</li> <li>• ITT with at least one efficacy measurement (WALOEC) -This was the primary ITT analysis of proportions. This analysis excluded randomised subjects who never initiated study treatment. Furthermore, at least one efficacy measurement of viral load should be available for subjects included in this population. This analysis was the one initially defined in the protocol. The principles of switch=failure and switch included were also applied to this population for all proportions calculations. For quantitative data, calculation were done on observed data. Numeric calculations ( mean and median plasma HIV RNA, CD4 and CD8) were performed only on ITT WALOEC population as all subjects randomized without efficacy criteria (ITT all randomized population) had no data to be taken into account for these calculations.</li> </ul> <p>The per protocol population referred to the as-treated population, in which only data collected for subjects while on</p>

randomised therapy contribute to the analysis. Subjects who discontinued or switched antiretroviral treatment are not included in this analysis population beyond the last dose of originally randomised drug. No imputation for missing data was done for this population. Additionally, subjects with viral load (of batch centralised analysis) at day 0 <1000 copies/mL were excluded.

The safety population was defined as all subjects who initiated study drug treatment (received  $\geq 1$  dose of study drug).

**Study Population:** Subjects aged  $\geq 18$  years of age with documented HIV-1 infection (Western blot) who were ART-naïve with a Karnofsky score  $\geq 60\%$  and an HIV-1 RNA level between 1,000 and 500,000 copies/mL were eligible for study participation. Subjects with an acute HIV infection or an active infection not related to HIV disease, who had received prior ART therapy, who had a history of an autoimmune disease syndrome event defining category C (1993 Center for Disease Control classification), or who were pregnant or breastfeeding were excluded from study participation.

<b>Number of Subjects:</b>	<b>COMB + ABC</b>	<b>COMB + NFV</b>
Planned, N	90	90
Randomised, N	98	97
Completed, n (%)	78 (79.6)	73 (75.3)
Total Number Subjects Withdrawn, n (%)	20 (21)	23 (25)
Withdrawn due to Adverse Events, n (%)	1 (0.01)	6 (0.07)
Withdrawn due to Lack of Efficacy, n (%)	0	0
Withdrawn for other reasons, n (%)	19 (19.4)	17 (17.6)
<b>Demographics</b>	<b>COMB + ABC</b>	<b>COMB + NFV</b>
N (ITT)	98	97
Females: Males	30:68	34:63
Median Age, years (range)	34 (18 ; 68)	(18 ; 66)
Race, n (%)	Not available (n/a)	n/a
Baseline median Plasma HIV-1 RNA, copies/mL (range) Plasma HIV-1 RNA copies/mL (range)	4.2 (1.7 ;5.2)	4.1 (1.7 ;5.4)
Baseline median CD4+ cell count, cells/mm <sup>3</sup> (range) CD4+ cell count/mm <sup>3</sup> (range)	387 (10; 1038)	449 (29; 1133)
<b>Primary Efficacy Results:</b>		
<b>ITT, Switch included</b>		
	<b>COMB + ABC N=98</b>	<b>COMB + NFV N=97</b>
Proportion of Subjects Achieving Plasma HIV-1 RNA Concentrations < 50 copies/mL at 48 weeks (range)	65% (56% - 75%)	61% (51 - 71%)
Difference between treatments	4%	
95% Confidence Interval (CI)	[-9 ; 18]	
p-value	0.517	
<b>ITT, Switch = failure</b>		
	<b>COMB + ABC N=98</b>	<b>COMB + NFV N=97</b>
Proportion of Subjects Achieving Plasma HIV-1 RNA Concentrations < 50 copies/mL at 48 weeks(range)	55% (45% - 65%)	55% (45% - 65%)
Difference between treatments	0%	
95% Confidence Interval	[-14; 14]	
<b>Secondary Outcome Variable(s):</b>		
	<b>COMB + ABC N=98</b>	<b>COMB + NFV N=97</b>
Proportion of Subjects with Plasma HIV-1 RNA < 50 copies/mL after 24 weeks of treatment	77%	72%
Difference between treatments	5%	
	n/a	
Changes from baseline in plasma HIV-1 RNA over 48 weeks	- 2.35	- 2.32
Changes from baseline CD4+ cell count over 48 weeks	110	120
Clinical progression	2%	2%
<b>Safety Results:</b> Safety population analysis is based on <b>all subjects who had taken at least one dose of study medication (i.e. during treatment period = on-therapy)</b> . All safety tabulations were derived from the safety population.		

Furthermore it is specified in clinical report (section safety analysis) that "As the treatment is defined by association of several drugs, which are generally never completely stopped, no post treatment period will be identified".		
	<b>COMB + ABC N=96</b>	<b>COMB + NFV N=92</b>
<b>Most Frequent Adverse Events - On-Therapy</b>	<b>n (%)</b>	<b>n (%)</b>
Subjects with any AE(s), n (%)	83 (86)	79 (86)
Diarrhoea	13 (14)	48 (52)
Nausea & vomiting	46 (48)	36 (39)
Headache	13 (14)	16 (17)
Viral respiratory infections	13 (14)	14 (15)
Malaise & fatigue	12 (13)	13 (14)
Abdominal discomfort & pain	11 (11)	12 (13)
Bronchitis	10 (10)	9 (10)
Decreased white cells	11 (11)	5 (5)
Musculoskeletal pain	10 (10)	4 (4)
Upper respiratory inflammation	9 (9)	3 (3)
<b>Serious Adverse Events - On-Therapy n (%) [n considered by the investigator to be related to study medication]</b>	<b>COMB + ABC N = 96</b>	<b>COMB + NFV N = 92</b>
	<b>n (%) [related]</b>	<b>n (%) [related]</b>
Subjects with non-fatal SAEs, n (%)	14 (15%) [4]	9 (10%) [4]
Viral respiratory infections	0	2 (2) [1]
Pancreatitis	2 (2) [0]	0
Hepatocellular disorders	0	2 (2) [2]
Cholestasis	0	1 (1) [1]
Allergies & Allergic Reactions	2 (2) [2]	0
Temperature Regulation Disturbance	1 (1) [1]	0
Psychosis	1 (1) [0]	0
Suicide & attempted suicide	0	1 (1) [0]
Depressive disorders	0	1 (1) [0]
Myocardial infarction	1 (1) [1]	1 (1) [1]
Hypotension	1 (1) [1]	0
Erythematous skin conditions	0	1 (1) [0]
Erythematous skin rashes	1 (1) [1]	0
Vesicular skin rashes	1 (1) [1]	0
Decreased white cells	1 (1) [1]	0
Anemia	1 (1) [1]	0
Compressed nerve syndromes	0	1 (1) [0]
Paralysis of cranial nerves	0	1 (1) [0]
Keratitis & conjunctivitis	0	1 (1) [0]
Retinopathies	1 (1) [1]	0
Nausea & vomiting	1 (1) [1]	0
Diarrhoea	0	1 (1) [1]
Pleural disorders	1 (1) [0]	0
Pneumonia	1 (1) [0]	0
Diabetes mellitus	0	1 (1) [1]
Bacterial musculoskeletal infection	1 (1) [0]	0
Renal signs & symptoms	0	1 (1) [0]
Subjects with fatal SAEs, n (%)	0	0

**Conclusion:** See publication below.

**Publications:**

Matheron S, Descamps D, Boue F, et al. Triple nucleoside combination zidovudine/lamivudine/abacavir versus zidovudine/lamivudine nelfinavir as first line therapy in HIV-1 infected adults: a randomised trial. *Antiviral therapy* 2003 April; 8(2): 163-171.

Date Updated: 21-Dec-2005