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Study No.: CNAF3016-MULTISUD
Title: A Pilot Study to assess the Efficacy and Safety of a quadritherapy with <i>Combivir</i> TM , <i>Abacavir</i> TM , Nelfinavir [®] switching from week 16 to (TZV) TM , Nelfinavir [®] for Antiretroviral Therapy in HIV-infected Naive Subjects with a viral load > 50 000 copies/mL
Rationale: At the time of this study, the current recommended initial treatment for human immunodeficiency virus (HIV) infection is usually a triple therapy with 2 nucleoside reverse transcriptase inhibitors plus a protease inhibitor, a non-nucleoside reverse transcriptase inhibitor, or a third nucleoside analogue. Some studies have suggested that decreases in plasma HIV-1 RNA concentrations to below the level of detection (<50 copies/ml) can be achieved more rapidly with the help of combinations of 4 or 5 drugs. The aim of this study was to investigate the effects of a quadruple therapy with the 3 nucleoside reverse transcriptase inhibitors abacavir (ABC), lamivudine (3TC), and zidovudine (ZDV), plus the protease inhibitor nelfinavir (NFV) on plasma HIV-1 RNA concentrations in HIV-infected antiretroviral therapy (ART)-naïve subjects with high plasma HIV-1 RNA (>50,000 copies/ml)
Phase: IIIb
Study Period: 26 October 1999 to 6 July 2001
Study Design: A multicentre, open-label, non-randomised study
Centres: 15 centres in France.
Indication: HIV-1 infection in ART-naïve subjects
Treatment: All subjects received a quadruple therapy regimen for 48 weeks. Initially they received a 3TC 150mg/ZDV 300mg combination table twice daily (<i>bis in die</i> , BID) plus ABC 300mg BID plus NFV 1250mg BID . At week 16, subjects switched to an ABC 300mg/ 3TC 150mg/ ZDV 300mg combination tablet BID plus NFV 1250mg BID.
Objectives The primary objective of this study was to investigate the effect of this treatment regimen on plasma HIV-1 RNA concentrations
Primary Outcome/Efficacy Variable: The proportion of subjects with undetectable plasma HIV-1 RNA (< 50 copies/ml) at week 48.
Secondary Outcome/Efficacy Variable(s): Rate of subjects with non-response and viral rebound at week 48 Change from baseline in CD4+ cell count at week 48 Medication adherence assessed by Electronic Adherence Caps and self-administered Subject Medication Adherence Questionnaire Safety/tolerability of the quadruple regimen
Statistical Methods: Time to undetectable plasma HIV-1 RNA was measured from the first dose of study drug and was analysed using the Kaplan-Meier time-to-event method with 2 definitions of the event: (1) the first time the plasma HIV-1 RNA value was <50 copies/ml and remained <50 copies/ml until the end of the follow-up period; and (2) the first time the plasma HIV-1 RNA value was <50 copies/ml for at least 2 successive measurements. Virological non-response was defined as HIV-1 RNA values ≥50 copies/ml at all pre-week 16 assessments and ≥1 HIV-1 RNA value ≥1000 copies/ml from week 16. Viral rebound was defined as 2 consecutive HIV-1 RNA values ≥1000 copies/ml from week 16 with 2 HIV-1 RNA values <50 copies/ml before week 16. Good adherence to study treatment was defined by an adherence score >95% and poor adherence ≤95%. Spearman's Rank Coefficient was used to test for correlation between adherence to treatment and plasma HIV-1 RNA concentration at week 48. The intent-to-treat (ITT) analysis population included all subjects who received ≥1 dose of study drug and who had ≥1 efficacy measurement. All subjects who discontinued or switched any ARV agent were included in the ITT switch-included (SI) analysis or considered as failures in the ITT switch = failure (S=F) analysis. The safety population was defined as all subjects who received ≥1dose of study drug.

Study Population: HIV-1 infected ART-naïve adults with plasma HIV-1 RNA >50,000 copies/ml and a Karnofsky performance status ≥60% were eligible for study participation. Exclusion criteria comprised: current acute HIV infection; pregnant or lactating women; malabsorption or other gastrointestinal condition; current treatment with radiotherapy, chemotherapy or immunosuppressant drugs; significant unexplained biological abnormality or disease.	
	ABC+3TC+ZDV+NFV
Number of Subjects:	
Planned, N	50
Entered, N	53
Completed, n (%)	39 (74)
Total Number Subjects Withdrawn, n (%)	12 (26)
Withdrawn due to Adverse Events, n (%)	3 (5)
Withdrawn due to Lack of Efficacy, n (%)	0
Withdrawn for other reasons, n (%)	11 (21)
Demographics	
N (ITT)	51
Females: Males	10:41
Mean Age, years (SD)	40.2 (8.6)
Primary Efficacy Results:	
Proportion of subjects with Plasma HIV-1 RNA < 50 copies/ml	ABC+3TC+ZDV+NFV N=51
ITT/switch = included, n (%)	29 (57)
95% Confidence Interval (CI)	42, 71
ITT/switch = failure, n (%)	21 (41)
95% CI	28, 56
Secondary Outcome Variable(s):	
	ABC+3TC+ZDV+NFV N=51
Proportion of Subjects with Non-Response and Viral Rebound at Week 48	7 (14)
95% CI	6 26
Change from Baseline in CD4+ Cell Count at Week 48 (cells/mm ³)	151.3
Medication Adherence : Prescribed Dose Taken, %	84
Safety Results: An On Therapy Adverse Event/ Serious Adverse Event (AE/SAE) was defined as an AE/SAE with onset on or after the start date of medication but no later than 350 days under study.	
	ABC+3TC+ZDV+NFV N=53
Most Frequent Adverse Events – On-Therapy	
Subjects with any AE(s), n (%)	43 (81)
Diarrhoea	23 (43)
Nausea and Vomiting	14 (26)
Malaise and Fatigue	9 (17)
Pruritus	8 (15)
Allergies and Allergic Reactions	8 (15)
Abdominal Discomfort and Pain	7 (13)
Viral Skin Infections	5 (9)
Decreased White Cells	5 (9)
Sinusitis	4 (8)
Sleep Disorders	4 (8)

Serious Adverse Events - On-Therapy n (%) [n considered by the investigator to be related to study medication]	
	ABC+3TC+ZDV+NFV N=53
Subjects with non-fatal SAEs, n (%)	11 (21) [0]
Allergies and Allergic Reactions	8 (15) [0]
Bacterial Infections	1 (2) [0]
Infections	1 (2) [0]
Lung Disorders	1 (2) [0]
Viral Respiratory Infections	1 (2) [0]
Cerebrovascular Accidents	1 (2) [0]
Abdominal Distention	1 (2) [0]
Diarrhea	1 (2) [0]
Nausea and Vomiting	1 (2) [0]
Hepatitis	1 (2) [0]
Subjects with fatal SAEs, n (%)	0

Conclusion:

The quadruple regimen abacavir/lamivudine/zidovudine/nelfinavir showed a decline in viral load in 29 (57%) of the subjects, who were adults with HIV who were ART-naive with high baseline viral load. Adverse events were reported in 43 (81%) subjects with the most frequently reported being diarrhea, nausea and vomiting, and malaise and fatigue. Serious adverse events were reported in 11 (21%) subjects, with the most frequently reported being allergies and allergic reactions. No fatal serious adverse events were reported.

Publications:

No Publication

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