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Study No.: QUAD001 (COL30470)		
Title: A Pilot, Randomised, Open-Label, Monocenter Study to Evaluate the Safety and Efficacy of a Quadruple Combination Therapy of Triple Combination Tablet (Trizivir) [abacavir, lamivudine, zidovudine] Plus Saquinavir-SGC/Ritonavir Versus Triple Combination Therapy of Combivir Plus Saquinavir-SGC/Ritonavir in treatment naïve HIV-1 Infected Subjects with High Plasma HIV-1 RNA Levels and Low CD4 Cell Count		
Rationale: The combination of abacavir/ lamivudine/ zidovudine (ABC/3TC/ZDV triple combination tablet) has many of the desirable characteristics of a compact regimen. The combination is very effective in suppressing viral replication: all the components have simple dosing requirements without restrictive dietary requirements; and there is low potential for drug-drug interactions with other therapies for HIV and opportunistic infections. This pilot study was designed to compare the antiviral effect and durability of response in subjects who receive abacavir/lamivudine/zidovudine (ABC/3TC/ZDV triple combination tablet + Saquinavir SGC/Ritonavir (TZV/SQV/r) versus AZT/3TC + Saquinavir SGC/Ritonavir (CBV/SQV/r) in therapy-naïve adults with high plasma viral load (VL) and low CD4 cell counts.		
Phase: IV		
Study Period: 10 October 2000 to 17 September 2002		
Study Design: A prospective, randomized, open-label, single centre pilot study		
Centres: A single centre in Germany		
Indication: HIV-1 infection		
Treatment: Therapy-naïve subjects with advanced HIV-1 infection (CD4 count <100/µl, VL >50.000cps/ml) received either quadruple therapy with AZT/3TC/ABC 300mg/150mg/300mg bid + Saquinavir/Ritonavir 100mg/100mg bid (TZV Arm) or triple therapy with AZT/3TC 300mg/150mg bid + Saquinavir/Ritonavir 100mg/100mg bid (CBV Arm) for 48 weeks		
Objectives: The primary objective was to evaluate the antiretroviral activity of ZDV/3TC/ABC/SQV/r vs ZDV/3TC/SQV/r as measured by the proportion of subjects with plasma HIV-1 RNA < 50 copies/ml at Week 24		
Primary Outcome/Efficacy Variable: The proportion of subjects with HIV-1 RNA < 50 copies/ml at Week 24		
Secondary Outcome/Efficacy Variable(s): Proportion of subjects with VL <50cps/ml (as-treated analysis) Absolute CD4 cell count at Week 24 and Week 48 Safety/tolerability of TZV/SQV/r vs. CBV/SQV/r.		
Statistical Methods: All randomized subjects were included in 1 of 2 Intent-to-treat (ITT) analysis populations: ITT, Switch Included summarized all available data of all randomised subjects irrespective of the actual treatment received at any timepoint but according to randomisation ITT, Switch=Failure summarized all available data of all randomised subjects but subjects were rated as treatment failure if any treatment switch occurred during the study A per-protocol (PP) population (or as-treated population) was also used for analysis. The PP population included all randomised subjects where major protocol violators or subjects taking prohibited medication were excluded. This PP population also only included data until withdrawal or the discontinuation of randomised treatment. Subjects without valid data of the primary efficacy criterion for ≥16 weeks of continuous treatment were not included to the PP population. The primary population for analysis of the primary efficacy criterion was the ITT (switch equals failure) population. For missing values at Week 24, a last observation carried forward (LOCF) analysis was done if a value was available for the preceding and the following study visit. The 2 arms were compared using a 2-sided Fisher's exact test.		
Study Population: Therapy-naïve HIV-1-infected subjects aged ≥18 years with advanced HIV-1 infection and advanced HIV-infection at baseline (CD4 count <100/µl, VL >50.000cps/ml) were eligible for study participation. Key exclusion criteria: prior antiretroviral treatment.		
Number of Subjects:	CBV/SQV/r	TZV/SQV/r
Planned, N	25	25
Randomized, N	30	29
Completed, n (%)	19 (63)	20 (69)
Total Number Subjects Withdrawn, n (%)	11 (37)	9 (31)
Withdrawn Due to Adverse Events, n (%)	8 (27)	8 (28)
Withdrawn Due to Lack of Efficacy, n (%)	0	0
Withdrawn For Other Reasons, n (%)	3 (10)	1 (3)

Demographics	CBV/SQV/r	TZV/SQV/r
N (ITT)	30	29
Females: Males	2 : 28	5 : 24
Mean Age, Years (SD)	40.4 (8.5)	37.7 (7.7)
Race, n (%)	Not Available	Not Available
Primary Efficacy Results:		
Proportion of Subjects with VL <50cps/ml at Week 24		
Rate	CBV/SQV/r N=30	TZV/SQV/r N=29
ITT (Switch=Failure), n/N (%)	16/30 (53)	18/29 (62)
p-value	>0.05	
ITT (Switch Included), n/N (%)	17/30 (57)	21/29 (72)
Secondary Efficacy Results:		
Proportion of subjects with VL <50cps/ml at Week 24 (PP Population), n/N (%)	17/20 (85)	21/22 (95)
Absolute CD4 cell count, Mean (SD)		
Baseline	36 (29)	34 (30)
Week 24	165 (86)	118 (66)
Week 48	212 (128)	191 (110)
Safety Results: An on therapy AE was defined as an AE with onset on or after the start date of study medication. An on therapy SAE was defined as an SAE with onset on or after the start date of study medication.		
	CBV/SQV/r N=30	TZV/SQV/r N=29
Most Frequent Adverse Events (AEs)– On-Therapy	n (%)	n (%)
Subjects with any AE(s), n (%)	30 (100)	29 (100)
Rash/Eczema	7 (23)	5 (17)
Pruritus	3 (10)	3 (10)
Muscular Weakness/Pain	3 (10)	1 (3)
Vertigo	4 (13)	5 (17)
Headache	2 (7)	4 (14)
Depression	4 (13)	1 (3)
Somnolence	1 (3)	2 (7)
Nausea	15 (50)	17 (59)
Diarrhoea	13 (43)	11 (38)
Vomiting	4 (13)	10 (34)
Flatulence	5 (17)	5 (17)
Dyspepsia	3 (10)	4 (14)
Abdominal Pain	1 (3)	4 (14)
Constipation	3 (10)	0
Haemorrhoids	2 (7)	1 (3)
Stomatitis	2 (7)	2 (7)
Coughing	6 (20)	3 (10)
Pharyngitis	2 (7)	1 (3)
Rhinitis	2 (7)	1 (3)
Bronchitis	0	3 (10)
Pneumonia	0	2 (7)
Anaemia	5 (17)	3 (10)
Lymphadenopathy	2 (7)	0
Nocturia	3 (10)	0
Renal Function Abnormalities	2 (7)	0
Fatigue	10 (33)	6 (21)
Influenza-like Symptoms	5 (17)	4 (14)
Fever	2 (7)	6 (21)

Allergic Reaction (not incl. Suspected ABC Hypersensitivity Reaction)	0	2 (7)
Suspected ABC Hypersensitivity Reaction	0 (4 (14)
Asthenia	1 (3)	4 (14)
Tuberculosis	0	2 (7)
Herpes Simplex Infection	2 (7)	4 (14)
Pneumocystis Carinii Pneumonia	2 (7)	2 (7)
Herpes Zoster	0	2 (7)
Serious Adverse Events (SAEs) - On-Therapy		
n (%) [n considered by the investigator to be related to study medication]		
	CBV/SQV/r N=30	TZV/SQV/r N=29
	n (%) [related]	n (%) [related]
Subjects With Non-fatal SAEs	7 (23) [1]	11 (38) [5]
Radicular Syndrome	0	1 (3) [0]
Hepatocellular Damage	0	1 (3) [1]
Weight Loss	0	1 (3) [0]
Phlebitis	0	1 (3) [0]
Pneumonia	2 (7) [0]	2 (7) [0]
Pneumothorax	1 (3) [0]	0
Renal Failure	1 (3) [1]	0
Allergic Reaction	0	3 (10) [3]
Tuberculosis	0	2 (7) [0]
Toxoplasmosis	1 (3) [0]	0
Pneumocystis Pneumonia	1 (3) [0]	1 (3) [1]
Herpes Simplex Infection	0	1 (3) [0]
Brain mass	0	1 (3) [0]
Dysphonia	0	1 (3) [0]
Anaesthetic complication	1 (3) [0]	0
Subjects With Fatal SAEs	1 (3) [0]	0
Non Hodgkin Lymphoma	1 (3) [0]	0

Conclusion:

See publication below.

Publications:

Staszewski et al: "The QUAD Study: A Pilot-Study to Assess the Efficacy and Safety of Trizivir + RTV-Boosted Saquinavir (TZV/SQVr) Compared to Combivir + RTV-Boosted Saquinavir (CBV/SQVr) in ART-Naive Patients with High viral load (VL) and Low CD4 Count. 24 Week Interim analysis. 9th European AIDS Conference, Warsaw, 25.-29.10.2003, abstract #F1/1

Date Updated: 23-Nov-2005