SYNOPSIS

Name of Sponsor/Company: University Medical Center Hamburg-Eppendorf Martinistr. 52, 20246 Hamburg	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	**(For National Authority Use only)**
Name of Finished Product: Reyataz®, Norvir®,		
Name of Active Ingredient: Atazanavir, Ritonavir		
Study Title	Immediate versus deferred antiretroviral therapy in HIV-infected patients presenting with acute AIDS-defining events (IDEAL-Study)	
Coordinating Investigator	Since 11.08.2015 Dr. med. Stefan Schmiedel Infectious Diseases Unit, Martinistr. 52, 20246 Hamburg 29.07.2011 – 10.08.2015 Prof. Dr. med. Jan van Lunzen, Infectious Diseases Unit, Martinistr. 52, 20246 Hamburg	
Study sites	Initiated sites: 1. Universitätsklinikum Hamburg-Eppendorf, Ambulanzzentrum Infektiologie, Martinistr. 52, 20246 Hamburg 2. ICH Study Center GmbH & CO. KG, Grindelallee 35, 20146 Hamburg 3. ifi Hamburg an der Asklepios Klinik St. Georg, Lohmühlenstr. 5, 20099 Hamburg 4. Klinikum Dortmund, Medizinische Klinik Nord, Münsterstr. 240, 44137 Dortmund 5. Universitätsklinikum Bonn, Innere Medizin I, Immunologische Ambulanz/Studienzentrale, Sigmund-Freud-Str. 25, 53127 Bonn 6. Universitätsklinikum Düsseldorf, Klinik für Gastroenterologie, Hepatologie und Infektiologie, MX1 und Ambulanz, Moorenstr. 5, 40225 Düsseldorf 7. Universitätsklinikum Essen, Hufelandstr. 55, 45122 Essen 8. Universitätsklinikum Frankfurt am Main, Medizinische Klinik II / Infektiologie, Theodor-Stern-Kai 7, 60590 Frankfurt 9. Universitätsklinikum Freiburg, Centrum Chronische Immundefizienz (CCI), Hugstetter Str. 55, 79106 Freiburg	

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10. Medizinische Hochschule Hannover, Klinik für Immunologie und Rheumatologie, Carl-Neuberg-Str. 1, 30625 Hannover
11. Klinikum der Universität München, Infektionsabteilung, Med. Poliklinik, Pettenkoferstr. 8a, 80336 München
12. Vivantes Auguste-Viktoria-Klinikum, Innere Klinik für Infektiologie/ Gastroenterologie, Rubensstrasse 125, 12157 Berlin
13. Universitätsklinikum Ulm, Comprehensive Infectious Diseases Center (CIDC), Sektion Infektiologie und Klinische Immunologie, Zentrum für Innere Medizin, Innere Medizin III, Albert-Einstein-Allee 23, 89081 Ulm
14. Universitätsklinikum Würzburg, Medizinische Klinik und Poliklinik II, Schwerpunkt Infektiologie, Oberdürrbacherstr. 6, 97080 Würzburg
15. Charitè Universitätsmedizin Berlin Campus Virchow Klinikum, Medizinische Klinik, Schwerpunkt Infektiologie, Augustenburger Platz 1, 13353 Berlin
16. Technische Universität München, Interdisziplinäres HIV-Zentrumamam Klinkum rechts der Isar (IZAR), Ismaniger Strasse 22, 81675 München
17. Uniklinik Köln, Klinik I für Innere Medizin, Kerperner Straße 62, 50937 Köln

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Protocol No.	IDEAL-Study (Sponsor), CTC09397 (CRO)	
EudraCT-No.	2010-022413-26	
Study Period	FSFV: 30 SEP 2011 LSLV: 28 APR 2015	
Phase of development	Phase IV, therapeutic use	
Primary Objective	**The primary objective of this clinical trial is as follows:** To compare the rates of clinical progression between both groups. Progression is defined as death, all new/relapsing opportunistic infections (OI), and other grade 4 clinical endpoints (evaluated by standardized toxicity tables) within 24 weeks after randomization.	
Secondary Objectives	**The secondary objectives of this clinical trial are:** • To evaluate and to compare hospitalization days after completion of initial OI treatment between both groups. • To evaluate the incidence of immune reconstitution inflammatory syndrome (IRIS, definition see Objectives) in both groups during the first 24 weeks. • To evaluate and to compare the virological outcome proportion in both groups. Virological outcome is assessed by HIV-1 plasma viral load at Week 24 (proportion of patients achieving HIV Ribonucleic acid (RNA) < 400/<50 copies/mL). For definition of virological failure, see below. • To evaluate and to compare the frequency changes in ART regimen for lack of efficacy or of toxicity in both groups. • To evaluate the quality of life (QOL) and the adherence to the ARV (AIDS-Associated Retrovirus) regimen in subjects starting tenofovir, emtricitabine and atazanavir/ritonavir at late stages of HIV-1-infection.	
Methodology	This was a phase IV, multicenter, prospective, randomized open-label clinical trial.	
Number of subjects	**Planned number of patients:** 105 randomized patients per arm (total of 210 patients planned) **Reached number of patients:** 61 patients were enrolled in the trial and 52 subjects completed the clinical trial.	

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Indication	Human immunodeficiency virus (HIV)-Infection	
Main criteria for inclusion	**Key Inclusion Criteria:** • Adult (18 years) HIV 1 infected subjects • Antiretroviral naïve (patients with no antiretroviral therapy for at least 6 months prior to screening and no evidence for prior virological failure due to resistance against NRTIs (Nucleoside reverse transcriptase inhibitors) and PIs were allowed) • HIV-1-infected patients who have developed an acute AIDS defining event, namely Pneumocystis Pneumonia ((PCP) or TE (Toxoplasmic encephalitis) (women receiving prior MTCT (Mother to Child Transmission) prophylaxis were enrolled) • Patients who were able to take or to receive antiretroviral treatment and who were able to give written consent **Key exclusion criteria:** • Renal failure or CrCl < 60 mL/min • Patients who were not able to initiate ART or with current contraindications against atazanavir/ ritonavir • Other AIDS-defining events than PCP or TE (exceptions see below) • Pregnancy/ Women of childbearing potential who wanted to become pregnant	
Duration of treatment	24 weeks	
Reference product, dose and mode of administration, batch no.	Atazanavir (ATV) capsules with 300 mg and ritonavir tablets with 100 mg, each to be taken QD with a meal. The standard NRTI backbone chosen by the treating physician was preferably the combination of emtricitabine and tenofovir DF tablets.	
Criteria for evaluation **Efficacy and Safety**	**Primary Endpoint:** Clinical Progression (death, all new or relapsing OI, other Grade 4 clinical endpoint) within 24 weeks. For G4 events standardized toxicity grading tables were used (http://www.ucdmc.ucdavis.edu/ clinicaltrials/documents/vaccine_toxicity_grading_table.pdf). For abnormalities not found in the Toxicity Tables, a Grade 4 event was defined as potentially life-threatening (extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care	

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	probable). Patients who drop out of study observation before end of week 12 are counted as clinical progression. **Secondary Endpoints:** • Hospitalization days after completion of OI treatment • Incidence of immune reconstitution inflammatory syndrome (IRIS) as judged by the site investigator (for definitions see below) compared in the two groups during the first 24 weeks. • Virological outcome at week 24 (proportion of patients achieving HIV RNA < 400 (<50 copies/mL). • Proportion of patients with changes in ARV regimen for lack of efficacy or of toxicity • to evaluate and to compare the immunological outcome proportion in both groups. • Quality of life (QOL), including overall self-reported QOL at Week 24 **Safety:** Safety data (Adverse Events (AEs), Serious Adverse Events (SAEs) and Vital Signs) was collected at all study visits. Laboratory safety test was performed and evaluated for the safety set. A Data Safety Monitoring Board (DSMB) was established in this clinical trial and was responsible for overseeing the safety of the study population	
Statistical methods	Originally intended statistical method (log-likelihood chi-square test for primary; Wilcoxon t and chi-square test for secondary endpoints) could not be applied every time due to low inclusion of patients (see above). In those cases, chi-square was replaced by Fisher´s exact test. The other tests were fully functional in spite of the small study population. Due to the too low sample size, all subgroup analyses pre-specified were discarded.	
Safety Reporting	In total, 18 SAEs were reported during the whole trial which occurred in 12 different patients out of a total of 61 study patients. 11 SAEs were observed in 8 patients of the deferred study arm and 7 SAEs were observed in 4 patients of the immediate study arm. None of the SAEs was suspected to be related to the study medication. One SAE (septic multiorgan failure) was fatal	
Over All Safety Conclusion	The observed SAE reporting range was within expected rate for	

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	HIV-1 infected patients with advanced stages of immunodeficiency treated with an antiretroviral therapy. No new information affecting the safety evaluation of the IMP could be detected. There was no new information giving cause for altering the safety assessment for the IMP. In general, the study medication was well tolerated. There were no unsuspected adverse events related to the study medication. Most adverse events were mild (grade 1, grade 2) and only few adverse events grade 4, severe adverse events, drop-outs occurred. The total number of events (drop-out, AE grade 4, SAE) was, considering the severity of the underlying condition, equally low in both treatment groups. Due to the small size of the two treatment groups, small differences of the incidence rates of SAE, i. e. incidence of opportunistic infections, might not have been detected.	
Efficacy Conclusion	The number of events were similar in both treatment groups (deferred: in 9 of 31 patients / immediate in 9 of 30 patients; Chi^2 0.0069, probability 0.9340). No causalities occurred in either of both groups. Within 24 weeks after onset of therapeutically treatment there were significant differences in the primary endpoint when recruitment target/goal was not achieved.	
Conclusion	Only 61 patients were enrolled into the study. Due to the small size of the two treatment groups, small differences of incidence rates of SAE might not have been detectable. In summary this small study supports the hypothesis that immediate initiation of antiretroviral therapy with an ritonavir-boosted proteinase-inhibitor and a combination of two nucleoside reverse transcriptase inhibitors is save and has no negative effects on incidence of disease progression or immune reconstitution inflammatory syndrome, nor on immunological and virological outcome or on quality of life.	
Date of Report	14 July 2017	