Randomized, stratified, placebo-controlled, parallel group trial to evaluate an oral dose of 10 mg Olanzapine (OLN) in combination with Riluzol (RIL) for the treatment of undesired weight lossthrough cachexia and malnutrition in patients with amyotrophic lateral sclerosis (ALS)

Investigational drug: Olanzapine

Eudra-CT Number: 2007-003775-39

Final Report

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Sponsor of the clinical trial:

Charité – Universitätsmedizin Berlin
Prof. Dr. Thomas Meyer

Principal investigator of the clinical trial:

Prof. Dr. Thomas Meyer

Author of the final report:

Dr. André Maier

Title of Study	Randomized, stratified, placebo-controlled, parallel group study on the evaluation of the effectiveness and tolerability of an oral dose of 20 mg Olanzapine (OLN) in combination with Riluzol (RIL) for the treatment of cachexia in patients with amyotrophic lateral sclerosis (ALS).
Type of project	Clinical Trial Phase II (AMG)
Independent Ethics Committee (IEC)	The study was positively evaluated by the Ethics Committee of the State of Berlin (reference number 07/0423 - ZS EK 15).
Sponsor / Deputy	Investigator Initiated Trial (IIT) Prof. Dr. Thomas Meyer Charité –Universitätsmedizin BerlinCampus Virchow-Klinikum Neurologische Klinik und Poliklinik Augustenburger Platz 1, 13353 Berlin Tel. 030.450-660032; 030.450-560132 (Sekretariat) Fax: 030.450-560907 E-Mail: thomas.meyer@charite.de
Principal investigator of the clinical trial	Prof. Dr. Thomas Meyer Charité –Universitätsmedizin BerlinCampus Virchow-Klinikum Neurologische Klinik und Poliklinik Augustenburger Platz 1, 13353 Berlin Tel. 030.450-660032; 030.450-560132 (Sekretariat) Fax: 030.450-560907 E-Mail: thomas.meyer@charite.de
Principal investigator in centers	Monocenter Trial
study centers:	Charité -Universitätsmedizin Berlin Augustenburger Platz 1, 13353 Berlin
Publication of the study (Reference)	Early termination, no results published
Study period	Planed recruitment: Patient recruiting 04-2009 until 10-2009; duration of the study including run-in phase: 64 weeks. Conclusion of the clinical study: 01-2011.
Study goals	An undesired weight loss in ALS of at least 10% of the outset weight (ALS cachexia) should be reduced through the weight increasing effect of OLN. The hypothesis of the efficacy study states that the undesired weight loss of ALS patients during treatment with 20 mg OLN and 100 mg Riluzol (RIL) is at least about 20% less than the weight loss of patients treated with placebo and 100 mg RIL. The hypothesis on the tolerability states that the number of undesired pharmacological effects, undesired events, and seriously undesirable events during treatment with 20 mg OLN and 100 mg RIL deviates no more than 20% from a treatment with placebo and 100 mg RIL.
Primary target parameter	Body Mass Index (BMI) measured as body weight (kg)/body height (m) squared, and as the monthly change of the BMI (monthly ΔBMI).
Secondary target parameters	• Number and severity of unexpected events (UE), severe adverse events (SAE) • Number of patients who complete treatment with OLN and RIL in comparison to number completing placebo and RIL. • Body weight in kg • Monthly change in body weight (monthly Δkg) • Percent change of body weight (ΔKG%) • Percent change of

	the BMI (ΔBMI%) • Number of patients with a BMI <18.5 kg/m2 • Body composition according to bioimpedemence spectroscopy • Serum concentrations of glucose, cholesterol, trigylcerides, and leptine • Evaluation of the ALS severity degree by means of the ALS-Functional Rating Scale, revised (ALS-FRS-R) • Monthly change of the ALS-FRS-R (monthly ΔALS-FRS-R) • Muscle strength measurement by means of Manual Muscle Testing (MMT) • Respiratory Function measured as forced vital capacity • Quality of sleep and daily tiredness, measured with a patient assessment scale (Epworth Sleeping Scale – ESS) • Number of patients who need a percutaneous endoscopic gastrostomy (PEG) • Number of patients who need a continuous non-invasive ventilation or a tracheostoma-supported invasive ventilation • Determination of the survival time or of the timepoint of a tracheotomy after the beginning of paresis
Study design	Randomized, stratified, placebo-controlled parallel group study for the evaluation of the efficacy, safety and tolerability of 5 mg OLN and weekly dose escalation to 20 mg OLN and subsequent treatment with 20 mg OLN for 52 weeks in combination with RIL as compared to placebo in combination with 100 mg RIL in patients with ALS and unintended weight loss. Before randomization, there is an open run-in phase for 12 weeks, during which the undesired weight loss before the beginning of pharmacological intervention will be measured. By measuring the BMI and body weight at the beginning and end of the run-in phase, it can be determined whether the inclusion criteria of weight-loss despite optimal eating is present and whether there is a high-degree body-weight loss (loss of > 2.5% of body weight during the run-in phase) or a low-degree body-weight loss (loss of < 2.5% of the initial weight). Randomization will take place according to the progression rate of the body-weight loss (body weight loss of > 2.5% vs. < 2.5% during the run-in phase). An intermediary evaluation is planned for when 15 patients in each the OLN therapy group and in the placebo group have reached visit 8 (the 28th treatment week).
Investigational medication / treatment strategy	Study Medication: OLN10mg (2coatedtablets ZYPREXA 5mg) in combination withRIL100mg.
Treatment/Intervention	5 mg OLN and weekly dose escalation to 20 mg OLN and subsequent treatment with 20 mg OLN for 52 weeks in combination with RIL as compared to placebo in combination with 100 mg RIL in patients with ALS and unintended weight loss.
Comparison condition/ medication	Placebo-controlled parallel group study for the evaluation of an oral dosage of 5mg OLN with a dose increase up to 10 mg OLN in combination with 100 mg RIL, in comparison to treatment with placebo in combination with 100 mg RIL
Total number of patients	40 (treatment of 20 patients with 20 mg OLN and 100 mg RIL and treatment of 20 patienten with placebo and 100 mg RIL)
Study population	The study was terminated prematurely because the recruitment goal was not achieved. The study population was not analyzed.

Inclusion criteria	• Patients between ages 25 and 80 • Clinical diagnosis of definitive, probable, and possible ALS (revised El Escorial criteria) or diagnosis of the clinical ALS variants of a progressive muscle atrophy (PMA) • Sporadic and familial ALS • Beginning of symptoms with pareses at least 6 months ago • Treatment with RIL 100 mg/day since at least 1 month • Loss ≥ 10% of the premorbid body weight for a BMI ≤ 25 kg/m2 or loss ≥ 5% of the des pre morbid body weight for a BMI ≤ 20 kg/m2 • No increase of body weight in the preceding 3 months before inclusion into the study • Progression rate of the ALS degree of severity according to the ALS-Functional Rating Scale, revised (ALS-FRS-R) with a monthly change of the ALS-FRS-R (monthly ΔALS-FRS-R) ≥ 0.2 per month • Sufficient swallowing function with a subscore of the ALS-Functional Rating Scale, revised (ALS-FRS-R) for swallowing funtion ≥ 2 • Patient consent
Exclusion criteria	• Patients with known oversensitivity to OLN or RIL • History of cardiopulmonary reanimation and prevention of sudden cardiac death • History of ventricular tachycardia • Pregnant or lactating women • Eating disorders • Onset of weight loss > 12 months before the beginning of paresis • Intentional weight loss • History of thrombotic events, including deep leg vein thrombosis and lung artery embolism • Clinically significant EKG changes, including a symptomatic bradycardia • Laboratory parameters outside the normal range which are linked to a clinically significant cardiovascular, pulmonological, hemotological, hepatological, metabolic, or renal illness • Patients with serum transaminase (ALT/ AST) elevated more then 3x the uppermost normal value • Patients with Bilirubin and Gamma-Glutamyl-Transferase levels (GGT) elevated above the normal range • Severe neutropenia (<750/mm3) • Treatment with substances that are metabolized by the Cytochrom P450 system CYP1A2 (e.g. Carbamazepin, Fluvoxamin, and Ciprofloxacin) • Simultaneous use of Valproat • Use of psychotropic substances within the past 12 months • Chronic use of alcohol with alcohol dependence syndrome • Clinically severe co-morbidities, including psychiatric illnesses • Diabetes mellitus • Prostate hyperplasia • History of paralytic ileus • Epilepsy or history of a seizure • Treatment with hepatotoxic medication • Treatment with another typical or atypical neuroleptic • Extrapyramidal movement disorders, including late dyskinesias

	• Hypotonia and history of recurring syncopes (> 1 syncope) • Dementia • insufficient patient competence to give informed consent • Treatment with an other study medication < 1 Monat before the beginning of this study
presentation of demography and baseline characteristics	The study was terminated prematurely because the recruitment goal was not achieved. The study population was not analyzed.
Presentation Effectiveness	The study was terminated prematurely because the recruitment goal was not achieved. The trial medication could not be tested for efficacy.
Display of the Safety	The study was terminated prematurely because the recruitment goal was not achieved. The trial medication could not be evaluated for safety according to the protocol.

SUMMARY:

The failure to meet the recruitment target (<10 participants) and the resulting premature termination of the study was not due to the investigational substance itself. Unfortunately, no further result of this study can be reported.