CLINICAL TRIAL PROTOCOL

(German Drug Law)

Efficacy, Safety and Tolerability Study of 1 mg Rasagiline in Patients with Amyotrophic Lateral Sclerosis (ALS) Receiving Standard Therapy (Riluzole)

– An AMG Trial with a market authorized substance

Short Title: RAS-ALS Trial

EudraCT: 2011-004482-32

Sponsor trial code: RAS-ALS

IZKS trial code: 2011-013

Final

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List of abbreviations

AE	Adverse event
ALS	Amyotrophic lateral sclerosis
ALAT	Alanine-Aminotransferase
ALSFRS-R	ALS Functional Rating Scale – Revised
AMG	German drug law (Arzneimittelgesetz)
ASAT	Aspartate-Aminotransferase
CK	Creatinkinase
CRF	Case report form
CV	Curriculum vitae
DMP	Data Management Plan
DSMB	Data Safety and Monitoring Board
EC/IEC	Ethics committee/Independent ethics committee
eCRF	Electronic case report form
fALS	Familial amyotrophic lateral sclerosis
FAS	Full Analysis Set
FPI	First patient in
GCP	Good clinical practice
GCP-V	GCP regulation
Hb	Hemoglobin
HCG	Human Choriongonatropin
Hct	Hematocrit
ICH	International conference on harmonization of technical requirements for registration of pharmaceuticals for human use
IMP	Investigational medicinal product
INN	International nonproprietary name
IRB	Institutional review board
ISF	Investigator site file
ITT	Intention-To-Treat
IZKS	Interdisciplinary Center for Clinical Trials
LKP	Clinical Trial Director according to AMG (Leiter der Klinischen Prüfung)
LPI	Last patient in
LPO	Last patient out
MAO	Monoaminooxidase
MCH	Mean corpuscular/cellular hemoglobin
MCHC	Mean corpuscular/cellular hemoglobin concentration
MCV	Mean cell volume
MedDRA	Medical dictionary for regulatory activities terminology
PLT	Thrombocytes, platelets
PPS	Per-protocol analysis set
RBC	Red blood cells
SAE	Serious adverse event
SAP	Statistical analysis plan
SDV	Source data verification
SEIQoL	Schedule for the Evaluation of Individual Quality of Life
SmPC	Summary of product characteristics
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse reaction
sVC	Slow vital capacity
TMF	Trial master file
WBC	White blood cells

Synopsis

Title	Efficacy, Safety and Tolerability Study of 1 mg Rasagiline in Patients with Amyotrophic Lateral Sclerosis (ALS) Receiving Standard Therapy (Riluzole) – An AMG Trial with a market authorized substance
Short title	RAS-ALS Trial
EudraCT	2011-004482-32
Sponsor trial code	RAS-ALS
IZKS trial code	2011-013
Indication	Amyotrophic Lateral Sclerosis (ALS)
Phase	IIb
Treatments	Test product: Rasagiline 1 mg over 18 months Control: Placebo Standard therapy: Riluzole 100 mg
Primary objective	Efficacy of rasagiline as add-on therapy to standard therapy with riluzole in patients with ALS compared to placebo in terms of survival (mortality exclusively defined as death).
Secondary objectives	Secondary objectives are to assess: • the change of total score of ALS Functional Rating Scale – Revised (ALSFRS-R) • the change in individual Quality of Life (SEIQoL, Schedule for the Evaluation of Individual Quality of Life) • the change of the slow vital capacity (sVC)
Trial design	Multicenter, randomized, stratified, parallel-group, double-blind, placebo-controlled phase IIb-study
Trial population	**Main inclusion criteria:** Patients meeting all of the following criteria will be considered for enrollment to the trial: - possible, probable (clinically or laboratory) or definite ALS according to the revised version of the El Escorial World Federation of Neurology criteria - disease duration more than 6 months and less than 3 years (inclusive). Disease onset defined as date of first muscle weakness, excluding fasciculations and cramps - vital capacity more than 50% of normal (slow vital capacity; best of three measurements) - age: ≥ 18 years - continuously treated with 100 mg riluzole for at least four weeks - capable of thoroughly understanding all information given and giving full informed consent according to GCP - women of childbearing age must be non-lactating and surgically sterile or using a highly effective method of birth control and have a negative pregnancy test **Main exclusion criteria:** Patients presenting 1 of the following criteria will not be enrolled in the trial: - previous participation in another clinical study within the preceding 12 weeks - tracheostomy or assisted ventilation of any type during the preceding three months - gastrostomy - any medical condition known to have an association with motor neuron dysfunction which might confound or obscure the diagnosis of ALS - presence of any concomitant life-threatening disease or impairment likely to interfere with functional assessment - patients on sympathomimetic agents, including pseudoephedrine, phenylephrine, phenylpropanolamine, and ephedrine - patients on analgesics with serotoninergic properties such as meperidine, tramadol, methadone and propoxyphen - patients on serotonin reuptake inhibitors (SSRIs),including fluoxetine or fluvoxamine - patients on serotonin noradrenalin reuptake-inhibitors (SNRIs) and patients on tricyclic and tetracyclic antidepressants - patients on dextromethorphan, St. John's wort, cyclobenzaprine or other MAO

	inhibitors (selective or non-selective) - confirmed hepatic insufficiency or abnormal liver function (ASAT and/or ALAT greater than 3 times the upper limit of the normal range) - renal insufficiency (serum creatinine more than 2.26 mg/dL) - evidence of major psychiatric disorder or clinically evident dementia precluding evaluation of symptoms - known hypersensitivity to any component of the study drug - liable to be not cooperative or comply with the trial requirements (as assessed by the investigator), or unable to be reached in the case of emergency - female with childbearing potential, if no adequate contraceptive measures are used - pregnancy or breast-feeding females
Trial duration and dates	The duration of the whole trial is 36 months: the length of recruitment period is 6 months, duration of treatment will be 18 months, the period for cleaning the data, carrying out statistical analyzes, and writing the final study report will be 12 months.
Number of patients	It is planned to enroll 250 patients (2 x 125 patients)
Number of sites	About 15 trial sites in Germany are planned to participate.
Primary endpoint	Primary efficacy endpoint: survival time (time to death).
Secondary endpoints	**Key secondary endpoints(s):** - change of total score of ALS Functional Rating Scale - Revised (ALSFRS-R) - change in individual Quality of Life (SEIQoL, Schedule for the Evaluation of Individual Quality of Life) - change of the slow vital capacity (sVC)
Safety variables	Vital signs Safety laboratory parameters Terms, frequency, relationship and seriousness of adverse events (AEs), and serious adverse events (SAEs)
Statistical analysis	**Efficacy:** The ITT analysis of the primary endpoint will be done in a confirmatory manner. All other analyzes of primary endpoint, all analyzes of the secondary endpoints, and all safety analyzes are exploratory. For confirmatory data analysis, the log-rank test (one-sided) will be performed. Additionally, the difference in the survival rate (18 months survival) between control group and experimental group will be calculated, incl. 97.5% confidence interval. For further analyzes of primary endpoint, Kaplan-Meier-plots and log-rank-tests will be used. **Secondary endpoints:** The secondary endpoints will be analyzed descriptively. Differences between experimental group and control group will be investigated using the Mann-Whitney-U-test. **Safety:** Listing of adverse events, performing of chi-square tests to compare frequencies between control group and experimental group.

Trial schedule

Visit / Action	Screening (V0)	Baseline (V1)	T1	V2	T2	V3	T3	V4	T4	V5
Months		Inclusion	1	2	3	6	9	12	15	18
Patient information and informed consent	X									
Inclusion/exclusion criteria checking	X	X								
Demographics (e.g. sex, age, race)	X									
Medical history	X									
Vital capacity	X	X		X		X		X		X
Status (El Escorial Criteria)	X									
Randomization		X								
Concomitant treatment	X	X	X	X	X	X	X	X	X	X
Physical examination	X									
Vital signs	X	X		X		X		X		X
Height (only at screening), Weight	X	X	X	X	X	X	X	X	X	X
ALSFRS-R		X	X	X	X	X	X	X	X	X
SEIQoL		X		X		X		X		X
Study Drug delivery		X		X		X		X		
Drug Accountability				X		X		X		X
Laboratory tests	X	X		X		X		X		X
Genetic testing (with consent of patient)		X								
Pregnancy test (serum HCG level)	X									
Compliance (asked for)			X	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X	X	X
End of trial (final visit)										X

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1 INTRODUCTION

1.1 Scientific background

Amyotrophic lateral sclerosis (ALS) is a severe neurodegenerative disease characterized by progressive degeneration of the anterior horn cells of the spinal cord, their homologues in the brain stem and the upper motor neurons in the primary motor cortex. Clinically, the disease progresses from initial asymmetric weakness, wasting and atrophy to complete loss of spinal and bulbar motor functions. The upper motor neuron component is clinically mirrored by hyperactive tendon jerks, pseudobulbar emotional lability, and less frequently spasticity.

The ALS Research Committee of the World Federation of Neurology has established research diagnostic guidelines, the El Escorial criteria [1, 2] (http://www.wfnals.org). ALS is considered an orphan disease: its incidence is estimated with 1.5 –3 /100000/year and prevalence rates are 3-6/100000 [3]. Treatment of ALS remains unsatisfactory; riluzole, a benzothiazole derivative and glutamate release blocker, has been approved for use in ALS because of its modest effect on survival [4]. The drug is generally well tolerated by the patients although liver toxicity must be controlled (http://www.cochrane.org).

Based on a rare cause of the disease, mutations in the gene for the cytosolic form of the copper/zinc superoxide dismutase (Cu/Zn SOD), a transgenic animal model has been developed. This G93A model of fALS has led to the discovery of several experimental drugs; in particular, a dose-dependent effect of rasagiline on survival (alone and in combination with riluzole) has been demonstrated in a mouse carrying a low copy number of the human disease-causing gene [5].

Rasagiline [N-propargyl-(1R)-aminoindan] is a selective irreversible second-generation monoaminooxidase (MAO)-B inhibitor with symptomatic efficacy in Parkinson´s disease (PD) with a favourable tolerability profile [6]. Preclinical studies have demonstrated that rasagiline has neuroprotective effects both in in vitro and in vivo models, suggested to be related to its propargyl moiety rather than MAO inhibition. Structure activity studies have established that N-propargylamine is essential for the neuronal cell survival activity of rasagiline since this moiety itself revealed similar protective effects and mechanisms of actions [5]

The mechanisms underlying disease-modifying effects of rasagiline have been investigated in detail in another neurodegenerative disease. Clinical studies using rasagiline showed the following: the TEMPO trial demonstrated that early Parkinson's Disease (PD) patients who received once-daily rasagiline (2 mg/d) for 1 year had significantly less deterioration in clinical scores than those who received 6 months of placebo treatment followed by 6 months treatment with 2 mg/d rasagiline [7]. The ADAGIO study [6] which had been designed to investigate prospectively the potential of rasagiline to delay disease progression and was performed in a total of 1176 patients with early PD. It could be demonstrated that early treatment with rasagiline 1 mg/d provided benefits that could not be achieved with delayed introduction of the same drug. These results are consistent with the hypothesis that rasagiline has a “disease modifying” effect, and possible explanations for such an effect could involve neuroprotection and/or preservation or enhancement of supportive compensatory mechanisms.

1.2 Trial rationale

ALS is seen as a rare disease; however, the current incidence rates in the industrialized world of 2.5-3/100000 imply that more than each 500th living German citizen will die of ALS. Up to now only one substance, riluzole, is approved for the treatment of patients with ALS [8]. However, this drug has only a modest effect on survival of these patients since - depending on the stage of the disease - this effect prolongs survival about three to six months. This situation remains unsatisfactory for the ALS patients and the physicians treating such patients. Therefore much more

effort is needed to develop further appropriate therapies that will slow or stop this devastating disease.

Rasagiline has demonstrated a significant, dose-dependent therapeutic effect on both preclinical and clinical motor function and survival of G93A mice. The largest extension of life span of about 20% was observed with the combination of riluzole and rasagiline and was also dose-dependent [5].

Rasagiline is an anti-apoptotic compound and has demonstrated neuroprotective effects in a variety of primary neuronal preparations and neuron-like cell lines [9]. Clinical studies have also demonstrated possible neuroprotective properties of rasagiline in human Parkinson patients who showed a decelerated disease progression after treatment with 1mg/day rasagiline (ADAGIO trial) [6].

These positive clinical results and the effects of rasagiline in the ALS mouse model justify a clinical study in patients with ALS.

Positive results of this trial could lead to a further development of the treatment of ALS patients.

1.3 Treatments and rationale for dose selection

Experimental group: Patients are treated with 100 mg/day riluzole (standard therapy for ALS) and additionally with 1mg/day rasagiline. Rasagiline is approved for the treatment of Parkinson's disease by the FDA and the EMA with a dose of 1mg/day and there is no evidence that additional benefit will be obtained from the administration of higher doses. Furthermore, higher doses will likely result in a loss of selectivity of rasagiline towards MAO-B with an increase in the inhibition of MAO-A.

Control group: Patients are treated with riluzole (standard therapy for ALS) and additionally with placebo.

The need for a double-blind, placebo-controlled, prospective trial is justified since - if positive – an attempt will be made to introduce rasagiline into routine treatment of ALS which needs to be accepted by the regulatory authorities (EMA, FDA).

1.4 Summarized risk-benefit assessment

ALS is a devastating disease which dramatically reduces the life expectancy and physical well-being of the patient. The potential risks of every treatment of ALS must be seen against this background.

Rasagiline is approved for the treatment of Parkinson's disease by the FDA and the EMA, hence the safety profile of rasagiline in humans is well-known. In patients with Parkinson's disease it was possible to show a disease-modifying effect by rasagiline (ADAGIO trial) [6]. Therefore it is considered justified and safe to assess the effect of rasagiline in patients with the neurodegenerative disease ALS.

Placebo as comparator is acceptable in this case since both placebo and rasagiline are given as add-on to the standard therapy riluzole.

A direct interaction of the two substances Rasagilin and Riluzol with adverse effects is not expected due to the different mechanism of action. Rasagiline is a substance presumably reducing oxidative stress by inhibition of monoamine oxidase B (MAO-B) [13]. However, neuroprotection with rasagiline has also been linked to its effects on preserving mitochondrial membrane potential [14]. The mechanism of action of riluzole is thought to be related to its stabilizing effect on sodium channels and the resulting reduction of presynaptic glutamate release [15]. The substance could be indicated as an antiglutamatergic drug to prevent the toxic effects of glutamate on motoneurones.

The neuroprotective effect of riluzole – the standard therapy for patients with ALS – could be increased by the neuroprotective effect of rasagiline. Therefore a stronger effect on the course of the disease in ALS patients is expected. The investigator will be informed about any relevant or new finding including AEs relating to treatment with the investigational medicinal product.

Evaluations which will be performed at the study visits comply with the routine assessments for ALS patients, except that there is higher frequency of performance. Routine assessments for ALS patients are usually performed approximately twice a year.

2 TRIAL OBJECTIVES

The purpose of this trial is to assess the efficacy of rasagiline (1mg/day) as add-on therapy to the standard therapy with riluzole in patients with ALS compared to placebo in terms of survival.

2.1 Primary objective

The primary objective of the trial is to investigate the survival time (the time from randomization until death or end of the trial) compared between control group and experimental group.

2.2 Secondary objectives

The secondary objectives of the trial are to assess:

- Change of total score of ALS Functional Rating Scale – Revised (ALSFRS-R) [10]
- Change in individual Quality of Life (SEIQoL [11], Schedule for the Evaluation of Individual Quality of Life)
- Change of the slow vital capacity (sVC)

2.3 Assessment of Safety

Assessment of clinical tolerability and safety will be performed by comparison of vital signs, adverse events terms and incidence, and clinical laboratory values across both treatment groups.

3 TRIAL DESIGN

This is a prospective, multicenter, randomized, stratified, parallel-group, double-blind trial comparing placebo with 1 mg/d rasagiline as add-on therapy to 100 mg riluzole in amyotrophic lateral sclerosis (ALS) in 250 enrolled patients. For entry, the El Escorial Criteria for the diagnosis of ALS will be used. The patients have to be stable on riluzole at least 4 weeks prior to randomization. After patients are screened for inclusion and exclusion criteria, they will be randomly assigned to treatment with either placebo or 1 mg/d rasagiline according to their stratum (bulbar onset vs. spinal onset). The trial requires an initial screening visit (V0), one baseline visit (V1), 3 subsequent control visits (V2 – V4), a final visit (V5) and four telephone contacts (T1 – T4). The population consists of 250 enrolled ALS patients as defined by the El Escorial criteria (revised version). 125 patients will be randomized to treatment with 1 mg/d rasagiline and 125 patients to treatment with placebo, respectively.

The gender distribution for ALS is in favor for men (2 men in 1 woman). There are no specific requirements concerning the gender distribution within this trial as there are no differences in the course of disease. This is a multicenter study including about 15 sites in Germany. Each trial site will recruit 10 to 30 patients.

3.1 Trial duration and schedule

The estimated duration of the whole trial will be about 36 months: 6 months for recruitment, 18 months for the treatment period and 12 months for cleaning the data, carrying out statistical analyzes, and writing the final study report. The actual overall trial duration or patient recruitment period may vary from this estimate.
The trial duration for each patient is expected to be up to 1 month for screening and 18 months for the treatment period.

The estimated time from first patient in to last patient out will be 24 months. Recruitment of patients will start in Q1, 2013, so the anticipated end of trial of the last patient will be in Q1 2015.

3.2 Number of patients

It is planned to enroll 250 patients in the clinical trial, i.e. 125 patients per treatment group.
A previous study [GERP ALS-Study; 12] showed a drop-out rate of about 15 %, screening failure was observed in about 10 %. Thus, in total 250 patients have to be allocated (with consideration of a drop-out rate) and a total number of 278 patients have to be assessed for eligibility.
Recruitment and treatment of patients is expected to be performed in about 15 trial centers.

3.3 Primary endpoint

The primary endpoint is the time to death. Mortality is exclusively defined as death.

3.4 Secondary endpoints

- Change of total score of ALS Functional Rating Scale - Revised (ALSFRS-R)
- Change in individual Quality of Life (SEIQoL, Schedule for the Evaluation of Individual Quality of Life)
- Change of the slow vital capacity (sVC)

3.5 Safety variables

Safety and tolerability of rasagiline will be investigated using the following parameters as vital signs, safety laboratory parameters, terms and frequencies of adverse and serious adverse events.

3.6 Measures taken to minimize/avoid bias

3.6.1 Randomization

This trial has two parallel groups (rasagiline versus placebo as add-on to standard treatment with riluzole), is randomized, and treatment groups are completely masked (double-blind trial). The randomization will be performed stratified according to bulbar onset or spinal onset of the disease, and separate for each trial center.

At the screening visit (V0), each patient will receive the next consecutive screening number.

At the randomization visit (V1), each patient eligible for study participation will receive the next consecutive randomization/patient number according to his stratum (bulbar onset vs. spinal onset) from a block of randomization numbers per site. Patients will be assigned to the bulbar or spinal stratum according to the location of the earliest experienced ALS symptom (defined by the first muscle weakness, or in the case of bulbar onset, by the presence of dysarthria and/or dysphagia). In the case of a patient with simultaneous onset of spinal and bulbar symptoms, onset will be defined as bulbar. Cervical and respiratory onsets are stratified to the spinal-onset stratum. This stratum assignment must be consistent with the diagnosis and clinical assessment (i.e., maximum score on bulbar scale and low score on manual muscle testing would contradict the assignment to bulbar stratum). The randomization list will be generated by the Institute of Epidemiology and

Medical Biometry Ulm University, Germany, using a validated system, which involves a pseudo-random number generator to ensure that the resulting treatment sequence will be both reproducible and non-predictable. Study medication will be packed by TEVA Pharma GmbH and blinded by the Pharmacy of the University Hospital Ulm, Germany, according to the randomization list. Each patient medication bottle will be sent together with the sealed unblinding codes to the sites. The investigator at the site takes care that each patient will be provided with the study medication box of the correct randomization number.

The randomization list will be kept in safe and confidential custody at Pharmacy of the University Hospital Ulm, Germany.

3.6.2 Blinding

Blinding of the investigator and patient is achieved by providing rasagiline and matching placebo tablets.
Together with the trial medication the investigator will receive a set of sealed envelopes, one for each randomization number. These envelopes contain information on the patient's trial medication and are to be opened only under circumstances in which it is medically imperative for diagnostic or therapeutic decisions to know what the patient is receiving. Date and reason for opening of a sealed envelope must be documented by the investigator or an authorized person on the open envelope, on the CRF and on the medical record of the patient. In either case before unblinding, the investigator should attempt to consult the coordinating investigator (LKP). The randomization envelopes are not to be opened by the investigator at the end of the trial. All envelopes will be checked and collected by the monitor at the end of the trial.

3.7 Selection and withdrawal of patients

No patient will be allowed to enroll in this trial more than once.

3.7.1 Inclusion criteria

Patients meeting all of the following criteria will be considered for admission to the trial:

- Possible, probable (clinically or laboratory) or definite ALS according to the revised version of the El Escorial World Federation of Neurology criteria
- Disease duration more than 6 months and less than 3 years (inclusive). Disease onset defined as date of first muscle weakness, excluding fasciculations and cramps
- Vital capacity more than 50% of normal (slow vital capacity; best of three measurements)
- Age: ≥ 18 years
- Continuously treated with 100 mg riluzole for at least four weeks
- Capable of thoroughly understanding all information given and giving full informed consent according to GCP
- Women of childbearing age must be non-lactating and surgically sterile or using a highly effective method of birth control and have a negative pregnancy test. Acceptable methods of birth control with a low failure rate i.e. less than 1% per year) when used consistently and correct are such as implants, injectables, combined oral contraceptives, hormonal intrauterine devices (IUDs), or double-barrier methods (condom or diaphragm with spermicidal agent or IUD), sexual abstinence or vasectomized partner

3.7.2 Exclusion criteria

Patients presenting with any of the following criteria will not be included in the trial:

- Previous participation in another clinical study within the preceding 12 weeks
- Tracheostomy or assisted ventilation of any type during the preceding three months
- Gastrostomy
- Any medical condition known to have an association with motor neuron dysfunction which might confound or obscure the diagnosis of ALS
- Presence of any concomitant life-threatening disease or impairment likely to interfere with functional assessment
- Patients on sympathomimetic agents. This includes pseudoephedrine, phenylephrine, phenylpropanolamine, and ephedrine.
- Patients on analgesics with serotoninergic properties such as meperidine, tramadol, methadone and propoxyphen.
- Patients on serotonin reuptake inhibitors (SSRIs). This includes fluoxetine or fluvoxamine.
- Patients on serotonin noradrenalin reuptake-inhibitors (SNRIs) and patients on tricyclic and tetracyclic antidepressants
- Patients on dextromethorphan, St. John's wort, cyclobenzaprine or other MAO inhibitors (selective or non-selective)
- Confirmed hepatic insufficiency or abnormal liver function (ASAT and/or ALAT greater than 3 times the upper limit of the normal range)
- Renal insufficiency (serum creatinine more than 2.26 mg/dL)
- Evidence of major psychiatric disorder or clinically evident dementia precluding evaluation of symptoms
- Known hypersensitivity to any component of the study drug
- Liable to be not cooperative or comply with the trial requirements (as assessed by the investigator), or unable to be reached in the case of emergency
- Female with childbearing potential, if no adequate contraceptive measures are used
- Pregnancy or breast-feeding females

3.7.3 Withdrawal criteria

Patients can withdraw their consent at their own request without given reasons at all times during the trial. This should be without disadvantages for the patient.

Whenever possible, all patients prematurely discontinuing study medication should perform an early termination visit including the same evaluations as scheduled for visit V5. The reason(s) for premature cessation of a patient's participation during the trial, other than death, should be specified on the case report form.

Study treatment may be stopped prematurely if any of the following events occur, according to the judgment of the investigator:

- Significant intolerance of the study medication, or significant clinical or laboratory findings, e.g. increase in ASAT or ALAT >3 times the upper limit of normal

- Significant intercurrent illness or emergency situation requiring cessation of the study
- The patient wishes to terminate his/her participation in the study
- Investigator judgment that it is in the best interest of the patient
- Failure to comply with the investigational procedures
- Pregnancy
- Technical reasons (change of physician, change of address of volunteer/patient)

Patients who have started double-blind treatment will not be replaced.

For any patient prematurely discontinuing the study, the investigator must:

- Recover all the treatment units given to the patients
- In as far as possible, carry out all the examinations and tests planned for the final visit after withdrawal of the patient from the study
- Fill in the corresponding pages of the case report form, specifying the date and reason for premature discontinuation
- When applicable, ask the patient the reason of his/her Informed Consent withdrawal while fully respecting the patient's rights
- Where possible prescribe a visit 2 weeks after withdrawal in order to control and document any change in the patient's clinical status. If a serious adverse event occurs, the Responsible Nominated Safety Contact must be informed according to the procedures described in section 6.2.2.5. "Immediate reporting of SAEs by investigator".
- All ongoing serious adverse events of withdrawn patients have to be followed up until no more signs and symptoms are verifiable or the investigator has assessed its sequelae, even after the end of the trial.

3.7.4 Premature closure of trial sites

The sponsor has the right to close a trial site due to the following reasons:

- Major protocol violations
- Violations of legal and ethical regulations (GCP)
- Poor recruitment, no patients
- Non-compliance of investigator

3.7.5 Premature closure of the clinical trial

The following reasons the whole trial may be discontinued at the discretion of the sponsor:

- New risks for patients become known.
- Inefficacy of the trial medication becomes evident.
- Occurrence of AEs unknown to date in respect of their nature, severity, and duration or the unexpected increase in the incidence of known AEs.
- Medical or ethical reasons affecting disadvantageous the continued performance of the trial.
- Difficulties in the recruitment of patients.

The ethic committees (EC) and the competent authorities must then be informed. Should the trial be closed prematurely, all trial material (completed, partially completed, blank CRF, randomization envelopes, investigational medicinal products, etc.) must be returned to the sponsor or will be collected by the monitor.

4 TRIAL TREATMENTS

4.1 Investigational treatments

4.1.1 General information about investigational medicinal product (IMP)

Rasagiline (AZILECT®)

Drug code:	N04BD02
International nonproprietary name (INN):	Rasagiline
Formulation:	1 mg tablet
Manufacturer:	Teva Pharma GmbH
Market authorization:	Yes, for the following indication: Parkinson's disease
Dosage authorized:	1 mg/day

Placebo

Drug code:	not applicable
International nonproprietary name (INN):	not applicable
Formulation:	tablet
Manufacturer:	Teva Pharma GmbH
Dosage authorized:	1 tablet/day

4.1.2 Therapeutic effects

Rasagiline is a selective and potent irreversible monoaminooxidase (MAO)-B inhibitor. The precise mechanisms of action of rasagiline are unknown. One mechanism is believed to be related to its MAO-B inhibitory activity, which causes an increase in extracellular levels of dopamine in the striatum. The elevated dopamine level and subsequent increased dopaminergic activity are likely to mediate rasagiline's beneficial effects seen in models of dopaminergic motor dysfunction.

4.1.3 Known side effects

The following information is based on the current version of the Summary of Product Characteristics (SmPC, December 2011). The investigators will be provided with updated versions of SmPC as soon as they become available.

Rasagiline was administered to approximately 1361 patients during all phase II/III clinical trials. The long-term safety profile was similar to that observed with shorter duration exposure. There were no significant differences in the safety profile based on age or gender.

Side effects with rasagiline monotherapy:

Very frequent (≥ 1/10): Headache

Frequent (≥ 1/100, <1/10)): Flu syndrome, skin carcinoma, leukopenia, allergic reaction, depression, hallucinations, conjunctivitis, vertigo, angina pectoris, rhinitis, flatulence, dermatitis, muscular pain, neck pain, arthritis, desire to urinate, fever, malaise

Infrequent (≥1/1.000, <1/100): Apoplexia, reduced appetite, vesiculobullous rash, myocardial infarction

Warnings and precautions:

- Risk for Hypertensive Crisis and nonselective MAO inhibition above the recommended Doses
- Melanoma (Epidemiological studies have shown that patients with Parkinson's disease have a higher risk (2- to approximately 6-fold higher) of developing melanoma than the general population. Whether the increased risk observed was due to Parkinson's disease or other factors, such as drugs like rasagiline used to treat Parkinson's disease, is unclear)
- Rasagiline may cause lower blood pressure, especially postural hypotension or increase blood pressure in different patients
- Rasagiline may cause or exacerbate hallucinations or potentially other manifestations of psychotic-like behavior

4.1.4 Treatment administration

Rasagiline (oral 1 mg/day) will be provided in bottles that contain enough tablets for 3 months and some reserve.

V1 (Baseline)
A) 1 bottle with 110 tablets rasagiline, 1 mg
B) 1 bottle with 110 tablets placebo matching rasagiline 1 mg

V2 (Month 2)
A) 1 bottle with 110 tablets rasagiline, 1 mg
B) 1 bottle with 110 tablets placebo matching rasagiline 1 mg

V3 (Month 6)
A) 2 bottles with 110 tablets rasagiline, 1 mg
B) 2 bottles with 110 tablets placebo matching rasagiline 1 mg

V4 (Month 12)
A) 2 bottles with 110 tablets rasagiline, 1 mg
B) 2 bottles with 110 tablets placebo matching rasagiline 1 mg

4.1.5 Overdose instructions

Reported signs and symptoms of rasagiline overdosage in the range of 3 mg to 100 mg included, alone or in combination, any of the following: dysphoria, hypomania, hypertensive crisis and Serotonin-syndrome

There is no specific antidote for rasagiline overdose. The following suggestions are offered based upon the assumption that rasagiline overdose may be modeled after non-selective MAO inhibitor poisoning. Treatment of overdose with non-selective MAO inhibitors is symptomatic and supportive. Respiration should be supported by appropriate measures, including management of the airway, use of supplemental oxygen, and mechanical ventilatory assistance, as required. Body temperature should be monitored closely. Intensive management of hyperpyrexia may be required. Maintenance of fluid and electrolyte balance is essential. For this reason, in cases of overdose with rasagiline, dietary tyramine restriction should be observed for several weeks to avoid the risk of a hypertensive/cheese reaction.

4.1.6 Treatment assignment

The trial medication will be administered only to patients included in this trial. The medication will be given to the patient by the investigator or trial personnel that has been authorized by the investigator. If a patient misses one visit, the medication can be handed out to a relative or can be sent. If a patient misses more than one visit, the investigator should contact the sponsor in order to determine how to proceed.
Patients withdrawn from the trial retain their identification codes (e.g. randomization number). New patients will always receive a new identification code. Treatment after end of trial
At the end of the study patients will be informed about further treatment and further care options by the investigator.

4.1.7 Packaging and labeling

The trial medication will be packed by TEVA Pharma GmbH and labeled by the Pharmacy of the University Hospital Ulm according to the randomization list.

The trial medication will be labeled according to §5 GCP regulation. The label contains at minimum the following details:

- For use in clinical trial only
- Name and address of the Sponsor
- Name and address of the CRO
- Name and dosage of investigational medication
- Batch number „Ch.-B. or code number”,
- Administration form (tablets)
- Content specified by weight, volume or quantity (may be omitted or encoded for blinding reasons)
- Application form (p.o.)
- Expiry date using note “usable until”
- Storage conditions
- Keep away from children
- Patient ID, randomization number, or other code to identify the patient
- Protocol ID,
- EudraCT Number (if not contained in an accompanying document handed out to patients)

Additional statements will be printed on the label(s) as required by local regulations.

IMP assignment and traceability as required by GCP-V § 5 (1) will be realized by accurate documentation of drug accountability and compliance on an accompanying document.

4.1.8 Drug storage, supplies and accountability

The investigator will take inventory and acknowledge the receipt of all shipments of the trial medication. All trial medication must be kept in a locked area with access restricted to designated trial staff.

The trial medication must be dryly stored in accordance with manufacturer’s instructions at temperatures of 25°C or below.

The investigator will also keep accurate records of the quantities of trial medication dispensed, used, and returned by each patient on the drug accountability form.

The site monitor will periodically check the supplies of trial medication held by the investigator to verify the correct accountability of all trial medication used. At the end of the trial, all unused trial medication and all medication bottles will be completely returned to the pharmacy in case no other procedure is agreed.

It will be assured that a final drug accountability report is prepared and maintained by the investigator.

4.1.9 Procedures for monitoring patient compliance

Trial medication will be dispensed to the patients by the investigator.

Patients will be instructed to bring all trial medication to the trial site at every visit (including all empty bottles and unused trial medication). Compliance will be assessed by counting of the remaining tablets. Details will be recorded in the CRF and on the drug accountability form in the investigator site file.

4.2 Not permitted medication

The following concomitant treatments are not permitted during the trial:
(Contraindications for rasagiline)

- Meperidine, tramadol, methadone or propoxyphene
- Dextromethorphan, St. John's wort or cyclobenzaprine
- Sympathomimetic amines, including amphetamines as well as cold products and weight-reducing preparations that contain vasoconstrictors (e.g., pseudoephedrine, phenylephrine and ephedrine).
- Serotonin reuptake inhibitors (SSRIs), including fluoxetine or fluvoxamine.
- Serotonin noradrenalin reuptake-inhibitors (SNRIs)
- Tricyclic and tetracyclic antidepressants
- Other MAO inhibitors (selective or non-selective)

Surgery: As with other MAO inhibitors, patients taking rasagiline should not undergo elective surgery requiring general anesthesia. Also, they should not be given local anesthesia containing cocaine or sympathomimetic vasoconstrictors. Rasagiline should be discontinued at least 14 days prior to elective surgery. If surgery is necessary sooner, benzodiazepines, mivacurium, fentanyl, morphine, and codeine may be used cautiously.

5 TRIAL SCHEDULE

5.1 Trial visits schedule

For the planned trial visits schedule the inclusion date is considered to be the reference date. The dates of the following visits specified in the protocol are calculated in relation to the date of this visit.

If the time of a visit is modified in relation to the visits schedule, the times of the following visits will always be determined with respect to the inclusion visit. The time window for each planned visit will be ± one week. The investigator must always ensure that the patient receives a sufficient quantity of treatment units to cover the period up to the next visit. The visits schedule is not modified by any unscheduled visits.

In the case of premature interruption of the study treatment, a complete examination identical to visit V5 should be carried out. Premature study discontinuation must be noted as such on the case report form. Patients prematurely leaving the study must not rejoin the trial.

Additionally a study physician will contact the patient by telephone 1, 3, 9, and 15 months after study enrolment.

An overview including the time schedule and evaluations for all visits is given on page 5. Evaluations performed at the study visits comply with the routine assessments for ALS patients, except that evaluations in patients outside of the clinical trial are performed less often (approximately twice a year).

Venous blood samples taken during the visits will be destroyed after determination of the required parameters. Only the samples collected for genetic testing will be stored and used as outlined in section 6.3.3. of the protocol.

Screening visit (V0)

A signed "Informed Consent" will be obtained from each patient prior to initiating any trial procedure. Presence of ALS diagnostic criteria will be documented as well as site of onset and ALS status at entry according to the revised El Escorial criteria. Venous blood will be taken for the determination of blood cell count, creatinine, CK, ASAT, ALAT, blood glucose, and HCG or urine pregnancy test (only in women with child bearing potential). The patients´ eligibility will be determined in accordance with the inclusion/exclusion criteria. Demographics and a detailed medical history will be taken, and concomitant medication will be recorded. A physical examination, including body weight, height, blood pressure, and radial pulse will be performed. Additionally lung function will be assessed by measuring the patient's vital capacity.

Baseline Visit 1 (V1)

Patients eligible for study participation will enter the study site within 4 weeks after the screening visit and will be randomized to one of the treatment arms.

Blood samples for the determination of blood cell count, creatinine, CK, ASAT, ALAT and blood glucose, will be obtained. A blood sample for genetic testing will be collected as outlined in section 6.3.3. if the patient provided consent to this analysis. Body weight, blood pressure and radial pulse will be documented and lung function will be assessed by measuring the patient's vital capacity. In addition ALSFRS-R and SEIQoL will be performed. The patient will receive study medication according to the randomization list and a study participant card (see appendix VIII).

Any changes in the concomitant medication and adverse events before and during visit 1 will be documented.

Visit 2-4 – Control Visits (V2, V3, V4)

Visit 2, 3, and 4 will be performed 2, 6, and 12 months after visit 1 respectively.

Venous blood samples will be taken for the determination of blood cell count, creatinine, CK, ASAT, ALAT and blood glucose. Body weight, blood pressure and radial pulse will be documented and lung function will be assessed by measuring the patient's vital capacity. In addition ALSFRS-R, and SEIQoL will be performed. Patient will be asked for compliance and drug accountability will be performed. Additionally the patient will be supplied with new study medication. Any changes in the concomitant medication and adverse events will be documented.

Visit 5 – Final Visit (V5)

Visit V5 will be performed 18 months after visit V1. Any adverse events and changes in concomitant medication will be documented.

Blood samples will be taken for the determination of blood cell count, creatinine, CK, ASAT, ALAT and blood glucose. Body weight, blood pressure and radial pulse will be documented and lung

function will be assessed by measuring the patient's vital capacity. In addition ALSFRS-R and SEIQoL will be performed. The patient will be asked for compliance and will return the study medication of V4. Additionally drug accountability will be performed.

Telephone contacts (T1 – T4)

At months 1, 3, 9, 15 the patient or its relative will be contacted by telephone to assess the following items:

- ALS FRS-R
- Weight
- Adverse events
- Changes in concomitant therapies
- Compliance to study drug regimen

If a patient misses a visit or telephone contact the subsequent visit or telephone contact will not be brought forward but will be performed on the scheduled day.

If a patient misses more than one visit, the investigator should contact the sponsor in order to determine how to proceed.

5.2 Unscheduled visits

Unscheduled visits may be carried out at any time during the study in the case of a medical emergency, when a patient would like to report a medical problem or when the investigator considers this necessary for the patient's well-being. These unscheduled visits must be recorded on the case report form. In no case must they lead to a modification in the study visits schedule stipulated by the protocol.

5.3 Visits following premature discontinuation of study treatment

If a patient discontinues participation in the study for whatever reason, every effort has to be undertaken to perform an early termination visit. In this case, the same investigations have to be performed as in visit V5.

6 TRIAL METHODS

6.1 Assessment of efficacy

Efficacy variables:

- Survival / date of death requiring a death certificate
- ALSFRS-R
- SEIQoL
- sVC

The Efficacy variables listed above will be determined at the study site using standard methods.

6.2 Assessment of safety

6.2.1 Safety Variables

- Blood cell count (RBC, WBC, Hb, Hct, MCV, MCH, MCHC, PLT)
- ASAT
- ALAT
- CK
- Creatinine
- Blood glucose
- Beta-HCG

6.2.2 Adverse events

6.2.2.1 Definitions

Adverse Event (AE)

According to GCP, an adverse event (AE) is defined as any untoward medical occurrence in a patient treated with a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal investigational product, whether or not related to that product.

An AE may be:

- a new symptom or medical condition
- a new diagnosis
- a change in laboratory parameters
- an intercurrent illness or accident
- worsening of a medical condition/diseases existing before the start of the clinical trial
- recurrence of a disease
- an increase in frequency or intensity of episodic diseases.

This definition also applies to events occurring in any comparative group (active treatment or placebo) or during the placebo-treatment phase or during periods when the patient is not receiving any study medication.

Surgical procedures themselves are not AEs; they are therapeutic measures for conditions that require surgery. The condition for which the surgery is required may be an AE. Planned surgical measures permitted by the clinical trial protocol and the condition(s) leading to these measures are not AEs, if the condition leading to the measure was present before inclusion in the trial. In the latter case the condition should be reported as medical history.

Change in laboratory parameters: The criteria for determining whether an abnormal test finding should be reported as an adverse event are as follows:

- Test result is associated with accompanying symptoms, and/or
- Test result requires additional diagnostic testing or medical/surgical intervention, and/or
- Test result leads to a change in trial dosing outside of protocol-stipulated dose adjustments, or discontinuation from the trial, significant additional concomitant drug treatment, or other therapy, and/or
- Test result is considered to be an adverse event by the investigator or sponsor.

Serious adverse event (SAE)

A serious adverse event (SAE) is one that at any dose (including overdose):

- results in death
- is life-threatening[1]
- requires patient hospitalization or prolongation of existing hospitalization[2]
- results in persistent or significant disability/incapacity[3] or
- is a congenital anomaly/birth defect
- is an important medical event[4].

[1]"Life-threatening" means that the patient was at immediate risk of death at the time of the serious adverse event; it does not refer to a serious adverse event that hypothetically might have caused death if it were more severe.

[2]If the admission is pre-planned (i.e., elective or scheduled surgery arranged prior to start of the trial) or not associated with an adverse event (e.g., social hospitalization for purpose) or results in a hospital stay less than 12 hours, the serious criterion "hospitalization" is not fulfilled. However, it should be noted that invasive treatment during a hospitalization may fulfill the criteria of "medically important" and may be reportable as a serious adverse event dependent on clinical judgment.

[3]"Persistent or significant disability or incapacity" means that there is a substantial disruption of a person's ability to carry out normal life functions. The irreversible injury of an organ function (e.g., paresis, diabetes, cardiac arrhythmia) fulfills this criterion.

[4]Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in situations where none of the outcomes listed above occurred. Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above should also usually be considered serious. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, convulsions that do not result in patient hospitalization, or the development of drug dependency or drug abuse. A diagnosis of cancer during the course of a treatment should be considered as medically important.

Clarification of the difference in meaning between "serious" and "severe":

The terms "serious" and "severe" are not synonymous but are often used interchangeably. The term 'severe' is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor significance (such as severe headache). This is not the same as "serious", which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations."

Adverse Reaction (AR)

An adverse reaction is any noxious and unintended response to an investigational medicinal product (the causal relationship between the medicinal product and the adverse event is at least a reasonable possibility).

Serious Adverse Reaction (SAR)

If there is a causal relationship between a serious adverse event and trial medication then the event is called serious adverse reaction (SAR).

Suspected Unexpected Serious Adverse Reaction (SUSAR)

A SUSAR is a serious adverse reaction which is unexpected.

An unexpected serious adverse reaction is any adverse reaction, the nature or severity of which is not consistent with the applicable product information (i.e., the Investigator's Brochure or the current SmPC).

6.2.2.2 Assessment of AEs by investigator

Patients must be carefully monitored for adverse events by the investigator. The intensity of the adverse events and the causal relation to trial medication and/or procedures are to be assessed.

Intensity/Severity

The intensity of an AE will be assessed by the investigator as follows:

Mild: Temporary event which is tolerated well by the patient and does not interfere with normal daily activities.

Moderate: Event which results in discomfort for the patient and impairs his/her normal activity.

Severe: Event which results in substantial impairment of normal activities of patient.

Causal relation to trial medication/procedures

The assessment of the relationship of an adverse event to the administration of study drug is a clinical decision based on all available information at the time of the completion of the case report form. The investigator will evaluate the causal relationship of each adverse event with the administration of the investigational product(s) and/or trial procedures according to modified criteria of WHO 1991.

Certain: A clinical event, including laboratory test abnormalities, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.

Probable: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge is not required to fulfill this definition.

Possible: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administrations of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.

Unlikely: A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.

Not related: A clinical event, including laboratory test abnormality, that does not follow a reasonable temporal sequence from trial participation and that is definitely caused by the patient's clinical state, other modes of therapy or other known etiology.

Outcome

The outcome of each AE must be assessed according to the following classification:

- completely recovered:	Patient has fully recovered with no observable residual effects
- not yet completely recovered:	Improvement in the patient's condition has occurred, but the Patient still has some residual effects
- deterioration:	Patient's overall condition has worsened
- permanent damage:	AE has resulted in a permanent impairment
- death:	Patient died due to the AE
- ongoing:	AE has not resolved
- unknown:	The outcome of the AE is not known because the patient did not return for follow-up (lost to follow-up)

6.2.2.3 Period of observation

In this trial, the period of observation for collection of adverse events extends from the time the patient has signed the informed consent document up to 14 days after the patient has routinely or prematurely terminated the study.

If the investigator detects a serious adverse event in a trial patient after the end of the period of observation, and considers the event possibly related to the prior trial, he should contact the sponsor to determine how the adverse event should be documented and reported.

6.2.2.4 Documentation of AEs and Follow up

At each visit after V0 the investigator must question the patient about the occurrence of any adverse event and note any abnormal laboratory findings. A neutral question such as "since the last visit have you felt any untoward or unusual symptoms other than those related to your illness?" elicits any adverse events experienced by the patient.
All AEs reported by the patient or detected by the investigator will be documented on the appropriate pages of the case report form (CRF). AEs must also be documented in the patient's medical records.

The following approach will be taken for documentation:

- All adverse events (whether serious or non-serious) must be documented on the "Adverse Event" page of the CRF.
- If the adverse event is serious (see Section 6.2.2.1), the investigator must complete, in addition to the "Adverse Event Page", a "Serious Adverse Event Form" at the time the serious adverse event is detected.

Every attempt should be made to describe the adverse event in terms of a diagnosis. If a clear diagnosis has been made, individual signs and symptoms will not be recorded unless they represent atypical or extreme manifestations of the diagnosis, in which case they should be reported as separate events. If a clear diagnosis cannot be established, each sign and symptom must be recorded individually.

All patients who have adverse events, whether considered associated with the use of the investigational products or not, must be monitored to determine the outcome. The clinical course of the adverse event will be followed up according to accepted standards of medical practice, even after the end of the period of observation, until a satisfactory explanation is found or the

investigator considers it medically justifiable to terminate follow-up, but no longer than 14 days after the end of the trial.

Should the adverse event result in death, a full pathologist's report should be supplied, if possible.

All questions on the completion and supply of adverse event report forms and any further forms issued to the investigator at a later date to clarify unresolved issues should be addressed to the sponsor.

6.2.2.5 Immediate reporting of SAEs by investigator

SAEs must immediately (within 24 hours of the investigator's awareness) be reported to:

Prof. Dr. J. Kassubek, MD
Department of Neurology
University of Ulm, Germany
Phone: +49 (0)731 177-1206
Fax: +49 (0)731 177-1202

Both the investigator and the sponsors safety contact will adhere to the requirements of the German GCP-Ordinance (§§12, 13) on documentation and notification.

The initial SAE Report should be as complete as possible including the essential details of patient's identification (screening number, random number), the serious adverse event (medical term, diagnosis), the trial medication and the assessment of the causal relationship between the event and the trial medication. The SAE report must be reviewed and signed by the investigator.

The investigator should provide related additional information on the clinical course and the outcome of each SAE as soon as possible (Follow up report).

The "Serious Adverse Event Form" is provided in the Investigator Site File.

The investigator should also inform the trial monitor in all cases.

The following are not considered to be serious adverse events:

- An event causing a brief visit to a hospital consultation, an open-door or day hospital,
- outpatient treatment in the emergency department although the reason for which this treatment was instituted may be serious, or
- admission to hospital (more than one night in a hospital bed) including surgical operations planned before or during the study if the condition was present before the study and provided that it does not worsen during the study.

The following are considered to be serious adverse events even if they do not comply with the definition:

- Adverse events caused by misuse or overdose,
- Any pregnancy discovered during the study.

Note: a state of pregnancy is an exclusion criterion. Hence contraceptive measures are necessary in women with childbearing potential throughout the study. However if pregnancy is discovered during the study the trial treatment must immediately be discontinued and the pregnancy followed to term.

Worsening of a sign or symptom of the condition under treatment will normally be measured by efficacy parameters. However, if the outcome fulfills the definition of "serious adverse event", it must be reported as such.

6.2.2.6 Immediate Reporting of pregnancy by investigator

Any **pregnancy** diagnosed in a female patient or in the female partner of a male patient during treatment with the investigational product must be reported immediately using the "Pregnancy Reporting Form" to:

Prof. Dr. J. Kassubek, MD
Department of Neurology
University of Ulm, Germany
Phone: +49 (0)731 177-1206
Fax: +49 (0)731 177-1202

Pregnancy occurring during the clinical trial, must be reported within the same timelines as a serious adverse event. The outcome of a pregnancy should be followed up carefully and abnormal outcome of mother or child should be reported if any.

6.2.2.7 Safety evaluation and Reporting by sponsor

The sponsor will ensure that all legal reporting requirements are met. According to GCP the sponsor is responsible for the continuous safety evaluation of the investigational product(s) and the clinical trial.
The sponsor will conduct the management of SAEs and the expedited reporting as required by German Drug Law (AMG) and GCP regulation (GCP-V). Suspected unexpected serious adverse reactions (SUSARs) and safety issues as defined by GCP-V are determined for expedited reporting. ~~The competent authorities and the ethics committees should be notified as soon as possible but not later than 15 calendar days if the event is non-fatal. In this trial on the fatal disease AL, the mortality is the efficacy endpoint and the integrity of the trial may be compromised when the blind is systematically broken for reporting of mortality related SUSARs. Therefore each mortality case will be treated as disease-related and will not be subject to systematic unblinding and expedited reporting. The reporting of these events will be completed within one month after last patient's last visit.~~
All investigators will be informed too.
The marketing authorization holder of the IMP has to be informed.

Work flow and procedures concerning SAE management will be described in a separate document (e.g. Safety manual).

During the clinical trial the sponsor will submit the Development Safety Update Report including a list of all serious adverse reactions to the ethics committee(s) and the competent authorities once a year.

The independent Data Safety and Monitoring Board (DSMB) will review the safety data every three month in the ongoing trial with recommendation to the sponsor whether to continue, modify or terminate the trial.

6.2.2.8 Emergency procedures

During and following a patient's participation in the trial, the investigator should ensure that adequate medical care is provided to a patient for any AEs including clinically significant laboratory values. The investigator should inform a patient when medical care is needed for intercurrent illness(es) of which the investigator becomes aware.

<u>Emergency Unblinding:</u>

In case of an emergency situation the investigator has the right to open the unblinding envelope, but every effort should be taken to avoid unblinding of patients except the information will be needed for the emergency treatment. Opened envelopes have to be signed, dated and the reason

for unblinding has to be documented. The envelope has then to be filed in the patient file and the sponsor or the responsible monitor has to be informed.

Additionally the sponsors' safety contact will receive a full set of sealed unblinding envelopes for emergency cases. As well every effort should be taken to avoid unblinding of patients except the information will be needed for the emergency treatment. Opened envelopes have to be signed, dated and the reason for unblinding has to be documented.

No other reason than an emergency may justify unblinding. After unblinding the investigator must note the date, time and reason on the case report form. The investigator must also immediately inform the trial monitor of the breaking of the blind.

Whenever possible, Prof. Dr. A. C. Ludolph (LKP) should be contacted before the blind is broken (see also chapter 3.6.2).

6.3 Other assessments

6.3.1 Prior and concomitant illnesses

Relevant additional illnesses present at the time of informed consent are regarded as concomitant illnesses and will be documented on the appropriate pages of the case report form (CRF), as well as clinically significant conditions that stopped within the last 5 years. In addition the following items have to be addressed specifically:

- Smoking habits within the last 12 months
- Alcohol consumption

6.3.2 Prior and concomitant treatments

All patients entering the study must have been continuously treated with the standard therapy for ALS of 100 mg riluzole for at least four weeks.

Relevant additional treatments administered to the patients on entry to the trial or at any time during the trial are regarded as concomitant treatments und must be documented on the appropriate pages of the CRF.

6.3.3 Genetic testing for polymorphisms in the MAO-B gene

The study drug Rasagiline is a second-generation monoaminooxidase (MAO)-B inhibitor which shows neuroprotective effects. As outlined in section 1, the study drug is registered for treatment of Parkinson's disease (PD). Previous studies showed that there are polymorphisms in the MAO-B gene which have been associated with PD [16] [17] [18]. Based on this observation it will be of interest to scan for these polymorphisms in subjects enrolled in this study. If a treatment effect will be identified in this study, DNA might be extracted from these blood samples to scan the MAO-B gene. This might help to stratify responders and non-responders. It is not planned to test for any other genes. The results from these tests will not be shared with the subjects.

Blood samples collected for genetic testing during Baseline Visit 1 will be double-coded before stored at the sponsor. Blood samples and corresponding DNA will be stored until the samples are exhausted, at the latest for up to 10 years after the study is ended.

7 STATISTICS

Details of the statistical analysis of the data collected in this trial will be documented in a Statistical Analysis Plan (SAP) that will be provided by the study statistician and finalized before closing the data base and prior to breaking the blind. The SAP is based on the protocol including all amendments. The document may modify the plans outlined in this protocol; however any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment. Any deviation from the original statistical plan must be described and justified in the final report. The statistical analysis will be conducted using SAS®.

7.1 Sample size

The sample size calculation is based on a comparison of two survival curves using the one-sided log-rank test. Following assumptions were made: Type one error 0.025, power 0.80, recruiting time 6 months, length of follow up period 18 months, 18 month survival rate of 70 % in the control group, 18 month survival rate of 85 % in the experimental group. Under the assumption of equal number of patients in each group, this scenario requires 106 patients in each group, i.e. 2 x 106 = 212 patients in whole trial.
A previous study [GERP ALS-Study; pioglitazone in ALS; NCT00690118, clinicaltrials.gov ID] showed a drop-out rate of about 15 %, screening failure was observed in about 10 %. Thus, in total 250 patients have to be allocated (with consideration of a drop-out rate) and a total number of 278 patients have to be assessed for eligibility.
The sample size calculation was performed using SAS® software, version 9.2, procedure power.

7.2 Analysis populations

All patients who signed informed consent / were assigned a randomization number are considered as enrolled/randomized patients, even if they did not receive any trial treatment. The following data sets will be analyzed:
Full Analysis Set (FAS): The primary efficacy analysis will be based on the Intention-To-Treat (ITT) population. All randomized patients who received at least one dose of trial treatment and with at least one available post-baseline assessment of the primary analysis variable will be included in the full analysis set and will be regarded as ITT population. This population is the primary analysis population. Within ITT population analyzes, patients will be assigned to the treatment to which they were randomized.

Per-protocol analysis set (PPS): The per-protocol analysis set will consist of all patients in the full analysis set without major protocol deviations. Patients with major protocol deviations will be excluded from the PPS.

Safety analysis set: The safety analysis set comprises all patients who received at least one dose of trial treatment. In analyzes of the safety population, patients will be assigned to the treatment which they actually received.

The classification of minor and major protocol deviations and the resulting definition of analysis sets will be provided prior to final statistical analysis and prior to unblinding of the study and will be approved by the sponsor. The primary analysis set for the efficacy evaluation is the full analysis set.

A more detailed description of protocol deviations and analysis sets will be included in the statistical analysis plan which will finalized before unblinding treatment allocation and before start of statistical analyzes.

7.3 Efficacy analyzes

The primary objective of this trial is to show the superiority of the test treatment compared to the standard treatment in terms of survival time.

7.3.1 Definition and analysis of primary endpoint

The primary endpoint is survival time, i.e. the time until death or the time until last contact to patient. Mortality is exclusively defined as death. Survival time will be calculated as difference from date of last contact and date of randomization. Date of last contact is defined as

- date of death for patients who will die during trial
- date of study termination for patients who are alive if date of study termination > date of last visit, otherwise the date of last visit will be used as date of last contact

Replacement of missing values for ITT analysis:
Date of death will be known for all patients who will die during trial. For patients who are alive at end of study/last contact, the following replacement of missing date will be performed. Any date of last contact with unknown day (xx/NA/xxxx) in patients who are alive will be replaced with the date for mid-month (xx/15/xxxx). Dates of last contact with unknown day and month or with unknown day and month and year will not be replaced.

Analysis of primary endpoint:
The statistical hypotheses are the following:
H_0: $\lambda_2/\lambda_1 \geq 1$
H_1: $\lambda_2/\lambda_1 < 1$
where λ_2/λ_1 is the hazard ratio, λ_1 denotes the hazard in the control group, λ_2 denotes the hazard in the experimental group. The hazard ratio is assumed to be constant across time. The null hypotheses will be tested using the logrank test. The type one error is set to alpha=0.025 (one-sided). For estimating the treatment effect, the hazard ratio, incl. the one-sided 97.5% confidence interval will be provided.
Only the ITT analysis of the primary endpoint will be regarded as confirmatory. All other analyzes of primary endpoint will be regarded as exploratory.

7.3.2 Analysis of secondary endpoints

All secondary endpoints (change of total score of ALSFRS-R, change in SEIQoL, change of sVC) will be analyzed descriptively and for the FAS only. The Wilcoxon rank sum test will be carried out for group comparisons. Replacement of missing values in the secondary endpoints will not be done. Each statistical test will be performed two-sided at a significance level of 5%. All analysis of secondary endpoint will be interpreted purely exploratory and not as proof of efficacy.

7.3.3 Analysis of Subgroups

Subgroup analyzes will be performed for the bulbar and spinal stratum.

7.3.4 Interim analyzes

No interim analyzes are planned.

7.4 Analysis of adverse events

All summaries and listings of safety data will be performed for the safety population.

Frequencies of patients experiencing at least one adverse event (AE) will be displayed by body system and preferred term according to MedDRA terminology. Detailed information collected for each AE will include: A description of the event, duration, whether the AE was serious, intensity, relationship to trial drug, action taken, clinical outcome. Summary tables will present the number of patients observed with AEs and corresponding percentages. Additional subcategories will be based on event intensity and relationship to trial drug.

A patient listing of all AEs will be prepared.

7.5 Analysis of clinical laboratory findings

Listings will be prepared for each laboratory measure and will be structured to permit review of the data per patient as they progress on treatment.

Summary tables will be prepared to examine the changes of laboratory measures over time. Additionally, shift tables will be provided to examine the changes of laboratory data from normal baseline to values outside the corresponding reference range during/after treatment.

8 QUALITY CONTROL AND QUALITY ASSURANCE

8.1 Requirements for investigational sites and staff

The investigator should be able to demonstrate (e.g. based on retrospective data) a potential for recruiting the required number of suitable patients within the agreed recruitment period.

The investigator should have sufficient time to properly conduct and complete the trial within the agreed trial period.

The investigator should have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely.

The investigator should ensure that all persons assisting with the trial are adequately qualified, informed about the protocol, any amendments to the protocol, the trials treatments, and their trial-related duties and functions.

8.2 Direct entries

Data entries to be entered in the CRF as Direct entries are listed in the Monitor Manual in the section source data control.

8.3 Direct access to source data/documents

The investigator/institution must permit trial-related monitoring and auditing by the sponsor and the IZKS Mainz, as well as inspections by the appropriate competent authorities and Ethics committees, providing direct access to source data/documents (Confidentiality see 10.3).

The patients will be informed that representatives of the sponsor, independent ethics committee (IEC) or competent authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

8.4 Investigator site file and archiving

The investigator will be provided with an investigator site file (ISF) at the start of the trial. The investigator will archive all trial data and relevant correspondence in the ISF. The ISF, all source data and all documents will be kept filed according to the requirements of the ICH-GCP guidelines after termination of the trial.

It is the responsibility of the investigator to ensure that the patient-identification sheets are stored for at least 10 years beyond the end of the clinical trial. All original patient files must be stored for the longest possible time permitted by the regulations at the hospital, research institute, or practice in question. If archiving can no longer be maintained at the site, the investigator will notify the sponsor.

Archiving of sponsor files is carried out by the following company:

Firma Pietsch
Maerkische Allee 45
14979 Grossbeeren

8.5 Monitoring

Monitoring will be done by personal visits from a clinical monitor according to SOPs of the IZKS Mainz.

To initiate the trial, the monitor will visit all participating local trial sites and trial centers. The monitor shall ensure that the investigators and their staff understand all requirements of the protocol and their regulatory responsibilities.

The monitor will ensure that the investigator will maintain a list of subinvestigators and other appropriately qualified persons to whom he or she has delegated significant trial-related duties (personnel log).

Each site will be visited by the monitor at regular intervals to ensure compliance with the trial protocol, GCP and legal aspects. The monitor will review the entries into the CRFs for completeness and correctness and verify the entries on the basis of the source documents. The presence of correct informed consents will be checked for every patient.

Details will be specified in the monitoring manual for this trial.

The investigator must allow the monitor to look at all relevant documents and must provide support at all times to the monitor.

By frequent communications (letters, telephone, fax), the monitor will ensure that the trial is conducted according to the protocol and regulatory requirements.

After all patients have finished treatment/follow-up, the trial is terminated and a close-out visit will be performed.

8.6 Inspection by authorities and audits

Competent authorities and by the sponsor authorized persons (auditor) may request access to all source documents, CRF, and other trial documentation in case of an inspection or audit. Direct access to these documents must be guaranteed by the investigator who must provide support at all times for these activities. Source data documents can be copied during inspection or audit in case the identity of the patient have been made unrecognizable.

8.7 Audits

No audits are planned for this trial.

9 DATA MANAGEMENT

9.1 Responsibilities

In case of discrepancies or correction of data errors the Data management team is authorized to contact the responsible person at trial site directly. The queries will be sent by the *IZKS Mainz* per fax, post or e-mail. For the response the investigator has to comply with a term defined by the *IZKS Mainz*. The investigator has to agree the contact per e-mail or phone.

A detailed methodology for the data management in this trial will be documented in a data management plan that will be dated and maintained by *IZKS Mainz*. This plan has to be signed by the sponsor, the head of the data management team and the responsible data manager. The document may modify the plans outlined in this protocol; however any major modifications of the data handling will also be reflected in a protocol amendment.

9.2 Data collection

This trial will be performed using an electronic case report form (eCRF) or remote data entry (RDE). The investigator and the trial site staff will receive system documentation, training and support for the use of the eCRF. In the case of new trial site staff the training can be performed by personnel of the trial site.
For support with data entry the IZKS Mainz can be contacted between 9:00 and 16:00 o'clock Monday to Thursday and from 9:00 to 12:00 o'clock on Fridays. Each trial site has one responsible person who supports the IZKS Mainz in implementation of technical and organizational processes. A list of these persons is enclosed to the DMP.
All protocol-required information collected during the trial must be entered by the investigator, or a designated representative in the eCRF. All data entry, modification or deletion will be recorded automatically in an electronic audit trail indicating the individual patient, the original value, the new value, the reason for change, who made the change and time and date of the change. All data changes will be clearly indicated. Former values can be viewed in the audit trail. All electronic data will be entered by the site (including an electronic audit trail) in compliance with applicable record retention regulations.

The system will be secured to prevent unauthorized access to the data or the system. Only people provided with a user ID and a password will be able to enter or change data. The investigator will maintain a list of individuals who are authorized to enter or correct data and their system ID.

Computer hardware and software (for accessing the data) will be maintained at or made available for the site in compliance with applicable regulations. All technical preconditions for each trial site are record in the DMP.

The system is capable to make exact copies of data in legible paper form for inspections and audits. The investigator or a designated subinvestigator, following review of the data in the eCRF, will confirm the validity of each patient's data by electronic signature or by signing a paper printout of a listing of all patients enrolled in the trial.

The architecture of the computer system will be described in the data management plan.

9.3 Data handling

During data entry integrity checks help to minimize entry failures. This data entry checks are based on the data validation plan, signed by the LKP. The data entry system allows the trial monitors to control the entry process with the help of the system-own review functions. Comments and requests can be processed by the trial site just in time.

After completion of data entry the database access will be inhibited and the database will be exported into the data transformation system as mother database.

After completion of data entry the access for data entries is blocked and checks for plausibility, consistency and completeness of the data will be performed. Based on these checks, queries will be produced. Any missing data or inconsistencies will be reported back to the respective site and clarified by the responsible investigator. A database audit will be accomplished to ensure and document the high-quality trial database. If no further corrections are to be made in the database it will be declared closed and used for statistical analysis.

All data management activities will be done according to the current Standard Operating Procedures (SOPs) of *IZKS Mainz*.

9.4 Storage and archiving of data

According to GCP, the investigator will archive all trial data (patient identification list, source data) and relevant correspondence in the Investigator Site File (ISF). The ISF, all source data and all documents itemized in section 8 of the ICH Consolidated Guideline on GCP will be archived after finalization of the trial for at least 10 years according to the legal regulations (GCP-V §13 (10).

Storage and archiving of the electronic data during the trial will be assured by *IZKS Mainz.* After completion of the trial all electronic data will be handed over to the sponsor.

10 ETHICAL AND LEGAL ASPECTS

10.1 Good clinical practice

The procedures set out in this trial protocol, pertaining to the conduct, evaluation, and documentation of this trial, are designed to ensure that all persons involved in the trial abide by good clinical practice (GCP) and the ethical principles described in the Declaration of Helsinki. The trial will be carried out in keeping with local legal and regulatory requirements.

The requirements of the AMG (German drug law), the GCP regulation, and the Federal Data Protection Law (BDSG) will be kept. The investigators will receive copies of the Declaration of Helsinki, an extract from the AMG and the GCP regulation together with the Investigator Site File.

10.2 Patient information and informed consent

Before being admitted to the clinical trial, the patient must consent to participate after being fully informed about the nature, scope, and possible consequences of the clinical trial.

The documents must be in a language understandable to the patient and must specify who informed the patient.

A copy of the signed informed consent document must be given to the patient. The original signed consent document will be retained by the investigator.

The investigator will not undertake any measures specifically required only for the clinical trial until valid consent has been obtained.

If the patient has a primary physician the investigator should inform the patient’s primary physician about the patient’s participation in the trial and if the patient agrees to the primary physician being informed.

After reading the informed consent document, the patient must give consent in writing. The patient's consent must be confirmed by the personally dated signature of the patient and by the personally dated signature of the person conducting the informed consent discussions.

If the patient is unable to read, oral presentation and explanation of the written informed consent form and information to be supplied to patients must take place in the presence of an impartial witness. Consent must be confirmed orally and by the personally dated signature of the patient or by a local legally recognized alternative (e.g., the patient's thumbprint or mark). The witness and the person conducting the informed consent discussions must also sign and personally date the consent document.

When admitted to the clinical trial patients receive a reimbursement of travelling expenses for each visit.

Recorded data of patients who withdraw their consent will be part of the study analysis.

10.3 Confidentiality

The name of the patients and other confidential information are subject to medical professional secrecy and the regulations of the German law on data protection (Bundesdatenschutzgesetz). During the clinical trial, patients will be identified solely by means of an individual identification code (e.g. patient number, randomization number). Trial findings stored on a computer will be stored in accordance with local data protection law and will be handled in strictest confidence. For protection of these data, organizational procedures are implemented to prevent distribution of data

to unauthorized persons. The appropriate regulations of data legislation will be fulfilled in its entirety.

The patient will declare in the written consent to release the investigator from the medical professional secrecy to allow identification of patient's name and/or inspection of original data for monitoring purposes by health authorities and authorized persons (monitors).

The investigator will maintain a personal patient identification list (patient numbers with the corresponding patient names) to enable records to be identified.

10.4 Responsibilities of investigator

The investigator will ensure that all persons assisting with the trial are adequately informed about the protocol, any amendments to the protocol, the trial treatments, and their trial-related duties and functions.

The investigator will maintain a list of subinvestigators and other appropriately qualified persons to whom he or she has delegated significant trial-related duties.
Any changes of the authorized trial personnel are to be communicated without delay to the *IZKS Mainz*.

10.5 Approval of trial protocol and substantial amendments

Before the start of the trial, the trial protocol, informed consent document, and any other appropriate documents will be submitted to the independent ethics committee (IEC)/institutional review board (IRB). Approval (respectively formal approval) by the IEC should preferably mention the title of the trial, the trial code, if applicable the trial site, and the documents they reviewed. It must mention the date on which the decision was made and must be officially signed by a committee member. This documentation must also include a list of members of the IEC present on the applicable EC meeting.

The documents will also be submitted to the competent authorities (in Germany approval by the highest competent authority, BfArM), in accordance with the respective local legal requirements.

Investigational products can only be supplied to the investigator after documentation on all ethical and legal requirements for starting the clinical trial has been received by the sponsor (*IZKS Mainz*: will signal "regulatory greenlight"). Before the first patient is enrolled in the trial, all ethical and legal requirements must be met.

Neither the investigator nor the sponsor nor the Steering Committee nor the *IZKS Mainz* will alter this trial protocol without obtaining the written agreement of the other. The IEC and, if applicable, the competent authorities must be informed of all subsequent protocol amendments and administrative changes, in accordance with the respective local legal requirements.

Amendments must be evaluated to determine whether formal approval must be sought and whether the informed consent document should also be revised.

The investigator must keep a record of all communications with the IEC and the competent authorities.

10.6 Continuous information to independent ethics committee/ institutional review board

The EC must be informed of all subsequent protocol amendments and administrative changes which require formal approval in accordance with the legal requirements.

The independent EC must be informed by the sponsor of serious AEs according to the current legal requirements (GCP-Ordinance §13) and the EC's vote.

The EC must be informed of trial process regularly if not otherwise stated in the vote. The EC must be informed of the end of the trial in accordance with legal requirements (within 90 days or within 15 days in case of premature closure of the clinical trial).

Unless otherwise instructed by the independent EC/institutional review board (IRB), the investigator must submit to the EC:

- Information on serious or unexpected adverse events from the investigator's site, as soon as possible.
- Expedited safety reports from the sponsor.
- Periodic reports on the progress of the clinical trial.

10.7 Submission to local regulatory/competent authorities

Before the start of trial, the sponsor is responsible for submission of all documents necessary to the competent authorities for approval. The local regulatory authority responsible for the investigator will be informed of the trial.

In case of any questions patients can use the following contact details of the higher federal authority:

Bundesinstitut für Arzneimittel und Medizinprodukte
Fachgebiet Klinische Prüfung / Inspektionen
Kurt-Georg-Kiesinger-Allee 3
53175 Bonn
Phone: 0228 / 207-4318 Fax: 0228 / 207-4355
E-mail: klinpruefung@bfarm.de

10.8 Data Safety and Monitoring Board (DSMB)

An independent Data Safety and Monitoring Board (DSMB) consisting of clinical and statistical experts will be established by the sponsor to review the safety data. The DSMB will have regularly telephone conferences at three months intervals and if necessary. The DSMB will have access to unblinded data upon request. Based on the results of the safety data the DSMB will give written recommendations to the sponsor to continue, to modify, to put on hold or to stop the trial.

The DSMB will act according to its own SOP and will prepare written minutes of its telephone conferences or meetings. In order not to disseminate unblinded data and to ensure that all staff involved in the conduct of the study remains blind to the results of the study, only the members of the DSMB and an unblinded statistician will have access to these data.

10.9 Insurance

According to § 40 AMG, the sponsor has to subscribe to an insurance policy covering, in its terms and provisions, its legal liability for injuries caused to participating persons and arising out of this research performed strictly in accordance with the scientific protocol as well as with applicable law and professional standards. The insurance was taken out at HDI-Gerling Industrie Versicherung AG, Riethorst 2, 30659 Hannover, represented by the branch office Düsseldorf, Am Schönenkamp 45, 40599 Düsseldorf (insurance number: 57 010315 03015, maximum limit: € 500.000,- per participating person).

Any impairment of health which might occur in consequence of trial participation must be notified to the insurance company. The patient is responsible for notification. The insured person will agree to all appropriate measures serving for clarification of the cause and the extent of damage as well as the reduction of damage.

During the conduct of the trial, the patient must not undergo other clinical treatment except for cases of emergency. The patient is bound to inform the investigator immediately about any treatment by another physician, any adverse events and additionally drugs taken. The terms and conditions of the insurance must be delivered to the patient indicating that policy conditions have to be observed.

Insurance coverage exists for each patient during the whole participation in the clinical trial.

Insurance provisions for this clinical trial are given in separate agreements.

10.10 Agreements

10.10.1 Financing of the trial

The trial is funded by the sponsor University Hospital Ulm and at least in part financially supported by TEVA Pharma GmbH.

The general conditions of financing for this trial are given in separate agreements.

10.10.2 Report

After conclusion of the trial, a report shall be written by the sponsor, in cooperation with the coordinating investigator. The report will include a statistical analysis and an appraisal of the results from a medical viewpoint. It will be based on the items listed in this trial protocol.

10.10.3 Publication policy

Any publication of the results, either in part or in total (articles in journals or newspapers, oral presentation, etc.) by the investigators or their representatives shall require the approval of the sponsor. It is planned to publish the results of the trial as an original article in an appropriate medical journal as well as presentation at congresses. The coordinating investigator is first author of the article and will present the data at the major congresses. The choice of the journal for the publication will be made by the Steering Committee in agreement with the co-authors. Besides the Principal Investigator, further authors of this article have to meet the following points:

- Substantial contribution to the recruitment of patients, i.e. one of the five best recruiting centers within the trial.
- Substantial contribution to interpretation of the data.
- Substantial contribution to drafting the article or revising it critically for important intellectual content.

11 SIGNATURES

The present trial protocol was subject to critical review and has been approved in the present version by the persons undersigned. The information contained is consistent with:

- The current risk-benefit assessment of the investigational medicinal product.
- The moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki and the principles of GCP.

Sponsor

Name **Prof. Dr. K.-M. Debatin**
Vorsitzender des Vorstands
des Universitätsklinikums Ulm
Albert-Einstein-Allee 29
89081 Ulm

05.08.14
Date Signature

Coordinating/Principal Investigator

Name Prof. Dr. M.C.

5.8.2014
Date Signature

Trial coordination

Name Stanislav Goeburev

14.08.2014
Date Signature

Biometrician

Name Prof. Dr. Reinhard Meyer

6.8.14
Date Signature

12 DECLARATION OF INVESTIGATOR

I have read the above trial protocol and I confirm that it contains all information to accordingly conduct the clinical trial. I pledge to conduct the clinical trial according to the protocol.

I will enroll the first patient only after all ethical and regulatory requirements are fulfilled. I pledge to obtain written consent for trial participation from all patients.

I know the requirements for accurate notification of serious adverse events and I pledge to document and notify such events as described in the protocol.

I pledge to retain all trial-related documents and source data as described. I will provide a Curriculum Vitae (CV) before trial start. I agree that the CV may be submitted to the responsible competent authorities.

I will conduct the trial in compliance with the protocol, GCP and the applicable regulatory requirements.

Investigator

Name
Address

Date	Signature

13 REFERENCES

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14 APPENDICES

I. Steering Committee

II. Data Safety and Monitoring Board (DSMB)

III. Sample SAE Report Form

IV. Study Participant Card

V. Summary of Changes Protocol Version 2.0

14.1 Appendix I. Steering Committee

Prof. Reinhard Dengler, MD
Director of the Department of Neurology
Medical School Hannover (MHH)
Carl-Neuberg-Strasse 1
30625 Hannover
Phone: +49 511 - 532 23 - 91

Prof. A. C. Ludolph, MD
Department of Neurology
University of Ulm
Oberer Eselsberg 45
89081 Ulm
Phone: +49 731 - 177 -1200

Prof. Stephan Zierz, MD
Department of Neurology
University of Halle Wittenberg
Ernst-Grube-Str. 40
06097 Halle / Saale
Phone: +49 345 - 557 2858

14.2 Appendix II. Data Safety and Monitoring Board (DSMB)

Prof. Jan Beyersmann
Institut für Statistik
Fakultät für Mathematik und Wirtschaftswissenschaften
Helmholtzstr. 18
89081 Ulm

Prof. Martin Hecht, MD
Ärztlicher Direktor Neurologische Klinik
Bezirkskrankenhaus Kaufbeuren, Bezirkskliniken
Schwaben
Am Klinikum Kaufbeuren
Dr. Gutermann-Str. 2
87600 Kaufbeuren

Prof. Jan Kassubek, MD
Department of Neurology
University of Ulm
Oberer Eselsberg 45
89081 Ulm

14.3 Appendix III. Sample SAE Report Form

SAE-Meldebogen

EUDRACT No. :

PROTOCOL IDENTIFICATION: *Short Titel*

INDICATION: *Indication*

SPONSOR*: Name*

Patient No.	Sex	Age (years))	Height (cm)	Weight (kg)	SAE No.
	☐ M ☐ F				

REPORT INFORMATION	NAME OF INVESTIGATOR:	
☐ INITIAL REPORT Date: ☐ FOLLOW-UP REPORT Date:	SITE NO.: INSTITUTION: Date investigator became aware of the SAE: Date: (DD/MM/YYY)	COUNTRY: TELEPHON: FAX: E-MAIL:

SERIOUSNESS CRITERIA OR REPORTABLE REASON

☐ results in death	☐ results in persistent or significant disability/incapacity
☐ life-threatening	☐ congenital anomaly / birth defect
☐ requires inpatient hospitalization / or prolongation	☐ other medically important condition

SERIOUS ADVERSE EVENT (SAE)

SAE: Diagnosis (if possible) including symptoms

Onset date of SAE (DD/MM/YYYY) _____

Date of resolution (DD/MM/YYYY) _____

Date of death (if applicable) (DD/MM/YYYY) _____

SEVERITY

Intensity: ☐ mild ☐ moderate ☐ severe

INVESTIGATIONAL DRUG(S) **UNBLINDING:** ☐ not applicable ☐ no ☐ yes

Brand Name® / Active Substance Name Batch No.	Date of first administration	Time interval (incl. unit) between last drug administration and start of event	Daily dose, unit, route of administration
1. Batch No.:			
Relatedness: ☐ related ☐ probably ☐ possibly ☐ unlikely ☐ not related ☐ not assessable			
2. Batch No.:			
Relatedness: ☐ related ☐ probably ☐ possibly ☐ unlikely ☐ not related ☐ not assessable			

SAE-Meldebogen

PLEASE TYPE OR PRINT LEGIBLY USING BLACK BALL-POINT PEN AND COMPLETE ALL INFORMATION				
PATIENT INFORMATION				
Patient- No.	Age (years)	SAE No.	☐ INITIAL REPORT Date: ☐ FOLLOW-UP Date:	
RELEVANT MEDICAL HISTORY (pre-existing / concurrent conditions)			Start date	Stop date
1.				
2.				
3.				

RELEVANT CONCOMITANT MEDICATION				
	Indication	Daily dose, unit, route of administration	Date of first administration	Date of last administration
1.				
2.				
3.				

RELEVANT LAB FINDINGS OR INVESTIGATIONS			
	Normal range	Date	Result
1.			
2.			
3.			
4.			

TREATMENT OF SAE	**ACTION TAKEN WITH TRIAL MEDICATION**	**OUTCOME OF SAE**
☐ none ☐ drug treatment ☐ others Specify: _____ _____ _____ _____ _____	☐ dose not changed ☐ dose reduced ☐ dose increased ☐ drug withdrawn, date: _____ Has a rechallenge been done? ☐ yes ☐ no ☐ unknown Did reaction recur on readministration? ☐ yes ☐ no ☐ unknown ☐ unknown ☐ not applicable	☐ recovered / resolved ☐ recovering / resolving ☐ not recovered / not resolved ☐ recovered / resolved with sequelae ☐ fatal cause of death: _____ autopsy? ☐ yes ☐ no ☐ unknown

IF HOSPITALIZED: Date of admission: _____ ; Date of discharge: _____ (DD/MM/YYYY)

COMMENT:

INVESTIGATOR SIGNATURE

Name Signature Date (DD/MM/YYYY)

FAX WITHIN 24 Hours TO: **FAX No. + 49 (0)731 177-1202**

Stand: 02.10.2012 2 von 2

IZKS Interdisziplinäres Zentrum Klinische Studien Mainz

14.4 Appendix IV. Study Participant Card

Bei Rückfragen oder im Notfall
bitte Kontakt aufnehmen mit:

Stempel Prüfarzt

Telefonnummer am Prüfzentrum für Notfallentblindung:

☎:

Patientenausweis

zur Teilnahme an einer klinischen Prüfung

STUDIE: Studie zur Wirksamkeit, Sicherheit und Verträglichkeit von 1 mg Rasagilin bei Patienten mit Amyotropher Lateralsklerose (ALS) unter Standardtherapie mit Riluzol

Bitte tragen sie diesen Ausweis immer bei sich!

Version 1 vom 21Nov2012

Termin 1 (V1):	Termin Telefonvisite T3:
Termin Telefonvisite T1:	Termin 4 (V4):
Termin 2 (V2):	Termin Telefonvisite T4:
Termin Telefonvisite T2:	Termin 5 (V5):
Termin 3 (V3):	

Sehr geehrte Patientin,
sehr geehrter Patient,

Sie nehmen an einer klinischen Studie teil (EudraCT-Nr.: 2011-004482-32). Bitte bringen Sie diesen Ausweis zusammen mit Ihrer Studienmedikation zu jeder Untersuchung mit.
Sollten Sie einen Termin nicht einhalten können, bitten wir um einen frühzeitigen Anruf zwecks Vereinbarung eines neuen Termins.

Folgender Patient nimmt an einer klinischen Prüfung teil:

Teilnehmender Patient:

Name: _____

Straße: _____

Wohnort: _____

Telefon: _____

Patientennummer:_____