**SYNOPSIS** ***ANNEX I***

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|---|---|---|
| Name of Sponsor/Company:<br><br>Klinikum der Universität München<br>Vertreten durch den Ärztlichen und den Kaufmännischen Direktor<br>Marchioninistr. 15<br>81377 München<br>Sponsor Delegated Person:<br>PD Dr. med. Stefan Lorenzl<br>Department of Neurology and Palliative Care<br>Tel.: 089 7095 7948<br>Fax: 089 7095 7929<br>Email: Stefan.lorenzl@med.uni-muenchen.de | Individual Study Table Referring to Part of the Dossier<br><br>not applicable | *(For National Authority Use only)* |
| Name of Finished Product:<br>Azilect | Volume:<br>not applicable | |
| Name of Active Ingredient:<br><br>Rasagiline | Page:<br>not applicable | |

Title of Study:

A Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to assess the Efficacy, Tolerability and Safety of Rasagiline in Subjects with Progressive Supranuclear Palsy (Phase III)
Short title: PROSPERA
EudraCT-Nr: 2008-007520-26, Vorlagen-Nr.: 4035832
Protocol version 3.0 / 02.11.2009
EC positive opinion on 09.11.2009, BfArM approval on 18.12.2009

Protocol version 4.0 / 16.06.2010
EC positive opinion on 24.06.2010, BfArM approval on 28.06.2010
The amendment contained changes to inclusion and exclusion criteria, allowed medication, as well as minor changes to the visit schedule.
No further amendments to the study protocol were necessary thereafter.

In 2011, it became evident that the planned number of patients couldn't be reached in a reasonable timeframe, because most patients suffering from PSP already received Rasagiline. The patient recruitment was stopped on 14.02.2012 and the complete study was terminated after last patient last visit (LPLV) on 14.06.2012.
The confirmation of the competent authority (BfArM) of the end of the study was on 31.10.2012.

Investigators:
Principal investigator:
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Sub-investigators
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Study centre(s):

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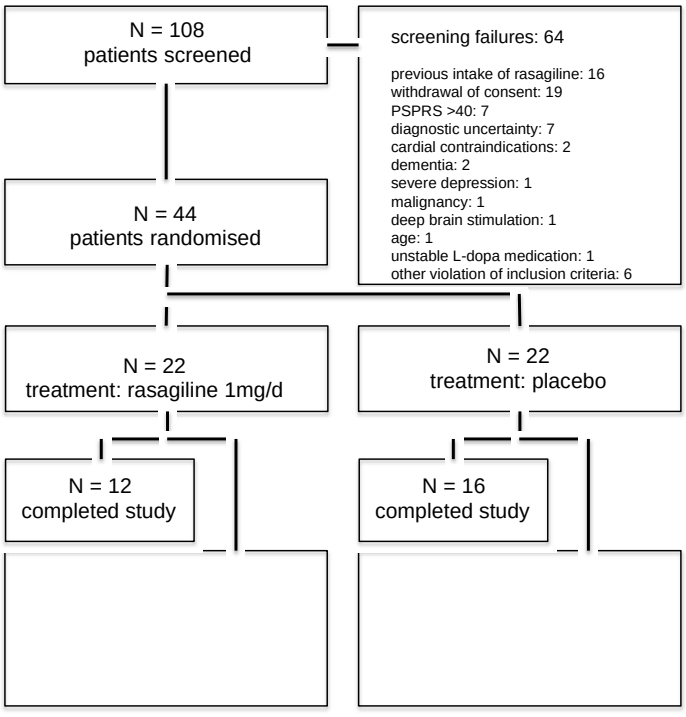
Publication (reference):
Part of the study results will be presented as a late breaking abstract (no number assigned) at the congress of the Movement Disorder Society in Sydney, June 16 – 20 2013

Studied period (years):
scheduled was one year for patient enrolment and one year interventional phase for each patient.
date of first enrolment (FPFV): 25.01.2010
date of last completed (LPLV): 14.06.2012
patient enrolment was stopped due to lack of recruitment on: 14.02.2012
end of study was LPLV (14.06.2012)

Phase of development:
Phase III




Primary Objective:

To assess the efficacy of Rasagiline using the PSP rating scale (PSPRS), aiming at a **33 % reduction** of the reported deterioration (Golbe et al., 2007), i.e. a mean yearly increase of 6.5 instead of 9.7 points.
To assess the need for additional L-DOPA therapy or the need to increase the dose of L-DOPA during the trial.

Secondary Objective:
Reduction of gait disturbances and postural stability (as documented with posturographic measurement)
Clinical safety and tolerability will be assessed by findings of physical and neurological examination, laboratory variables, adverse events incidence, vital signs, ECG, assessment of survival time
Number of Subjects (%) who discontinue the study
Number of Subjects (%) who discontinue the study due to AEs
Assessment of survival time

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|---|
| Additional endpoints: Secondary efficacy variables also will include incidence of dysphagia, gastrostomia, depression and pneumonia |
| Methodology:<br>Monocenter, Prospective, Randomized, Double-Blind, Placebo-Controlled Parallel Group Study |
| Number of patients (planned and analysed):<br><br>planned: 112<br><br>analysed: 44 |
| Diagnosis and main criteria for inclusion:<br><br>diagnosis: progressive supranuclear palsy (PSP)<br><br>inclusion criteria: Subjects must meet all inclusion criteria to be eligible:<br><br>1. Clinical signs of PSP. Diagnosis will be made for patients with clinically probable PSP (Litvan et al., 1996). Patients will be included with PSP stage </= II (Golbe et al., 1997), at least with a PSPRS < 40 (Golbe et al., 2007) and according to the diagnostic criteria resumed after the NNIPPS trial (Bensimon et al., 2009)<br>2. Patients, male or female, aged 50 to 80 years<br>3. Subjects whose clinical condition at the time of enrolment does not or requires a low [ 500 mg /day] stable dose of L-DOPA for at least 2 weeks prior to study entry<br>4. Capability and willingness to give written signed and dated in-formed consent document indicating that the subject has been in-formed of all pertinent aspects of the study |
| Test product, dose and mode of administration, batch number:<br><br>Rasagiline 1mg, one tablet per day, administration per os<br>batch no: Azilect® 1mg Tabletten (30St.) Batch# R13125 Exp. 07/2012 |
| Duration of treatment:<br><br>12 months |
| Reference therapy, dose and mode of administration, batch number:<br><br>placebo, one tablet per day, administration per os<br><br>Placebo for Rasagiline Mesylate Tablets (110 St.) Batch# K-37627 Exp. 10/2009 (->Extended expiry date: 11/2011)<br><br>Placebo for Rasagiline Mesylate Tablets (30 St.) Batch# PLR001 Exp. 05/2014 |

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Criteria for evaluation:

**Efficacy:**

Primary Efficacy Endpoint:

The primary outcome measure will be the integral of the PSPRS changes from baseline over time measured during visits at 3, 6, 9, 12 months

The need for additional L-DOPA therapy or the need to increase the dose of L-DOPA during the trial

Secondary Efficacy Endpoints:

Development of gait disturbance/postural instability from base-line in posturographic measurement and corresponding costs

Change from baseline in pulmonary function

Time to pneumonia and corresponding costs

Time to gastrostomia and corresponding costs

Time to develop / progress of dementia and corresponding costs

Change from baseline in depression scale and corresponding costs

Changes from baseline in individual quality of life

Changes from baseline in disease-related quality of life

Time to death

**Safety:**

Secondary Endpoints for Safety and Tolerability:

Tolerability

Number of subjects (%) who discontinue the study

Number of subjects (%) who discontinue the study due to AEs

Safety

AE incidence

Safety laboratory values (blood cell count, ASAT, ALAT, creatinine)

Vital signs

ECG

Physical and neurological examination

Statistical methods:
Primary statistical analysis was based on two outcome variables:
(1) The integral of the changes in PSPRS scores over time, determined as area under the curve under the line connecting the PSPRS ratings at 0, 3, 6, 9, and 12 months.
(2) L-DOPA dose increase during the trial (including initiation of L-DOPA therapy).
Both hypotheses were tested in a closed test procedure that involved logistic regression for testing the intersection hypothesis in a first stage, using PSPRS score changes and L-DOPA dose increases as potential predictors of treatment group. Only in case of a significant result of the likelihood ratio test for the full model, a Kruskal-Wallis test for the PSPRS changes, and Fisher's exact test for comparison of the dose increase rates were applied. Tests for efficacy analyses were two-sided on an alpha level of 5%

Exploratory analyses of secondary endpoints were based on random intercept models using the fixed effects treatment group, visit, and the interaction of treatment group and visit. Exploratory statistical inferences were based on the type 3 tests of the interaction on an alpha level of 5%. Comparisons of AE rates were one-sided. Due to the exploratory character of these analyses, no alpha adjustment for multiple testing was undertaken.

Summary – Conclusions

Efficacy results: Rasagiline 1mg/d was not superior to placebo concerning the combined endpoint "disease progression" and "requirement of rescue medication" (likelihood ratio test: $\chi^2$[df=2]=1.4034, p=0.4957). Both groups experienced marked increases of PSPRS values. The mean increase was (m ± s) 10.6 ± 6.7 (95% CI: 7.2 to 14.0) in the placebo group versus 12.1 ± 6.7 (95% CI: 9.2 to 14.9) in the rasagiline group. 15/22 placebo versus 17/22 rasagiline patients were classified as having experienced an L-dopa dose increase. This translates to RR = 0.88 in favour of placebo (95% CI: 0.61 to 1.27). None of the exploratory tests of the secondary outcomes yielded evidence for a beneficial effect of Rasagiline.

Safety results: The use of Rasagiline 1mg/d is safe and well tolerated in patients suffering from progressive supranuclear palsy, but has no beneficial effect.

Conclusion: As the planned number of patients was not reached (planned 112, included 44), the study is severely underpowered. The power for the detection of the initially expected differences in PSPRS score changes was only 48%. The conclusions of the trial have to be treated with caution. Since several point estimates for the primary and secondary outcomes are actually in favour of placebo, lack of statistical power may not be the only explanation for the null results.

Date of report

14.06.2013