STUDY PROTOCOL – SYNOPSIS

A 12-week, multicenter, randomized, double-blind, placebo-controlled trial of Bupropion for the treatment of apathy in Alzheimer’s Dementia

Short title: Apa-AD

EudraCT: 2007-005352-17

Sponsor-ID: apaalz01

Phase: III

Investigational drug: Bupropion

Date: 06.10.2011
**A 12-week, multicenter, randomized, double-blind, placebo-controlled trial of Bupropion for the treatment of apathy in Alzheimer’s Dementia**

**EudraCT:** 2007-005352-17  
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<table>
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<tr>
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<tbody>
<tr>
<td>Principal Investigator</td>
<td>Prof. Dr. med. Frank Jessen (See above)</td>
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<tr>
<td>Study title</td>
<td>A 12-week, multicenter, randomized, double-blind, placebo-controlled trial of Bupropion for the treatment of apathy in Alzheimer’s Dementia</td>
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<tr>
<td>Investigational drug</td>
<td>Bupropion (Elontril®)</td>
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<td>Indication</td>
<td>Apathy in Alzheimer’s dementia</td>
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</table>
| Time frame | Submission of the study to the institutional review board and state authorities: June 2009  
Study accepted by institutional review board and state authorities: January 2010  
Inclusion of first patient: July 2010 |

**apaalz01:** Study protocol version 1.3 date: 06.10.2011
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| Inclusion of last patient: November 2012 |
| Completion of last patient: February 2013 |
| Close out: March 2013 |
| Completion of statistical analysis: May 2013 |
| Final report: June 2013 |

**Phase:** III

**Setting / sites:** Multi-center, national study (11-13 sites in Germany)

| Primary Outcome |
| Change score on the German version of the apathy evaluation scale (AES) |

| Secondary Outcomes |
| Change on the German version of the neuropsychiatric inventory (NPI) |
| Change on the German version of the NPI caregiver distress scale |
| Change on the German version of the Alzheimer’s Disease Consortium Activities of daily living scale (ADCS-ADL) |
| Change on the German version of the Quality of Live AD-Scale (QoL-AD) |
| Change on the German version of the Resources Utility Questionnaire (RUD) |
| Change on the German version of the Alzheimer’s Disease Assessment Scale (ADAScog) |
| Change on the German version of the Mini-Mental State Examination (MMSE) |

**Design**

Two-armed, randomized, double-blind, placebo-controlled trial
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| Number of patients | 216 patients (108 patients in the bupropion group, 108 in the placebo group)  
Recruitment period: 18 months  
Interim analysis after the inclusion of 108 patients added |
|-------------------|------------------------------------------------------------------|
| Inclusion Criteria | • Informed consent for study participation  
• mild to moderate Alzheimer’s dementia (NINCDS/ADRDA-criteria)  
• age between 55 and 90 years (including)  
• Mini-Mental State Examination (MMSE): 10 to 23 25 points (including)  
• ≥4 points on the apathy items of the neuropsychiatric inventory (NPI)  
• Fulfillment of the revised Starkstein Apathy criteria  
• outpatient setting  
• Availability of a caregiver  
• no concomitant treatment with anti-dementia drugs or stable treatment with anti-dementia drugs for the last three months without changes in the medication plan prior to inclusion  
• for females: Postmenopausal  
• cerebral brain scan (cCT, cMRI), which is consistent with the diagnosis of probable Alzheimer’s disease |
| Exclusion Criteria | • Dementias with other etiology than Alzheimer’s disease (e.g. vascular dementia, Lewy Body dementia, frontotemporal dementia, mixed forms) |
### Inclusion Criteria

- Major depressive disorder, defined by the modified DSM IV criteria (depressed mood must be present)
- ≥4 points on the NPI depression item
- Present alcohol- or benzodiazepine addiction
- Continuous treatment (present or during the last four weeks) with neuroleptic or antidepressive medication (including Hypericum perforatum)
- Continuous treatment (present or during the last four weeks) with dopaminergic drugs or Amantadine
- Continuous treatment (present or during the last four weeks) with benzodiazepines
- Continuous treatment (present or during the last four weeks) with mono-amino-oxidase inhibitors
- Known sensitivity towards bupropion
- Severe psychiatric disease during the last 6 months that resulted in hospitalization
- History of suicide attempts
- Acute psychotic symptoms
- Severe physical illness which does not allow the participation throughout the 12 week treatment period
- History of seizures
- History of central nervous system tumors
- History of severe brain injury with cerebral lesions
- Clinically relevant kidney failure and/or hepatic failure
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<table>
<thead>
<tr>
<th>Investigational drug, dose, route of administration</th>
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<tr>
<td><strong>Study drug: Bupropion</strong></td>
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<td>The verum group receives 1×150 mg Bupropion orally. After four weeks, the first efficacy assessment will be performed.</td>
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</table>

- concomitant treatment with medication that lower the seizure threshold (e.g. neuroleptics, antidepressive medication, Malaria medication, tramadol, theophylline, systemic steroids in higher dosages, Chinolone, sedative antihistamines)
- concomitant treatment with medication which is metabolized by Cytochrom P450-Isoenzyme 2D6 (e.g. the following beta-blocker Metoprolol, Propanolol, Timolol, Carvediol, Nebivolol, Type 1C antiarrhythmics such as Propafenone, Flecainid), excluding Donepezil and Galantamine
- concomitant treatment with medication which might interfere with bupropion metabolization (e.g. Carbamazepine, Phenytoine, Valproat, Ritonavir, Lopinavir)
- poorly controlled but medically treated Diabetes mellitus
- concomitant treatment with stimulants or appetite suppressants
- Participation in another clinical study during the last three months
- history of lactulose intolerance
- present suicidality

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<table>
<thead>
<tr>
<th>Duration of treatment:</th>
<th>12 weeks</th>
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<tr>
<td>Placebo, dose, route of administration</td>
<td>Placebo</td>
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<tr>
<td></td>
<td>The placebo group receives 1 tablet of placebo orally. After four weeks, the placebo group receives 2 tablets. If the patient does not tolerate 2 tablets, he/she may be down titrated to 1 tablet, which will then be the fixed dose throughout the study.</td>
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<tr>
<td>Efficacy criteria</td>
<td>Efficacy:</td>
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<tr>
<td></td>
<td>• mean difference between the bupropion group and the placebo group on the change on the Apathy Evaluation Scale after 12 weeks</td>
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<td>Safety:</td>
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<tr>
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<td>• documentation of side effects and adverse events</td>
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<tr>
<td>Statistician</td>
<td>Prof. Dr. Martin Hellmich</td>
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<td>Tel. 0221-478 6503</td>
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**Statistical methods**

Analysis of covariance (ANCOVA) was used to analyze the differences between the two treatment groups regarding the primary outcome (individual change on the AES between baseline and 12 weeks). The ANCOVA was stratified for the AES-baseline score, site, and co-medication with donepezil/galantamine.

Level of significance was set at 5% (two-tailed).

The intention-to-treat (ITT) population was used for primary and secondary efficacy analyses.

The per-protocol (PP) population was used for sensitivity analyses.

**GCP-conformity:**

This trial will be carried out in accordance with the internationally accepted “Good Clinical Practice-Guidelines (ICH-GCP)” as well as in accordance with the national law (AMG, GCP-V)

**Funding**

German Ministry of Education and Research (Bundesministerium für Bildung und Forschung, BMBF); grant number: 01KG0909)