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A randomised, single-blinded, placebo-controlled, multicentre study to investigate the pharmacodynamic effects of lithium on glycogen synthase kinase-3 (GSK-3) activity in patients with Alzheimer's disease

Submission date	Recruitment status	[ ] Prospectively registered
19/05/2008	No longer recruiting	[ ] Protocol
Registration date	**Overall study status**	[ ] Statistical analysis plan
02/07/2008	Completed	[X] Results
Last Edited	**Condition category**	[ ] Individual participant data
28/07/2009	Nervous System Diseases	

Plain English summary of protocol
Not provided at time of registration

Contact information

Type(s)
Scientific

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Additional identifiers

Protocol serial number
D0200C00001

Study information

Scientific Title

Study objectives
Ten-week treatment with lithium affects glycogen synthase kinase-3 (GSK-3) activity and cerebrospinal fluid (CSF) levels of phosphorylated tau (p-tau) in patients with mild Alzheimer's disease.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Ethics approval received from:
1. Ethics Committee of the Medical Faculty of the Ludwig-Maximilians University of Munich (Ethikkommission der Medizinischen Fakultät der Ludwig-Maximilians Universität München) on the 10th September 2004 (ref: 208/04)
2. Ethics Commitee of the Ruprecht-Karl University of Heidelberg (Ethikkommission der Ruprecht-Karl-Universität Heidelberg) on the 12th November 2004 (ref: 366/2004)
3. Ethics Committee of the Ruprecht-Karl University of Heidelberg, Faculty for Clinical Medicine Mannheim on the 18th November 2004 (ref: 220/04)
4: Ethics Committee of Charité Berlin (Ethikkommission der Charité Berlin) on the 11th November 2004 (ref: EA4/036/04)
5: Ethics Committee of the University of Tübingen (Ethikkommission der Universität Tübingen) on the 12th October 2004 (ref: 341/2004G)
6. Ethics Committee of the Faculty for Medicine of the Technical University of Munich (Ethikkommission der Fakultät für Medizin der Technischen Universität München) on the 3rd November (ref: 1191/04)

Study design
Randomised, single-blind, placebo controlled, parallel-group multicentre study

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Alzheimer's disease

Interventions
Following enrolment visit and baseline assessments, eligible patients were randomised to receive lithium sulphate (Lithionit®) or placebo (randomised 1:1), and entered into a titration phase of six weeks. During the titration phase, there were weekly visits to adjust the lithium dose to the target serum lithium concentration of 0.5 - 0.8 mmol/L. The starting dose of lithium

sulphate, 42 mg (6 mmol Li+), was 1 + 1 tablets daily (one tablet in the morning and one tablet in the evening approximately 12 hours apart). Dosages were escalated at weekly intervals until the target serum lithium concentration of 0.5 - 0.8 mmol/L (measured 12 hours from last dose) was reached, with 4 + 4 tablets taken during the maintenance phase.

Total duration of treatment: 10 weeks
Follow-up: at baseline and end of treatment (10 weeks)

Intervention Type
Drug

Phase
Not Specified

Drug/device/biological/vaccine name(s)
Lithium

Primary outcome(s)
The following were assessed at baseline and the end of treatment (10 weeks):
1. Change in GSK-3 activity in lymphocytes
2. Change in p-tau181 and p-tau231 in CSF

Key secondary outcome(s))
The following were assessed at baseline and the end of treatment (10 weeks):
1. Change in beta-amyloid (1-42) in CSF and blood
2. Change in tau in CSF
3. Change in cognitive function as measured by cognitive subscore of the Alzheimer's Disease Assessment Scale (ADAScog) and Neuropsychiatric Inventory (NPI)
4. To monitor safety and tolerability

Completion date
29/07/2005

Eligibility

Key inclusion criteria
1. Provision of informed consent
2. Female, without child bearing potential (post-menopausal for at least one year or surgically sterile) or male, aged 50 - 85 years
3. Clinical diagnosis of mild Alzheimer's disease
4. Diagnosis of Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria for primary degenerative dementia of the Alzheimer's type
5. National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for Alzheimer's disease
6. Stable dose of cholinesterase inhibitors (ChEI) for at least six months or no prior treatment with ChEI. Limited treatment periods with ChEI such as days or weeks after which treatment was stopped, not regarded as having any effects on the disease.
7. Willingness and ability to complete all study-related procedures and to understand patient information

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Sex
All

Key exclusion criteria
1. Any other clinically significant condition or laboratory abnormality that may interfere with the patient's ability to participate in the study or the study results, as judged by the investigator
2. Electrocardiogram (ECG) changes and/or signs indicative of significant cardiovascular disease, or other conditions in which lithium treatment is contraindicated, as judged by the investigator
3. Untreated hypothyroidism
4. Concomitant use of valproic acid, memantine, neuroleptics, coumarin, anticoagulants, or non-steroidal non-inflammatory drugs (NSAIDs)
5. Salt-restricted diet
6. Clinically significant liver disease or an elevation in alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST) or total bilirubin of 1.5 times the upper limit of the reference range
7. Known or suspected drug or alcohol abuse
8. Contraindications as detailed in the country-specific prescribing information for lithium
9. Participation in another drug trial within four weeks prior enrolment into this study or longer in accordance with local requirements
10. Involvement in the planning and conduct of the study (applies to both AstraZeneca staff or staff at the investigational sites)
11. Previous enrolment or randomisation of treatment in the present study

Date of first enrolment
22/11/2004

Date of final enrolment
29/07/2005

Locations

Countries of recruitment
Germany

Ireland

Study participating centre

Discipline of Psychiatry
Dublin
Ireland
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Sponsor information

Organisation
AstraZeneca (Sweden)

ROR
https://ror.org/04wwrrg31

Funder(s)

Funder type
Industry

Funder Name
AstraZeneca (Sweden)

Alternative Name(s)
AstraZeneca PLC, Pearl Therapeutics, AZ

Funding Body Type
Government organisation

Funding Body Subtype
For-profit companies (industry)

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?

Results article	results	01/06/2009	Yes	No