National Institute on Aging

AlzPED

Increasing Transparent Reporting and Rigorous Study Design of AD Preclinical Efficacy Studies

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We are targeting the wrong pathophysiological mechanisms
Drugs do not engage with the intended target
Interventions are started at the wrong stage of the disease
Lack of translatable pharmacodynamic biomarkers
Poor predictive power of animal model preclinical efficacy testing
Complexity of disease
Complexity of the physiologic response to therapeutic intervention

ScienceAlert

New Alzheimer's treatment fully restores memory function

TIME

This Alzheimer's Breakthrough Could Be a Game Changer

PRI

Mouse study hints at possible Alzheimer's cure

The Telegraph

Has Stanford University found a cure for Alzheimer's disease

More than 300 therapeutic agents have been reported to be efficacious in ameliorating pathology and/or cognitive deficits in transgenic AD animal models. None of these agents have been advanced to the FDA for approval to market as an effective disease modifying therapy for AD.

Zahs & Ashe Trends in Neurosciences, 2010

Neurobiology of Disease **10**, 268–278 (2002)
doi:10.1006/nbdi.2002.0487

Minocycline Slows Disease Progression in a Mouse Model of Amyotrophic Lateral Sclerosis

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NEUROPHARMACOLOGY AND NEUROTOXICOLOGY NEUROREPORT

Minocycline delays disease onset and mortality in a transgenic model of ALS

Ludo Van Den Bosch,[CA] Petra Tilkin, Griet Lemmens and Wim Robberecht

letters to nature

Minocycline inhibits cytochrome *c* release and delays progression of amyotrophic lateral sclerosis in mice

Shan Zhu*, Irina G. Stavrovskaya†, Martin Drozda*, Betty Y. S. Kim*, Victor Ona*, Mingwei Li*, Satinder Sarang‡, Allen S. Liu*, Dean M. Hartley§, Du Chu Wu‖, Steven Gullans‡, Robert J. Ferrante¶#, Serge Przedborski‖☆, Bruce S. Kristal† & Robert M. Friedlander***

Efficacy of minocycline in patients with amyotrophic lateral sclerosis: a phase III randomised trial

*Paul H Gordon, Dan H Moore, Robert G Miller, Julaine M Florence, Joseph L Verheijde, Carolyn Doorish, Joan F Hilton, G Mark Spitalny, Robert B MacArthur, Hiroshi Mitsumoto, Hans E Neville, Kevin Boylan, Tahseen Mozaffar, Jerry M Belsh, John Ravits, Richard S Bedlack, Michael C Graves, Leo F McCluskey, Richard J Barohn, Rup Tandan, for the Western ALS Study Group**

Summary

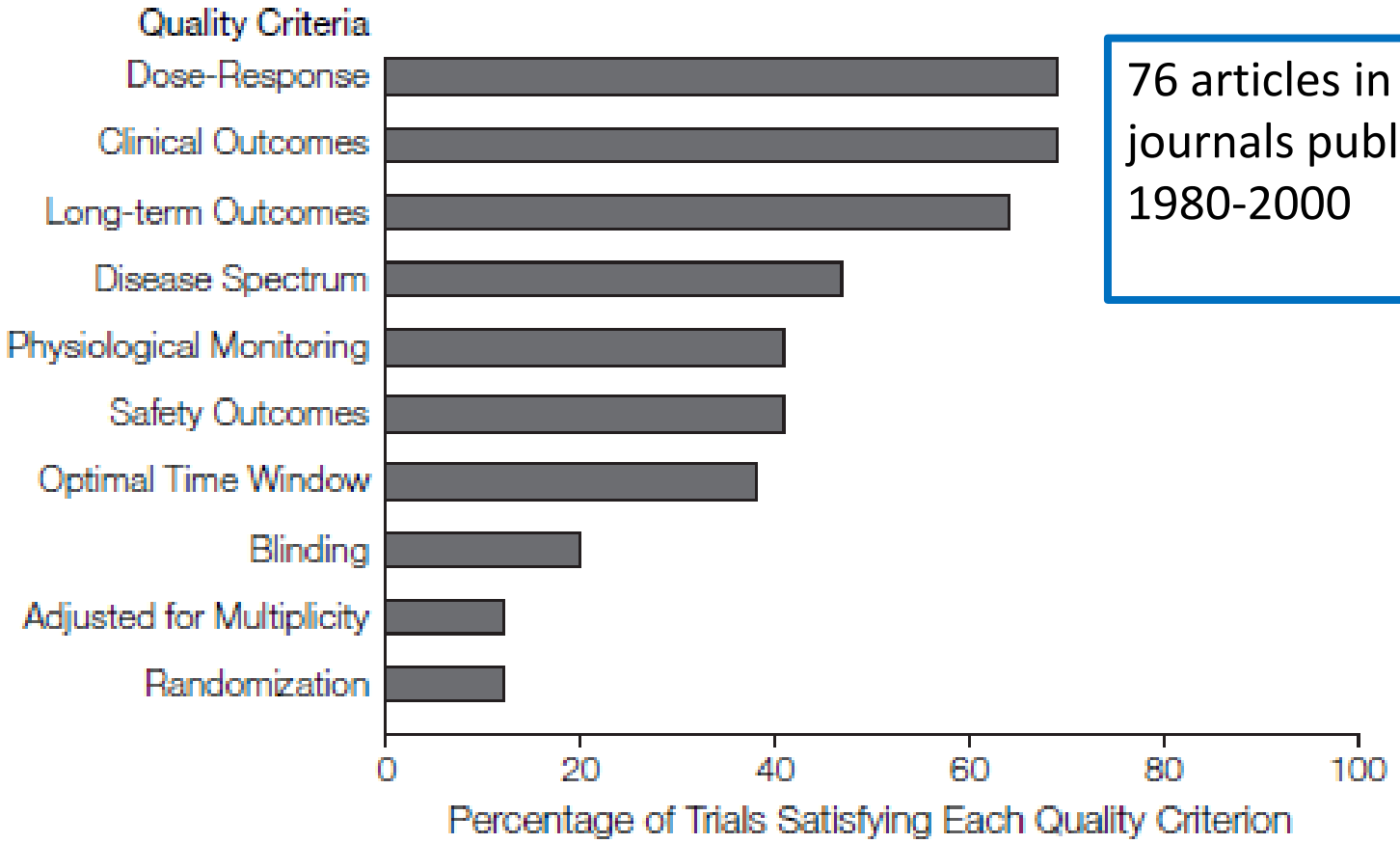
Background Minocycline has anti-apoptotic and anti-inflammatory effects in vitro, and extends survival in mouse models of some neurological conditions. Several trials are planned or are in progress to assess whether minocycline slows human neurodegeneration. We aimed to test the efficacy of minocycline as a treatment for amyotrophic lateral sclerosis (ALS).

Methods We did a multicentre, randomised placebo-controlled phase III trial. After a 4-month lead-in phase, 412 patients were randomly assigned to receive placebo or minocycline in escalating doses of up to 400 mg/day for 9 months. The primary outcome measure was the difference in rate of change in the revised ALS functional rating scale (ALSFRS-R). Secondary outcome measures were forced vital capacity (FVC), manual muscle testing (MMT), quality of life, survival, and safety. Analysis was by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00047723.

Findings ALSFRS-R score deterioration was faster in the minocycline group than in the placebo group (–1·30 *vs* –1·04 units/month, 95% CI for difference –0·44 to –0·08; p=0·005). Patients on minocycline also had non-significant tendencies towards faster decline in FVC (–3·48 *vs* –3·01, –1·03 to 0·11; p=0·11) and MMT score (–0·30 *vs* –0·26, –0·08 to 0·01; p=0·11), and greater mortality during the 9-month treatment phase (hazard ratio=1·32, 95% CI 0·83 to 2·10; p=0·23) than did patients on placebo. Quality-of-life scores did not differ between the treatment groups. Non-serious gastrointestinal and neurological adverse events were more common in the minocycline group than in the placebo group, but these events were not significantly related to the decline in ALSFRS-R score.

Interpretation Our finding that minocycline has a harmful effect on patients with ALS has implications for trials of minocycline in patients with other neurological disorders, and for how potential neuroprotective agents are screened for use in patients with ALS.

Figure 1. Methodological Quality of Animal Trials (n=76)



76 articles in 7 leading scientific journals published between 1980-2000

DG Hackam, JAMA , 296:1731-2, 2006

Advisory Meetings Examining the Causes of the Poor Translatability of Animal Models Preclinical Efficacy studies

- **National Institute on Aging**
  - -Advisory Meeting 2010
  - -NIH AD Summit 2012
  - -NIH AD Summit 2015

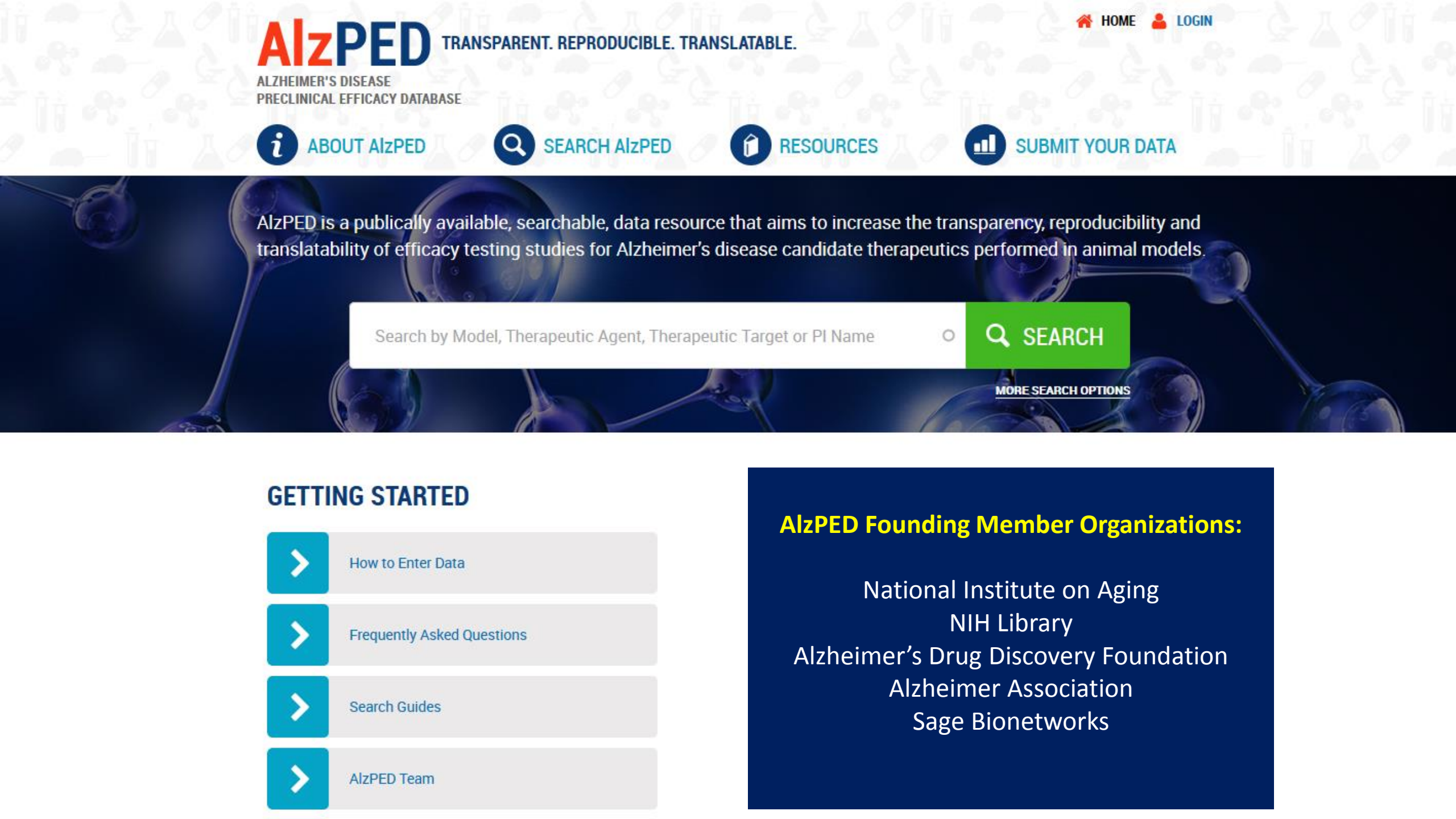
- **Alzheimer's Drug Discovery Foundation**
  - -Advisory Panel 2010

- **National Institute of Neurological Disorders and Stroke**
  - - Workshop 2012
- **Institute of Medicine**
  - - Workshop 2012

KEY FACTORS CONTRIBUTING TO THE POOR PREDICTIVE POWER OF PRE-CLINICAL EFFICACY TESTING STUDIES IN AD ANIMAL MODELS

- The limitations of transgenic animal models used in AD drug development
- Lack of translatable biomarkers
- Failure to match outcome measures used in clinical studies
- Lack of standard/rigor in study design and analysis of data
- Poor reproducibility of published studies and publication bias due to under-reporting of negative results in the literature

Shineman et. al. 2011; Landis et al. 2012; Snyder et al. 2016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AlzPED is a publically available, searchable, data resource that aims to increase the transparency, reproducibility and translatability of efficacy testing studies for Alzheimer's disease candidate therapeutics performed in animal models.
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PRECLINICAL EFFICACY DATABASE

- Raise awareness about the elements of rigorous study design and requirements for transparent reporting.
- Provide researchers and information scientists with a facile way to survey and analyze existing AD preclinical therapy development literature.
- Reduce the publication bias that favors studies with positive findings by providing a platform for reporting on studies with negative findings.
- Provide funding agencies with a tool for enforcement of requirements for transparent reporting and rigorous study design.

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PRECLINICAL EFFICACY DATABASE

- Searchable (by target, animal model, therapeutic agent, funding agency) summaries of the experimental design and findings of published preclinical efficacy testing studies. (over 550 curated manuscripts).

- Links to databases on:
  - related publications - PubMed
  - therapeutic targets (Open Targets/Pharos)
  - therapeutic agents (PubChem)
  - clinical trials (ClinicalTrials.gov)
  - patents (USTPO/Google Patents)

- Provides a platform for creating citable and searchable summary reports of unpublished studies (full reports and primary data hosted on Synapse/AMP-AD Knowledge Portal). just launched - beta

Begacestat (GSI-953): a novel, selective thiophene sulfonamide inhibitor of amyloid precursor protein gamma-secretase for the treatment of Alzheimer's disease.

VIEW | EDIT | UNPUBLISH

BIBLIOGRAPHIC | THERAPEUTIC AGENT | ANIMAL MODEL | EXPERIMENTAL DESIGN | OUTC

Bibliographic

Published: Published

Year of Publication: 2009

PI First Name: J

PI Last Name: Jacobsen

PI Middle Initial: Steven

Author Affiliation: Wyeth Research, Departments of Discovery Neuroscience

Primary Reference (PubMED ID): 19671883

Funding Source: Wyeth Research

Therapeutic Agent

Therapy Type: Small Molecule

Therapeutic Agent: GSI-begacestat

Therapeutic Target: Gamma secretase

Link to PubChem, PubMED, Clinical Trials, Patents:

PubChem-begacestat

PubMED- gamma secretase inhibitors

PubMED-begacestat

Clinical Trials-begacestat

Clinical Trials-gamma secretase inhibitor/Alzheimer's

Patents-begacestat

Patents -gamma secretase inhibitor/Alzheimer's

Animal Model

Model Information:

Species: Mouse

Model Type (Genes): APP

Model Name: Tg2576

Strain/Genetic Background: not reported

Species: Rat

Model Type (Genes): Wild Type

Model Name: Sprague-Dawley

Strain/Genetic Background: not reported

Species: Dog

Model Type (Genes): Wild Type

Model Name: not reported

Strain/Genetic Background: not reported

Experimental Design

Is the following information reported in the study?:

✗ Power Calculation	✗ Randomized into Groups
✗ Blinded for Treatment	✗ Blinded for Outcome Measures
✓ Pharmacokinetic Measures	✓ Pharmacodynamic Measures
✓ Toxicology Measures	✗ ADME Measures
✓ Use of Biomarkers	✓ Dosage
✓ Formulation	✓ Route of Delivery
✓ Duration of Treatment	✓ Frequency of Delivery
✓ Age at the Beginning of Treatment	✓ Age at the End of Treatment
✗ Gender	✗ Study Balanced for Gender
✗ Number of Premature Deaths	✗ Number of Excluded Animals
✓ Statistical Test	✓ Statistical Significance (P Value)

Outcomes

Study Goal and Principal Findings:

The goal of this study was to report the pharmacological properties of a novel thiophene sulfonamide gamma secretase inhibitor (GSI), GSI-953 (also known as begacestat).In summary, the preclinical data for GSI-953 demonstrating potent Abeta lowering, with nano molar potency, and in vitro selectivity against Notch processing, robust in vivo efficacy for the lowering of brain, CSF, and plasma Abeta levels, reversal of Abeta-dependent cognitive deficits in Tg2576 mice, and the lowering of plasma Abeta levels in humans, provides evidence supporting that GSI-953 treatment has the potential for disease modification in the development of AD.

Outcomes:

Outcome Measured: Behavioral
Specific Outcomes: Contextual fear conditioning test

Outcome Measured: Biochemical
Specific Outcomes: in vitro-beta amyloid peptides 40 and 42

Outcome Measured: Biochemical
Specific Outcomes: Notch Selectivity

Outcome Measured: Biochemical
Specific Outcomes: binding to gamma secretase

Outcome Measured: Biochemical
Specific Outcomes: brain- beta amyloid peptides 40 and 42

Outcome Measured: Biochemical
Specific Outcomes: plasma- beta amyloid peptides 40 and 42

Outcome Measured: Biochemical
Specific Outcomes: CSF- beta mayloid peptides 40 and 42

Outcome Measured: Pharmacokinetics
Specific Outcomes: Cmax

Outcome Measured: Pharmacokinetics
Specific Outcomes: AUC

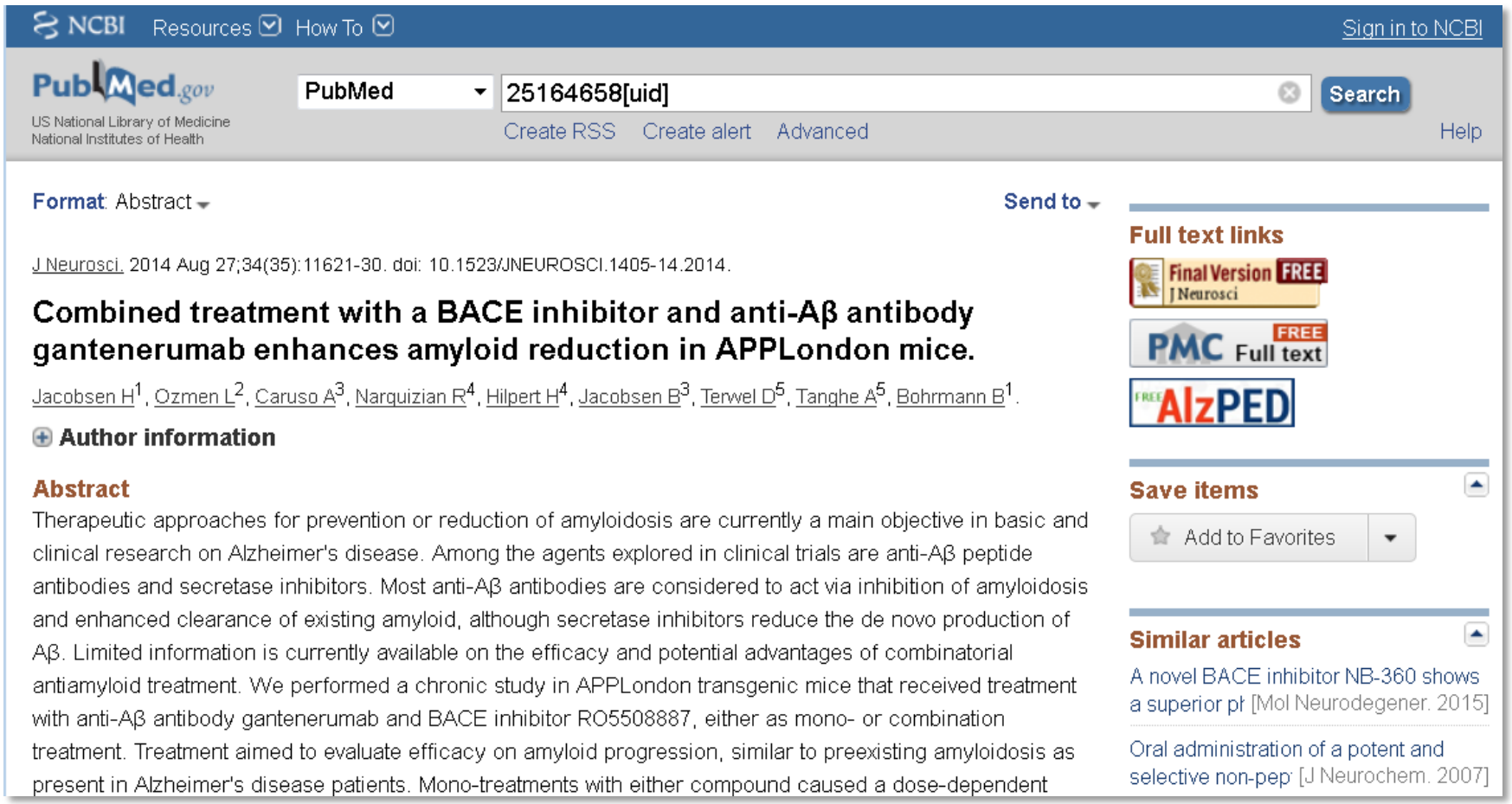
Outcome Measured: Pharmacokinetics
Specific Outcomes: B/P ratio

Experimental Design

Is the following information reported in the study?:

- ✗ Power/Sample Size Calculation
- ✗ Blinded for Treatment
- ✗ Pharmacokinetic Measures
- ✓ Toxicology Measures
- ✓ Biomarkers
- ✓ Formulation
- ✓ Duration of Treatment
- ✓ Age of Animal at the Beginning of Treatment
- ✓ Gender
- ✗ Number of Premature Deaths
- ✓ Statistical Plan
- ✗ Inclusion/Exclusion Criteria Included
- ✓ Randomized into Groups
- ✓ Blinded for Outcome Measures
- ✗ Pharmacodynamic Measures
- ✗ ADME Measures
- ✓ Dose
- ✓ Route of Delivery
- ✓ Frequency of Administration
- ✓ Age of Animal at the End of Treatment
- ✓ Study Balanced for Gender
- ✗ Number of Excluded Animals
- ✗ Conflict of Interest

AlzPED – PubMED Cross-Reference



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