

Principal Investigator

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General Information

Key Personnel (in addition to PI):

First Name: W. M.

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First Name: E.G.B.

Last name: Vijverberg

Degree: Neurologist, dr.

Primary Affiliation: Neurologist/Principal Investigator, Senior researcher

First Name: L.

Last name: Ottenhoff

Degree: Msc

Primary Affiliation: neuropsychologist and PhD student

Are external grants or funds being used to support this research?: External grants or funds are being used to support this research.

Project Funding Source: Health~Holland, Top Sector Life Sciences & Health/ Brain Research Center, Amsterdam

How did you learn about the YODA Project?: Data Holder (Company)

Conflict of Interest

https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2019_jv.pdf

https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2019_lo.pdf

https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2019_van_der_flier.pdf

https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2019_sams.pdf

https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2019_sams2.0.pdf

Certification

Certification: All information is complete; I (PI) am responsible for the research; data will not be used to support litigious/commercial aims.

Data Use Agreement Training: As the Principal Investigator of this study, I certify that I have completed the YODA Project Data Use Agreement Training

1. [NCT00575055 - ELN115727-302 - A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Efficacy and Safety Trial of Bapineuzumab \(AAB-001, ELN115727\) In Patients With Mild to Moderate Alzheimer's Disease Who Are Apolipoprotein E4 Carriers](#)
2. [NCT00574132 - ELN115727-301 - A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Efficacy and Safety Trial of Bapineuzumab \(AAB-001, ELN115727\) In Patients With Mild to Moderate Alzheimer's Disease Who Are Apolipoprotein E4 Non- Carriers](#)

What type of data are you looking for?: Individual Participant-Level Data, which includes Full CSR and all supporting documentation

Research Proposal

Project Title

Optimizing Trial design to Achieve Personalized prevention of Alzheimer's disease

Narrative Summary:

We aim to improve trial design with the ultimate objective to achieve a future of effective and efficient personalized prevention of AD. To achieve this goal, we will identify subgroups of patients responding to specific compounds in existing trial data sets of patients with early AD.

We will evaluate disease course over time in terms of (i) clinical progression to MCI or dementia, (ii) cognitive decline over time in different cognitive domains, (iii) functional decline (instrumental activities of daily living), and (iv) behavioral outcomes.

Scientific Abstract:

Background: With more than 40 million worldwide, Alzheimer disease (AD) is among the largest health care challenges of our century. However, curative therapy is not yet available. This may be due to a number of factors. Trials should focus on pre-dementia stage, trials need to evaluate different mechanism-based approaches as well and inclusion criteria do not reflect the mode of action of specific drugs and outcome measures lack sensitivity.

Objective: We aim to improve trial design with the ultimate objective to achieve a future of effective and efficient personalized prevention of AD.

Study Design: meta analyses

Participants: We will identify subgroups of patients responding to specific compounds in existing trial data sets of patients with early AD. We want to use trial data sets trials in early AD (prodromal/ early dementia)

Main Outcome Measure: We will evaluate disease course over time in terms of (i) clinical progression to MCI or dementia, (ii) cognitive decline over time in different cognitive domains, (iii) functional decline (instrumental activities of daily living), and (iv) behavioral outcomes.

Statistical Analysis. We will define "positive response" based on the primary and secondary outcome measures in each of the trial data sets. In the first step, we will define responders using different approaches; early endpoints (biomarker, cognitive and functional improvement/stabilization (primary cognitive outcome measure). Second; change of cognitive status, i.e. clinical progression to MCI; change of cognitive status, i.e. clinical progression to AD.

Brief Project Background and Statement of Project Significance:

With more than 250.000 patients in the Netherlands and more than 40 million worldwide, Alzheimer disease (AD) is

among the largest health care challenges of our century. However, curative therapy is not yet available. This may be due to a number of factors, that are slowly becoming clear as our understanding of the disease grows. First, AD develops gradually, in the course of decades. Studies using biomarkers (Amyloid or Tau) and imaging (MRI or PET) have shown that brain changes associated with AD are present until 20 years before clinical manifestation of the disease. The stage of dementia is too late to reverse the brain damage which has accumulated over the decades before. This novel knowledge implies that trials should focus on pre-dementia stage, and hence that future treatment strategies for AD will have the form of secondary prevention.

Second, AD is a complex, diverse disease. Most drugs tested have focused on the amyloid pathway. It could be that amyloid is simply the wrong target. While this notion cannot be excluded, literature strongly supports an important role for amyloid in onset and progression of the disease. Nonetheless, it is essential to select the right patients most likely to benefit from anti-amyloid therapy with the right mode of action. In addition, it is increasingly recognized that amyloid does not explain the disease in its entirety. Therefore, trials need to evaluate different mechanism-based approaches as well, e.g. anti-tau with active or passive immunization, anti-inflammatory drugs and neuroprotective compounds, and we should find out which patients benefit most from with strategy.

Finally, taking and into account, one realizes that trial designs have been too crude; inclusion criteria do not reflect the mode of action of specific drugs and outcome measures lack sensitivity. To bring closer a future of personalized prevention of AD, we need to focus on early, pre-dementia disease stages, taking into account de diverse patient group

Specific Aims of the Project:

We aim to improve trial design with the ultimate objective to achieve a future of effective and efficient personalized prevention of AD. To achieve this goal, we will identify subgroups of patients responding to specific compounds in existing trial data sets of patients with early AD.

We will evaluate disease course over time in terms of (i) clinical progression to MCI or dementia, (ii) cognitive decline over time in different cognitive domains, (iii) functional decline (instrumental activities of daily living), and (iv) behavioral outcomes.

What is the purpose of the analysis being proposed? Please select all that apply.

Summary-level data meta-analysis pooling data from YODA Project with other additional data sources

Participant-level data meta-analysis

Participant-level data meta-analysis pooling data from YODA Project with other additional data sources

Develop or refine statistical methods

Research on clinical trial methods

Research on comparison group

Research on clinical prediction or risk prediction

Research Methods

Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:

For this project, we want to use trial data sets trials in early AD (prodromal/ early dementia) which have recently been finalized. We would like to include data sets of trials using compounds with different modes of action, in particular (i) anti-amyloid, (ii) anti-inflammation, and (iii) neuroprotective treatment strategies. We'd like to use trial data sets which include patients with MCI due to AD or mild AD from 50-90 years. Mini-Mental State Examination (MMSE) score range from 18 to 28. Inclusion criteria further comprise evidence of amyloid pathology by Amyloid PET determined by visual inspection or based on concentration of abeta 1-42 in cerebrospinal fluid derived by lumbar puncture (if available).

NCT01424436

NCT00459550

NCT02423200

NCT01739348

NCT01953601

NCT00762411

NCT00594568

NCT02337907

Main Outcome Measure and how it will be categorized/defined for your study:

We will define “positive response” based on the primary and secondary outcome measures in each of the trial data sets. We will then make a codebook of existing variables, including demographic variables, clinical data, genetic markers and biomarker values available in each of the data sets.

Main Predictor/Independent Variable and how it will be categorized/defined for your study:

In the first step, we will define responders using different approaches:

1) early endpoints:

- a) biomarker improvement/stabilization;
- b) cognitive improvement/stabilization (primary cognitive outcome measure),
- c) cognitive improvement/stabilization and functional improvement/stabilization (primary cognitive & functional outcome measures),

2) late endpoints:

- a) change of cognitive status, i.e. clinical progression to MCI;
- b) change of cognitive status, i.e. clinical progression to AD dementia

we will define studies on their target: anti-amyloid, anti-tau and anti inflammation.

Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:

The table provides an overview of data that may be available.

- Demographic variables (age, sex, education)
- Diagnostic markers (Abeta 1-42, Tau, P- tau).
- Safety parameters (vital signs, blood pressure, heart rate)
- Physical examination
- Neurological examination
- Brain MRI (atrophy, white matter hyperintensities, microbleeds)
- Neuropsychological outcomes (tests for memory, attention, executive functions)
- Instrumental activities of daily living
- Genetic markers (e.g. APOE)
- Exploratory biomarkers such as
 - o QC enzyme.
 - o Panel of Abeta peptide versions of various length (X-40/42).
 - o Panel for pGluAbeta and its substrates Abeta 3-40/42 and 11-40/42.
 - o Panel of Abeta-Oligomers of different a length.
 - o Neurofilament light

Statistical Analysis Plan:

In two steps, we aim to identify a combination of patient characteristics (demographic, clinical, biomarker) associated with a positive response to treatment.

In the first step, we will define responders using different approaches:

1) early endpoints:

- a) biomarker improvement/stabilization;
- b) cognitive improvement/stabilization (primary cognitive outcome measure),
- c) cognitive improvement/stabilization and functional improvement/stabilization (primary cognitive & functional outcome measures),

2) late endpoints:

- a) change of cognitive status, i.e. clinical progression to Mild Cognitive Impairment (MCI);
- b) change of cognitive status, i.e. clinical progression to AD dementia

Different responder definitions (1abc and 2ab) will be used to dichotomize treatment response. In the second step, we will model treatment effect, by applying a Causal Forest machine learning model. This predictive technique is a flexible and powerful predictor, in particular when higher order interactions are expected [Wager and Athey, 2018]. Using this model, we can model treatment-specific effects of medication. The following characteristics will be included in the model: age, sex, disease status, ethnicity, presence or absence of co-morbidities, baseline cognitive

status, biomarkers of tau and amyloid. Based on these analyses, we will develop new knowledge on which combination of patient characteristics (demographic, clinical, biomarker) predisposes for a treatment effect to which type of drugs.

Software Used:

I am not analyzing participant-level data / plan to use another secure data sharing platform

Project Timeline:

We planned one year in total for preparing data sets, and one year to do (responder) analyses.

Task 1: Trial data sets ready for analysis (M7)

Expected: Q3 2021

Task 2: Variables for patient stratification identified (M24)

Expected: Q3 2021

Task 3: date of data analysis completion

Expected Q1/2 2022

Task 3: date of manuscript completion

Expected Q2 2022

Dissemination Plan:

This report can guide pharmaceutical companies and CRO's in the effective and efficient design of prevention trials.

Alzheimers Research & Therapy

Alzheimer's & Dementia

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