The YODA Project
Research Proposal Review

The following page contains the final YODA Project review approving this proposal.

The Yale University Open Data Access (YODA) Project
Yale University Center for Outcomes Research and Evaluation (CORE)
195 Church Street, 5th Floor, New Haven, CT 06510

The YODA Project
Research Proposal Review - Final
(Protocol #: 2024-0692)

Reviewers:

- ☐ Nihar Desai
- ☐ Cary Gross
- ☐ Harlan Krumholz
- ☒ Richard Lehman
- ☒ Joseph Ross
- ☒ Joshua Wallach

Review Questions:	**Decision:**
1. Is the scientific purpose of the research proposal clearly described?	Yes
2. Will request create or materially enhance generalizable scientific and/or medical knowledge to inform science and public health?	Yes
3. Can the proposed research be reasonably addressed using the requested data?	Yes, or it's highly likely
4. Recommendation for this data request:	Approve

Comments:

No additional comments

The YODA Project
Research Proposal Review

Revisions were requested during review of this proposal.
The following pages contain the original YODA Project review and the original submitted proposal.

The Yale University Open Data Access (YODA) Project
Yale University Center for Outcomes Research and Evaluation (CORE)
195 Church Street, 5th Floor, New Haven, CT 06510

The YODA Project
Research Proposal Review - Revisions Requested
(Protocol #: 2024-0692)

Reviewers:

- ☐ Nihar Desai
- ☐ Cary Gross
- ☐ Harlan Krumholz
- ☒ Richard Lehman
- ☒ Joseph Ross
- ☒ Joshua Wallach

Review Questions:	**Decision:**
1. Is the scientific purpose of the research proposal clearly described?	Yes
2. Will request create or materially enhance generalizable scientific and/or medical knowledge to inform science and public health?	Yes
3. Can the proposed research be reasonably addressed using the requested data?	Unsure, would defer to Data Holder Due Diligence Assessmen
4. Recommendation for this data request:	Not Approve

Comments:

Additional information is needed in the statistical analysis section- please provide more detail regarding how the data will be analyzed.

Principal Investigator

First Name: David
Last Name: Jakabek
Degree: MBBS
Primary Affiliation: University College London
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State or Province: UK
Country: United Kingdom

General Information

Key Personnel (other than PI):
First Name: Nick
Last name: Fox
Degree: MBBS, MD
Primary Affiliation: University College London
SCOPUS ID:
Requires Data Access? No

Are external grants or funds being used to support this research?: No external grants or funds are being used to support this research.
How did you learn about the YODA Project?: Colleague

Conflict of Interest

https://yoda.yale.edu/wp-content/uploads/2024/08/Yoda_COI_DJ.pdf
https://yoda.yale.edu/wp-content/uploads/2024/08/Yoda_COI_NF.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

Associations of brain volumetric changes with Alzheimer's disease biomarkers and clinical outcomes in bapineuzumab treatment.

Narrative Summary:

New medications for Alzheimer's disease are known to slightly reduce the size of some parts of the brain. Although it remains unknown why this occurs. This study will look at how brain size changes with bapineuzumab treatment, and whether brain size changes are associated with markers of Alzheimer's disease or performance on memory and thinking tests. Results will provide additional safety information about bapineuzumab specifically and by extension to newer types of Alzheimer's disease medications.

Scientific Abstract:

Background: Anti-amyloid monoclonal antibodies are known to cause brain and ventricle volume changes. Although this has raised safety concerns about the use of these medications, there are presently limited patient-level analyses of volume changes.
Objective: Determine the association of both 1) amyloid and tau markers, and 2) cognitive and functional scales, with brain volume changes.
Study design: Secondary analyses of two phase 3 trials of bapineuzumab.
Participants: Participants with Alzheimer's disease in all study arms
Primary outcome measure: Associations between 1) amyloid and tau markers, and 2) cognitive and functional scales, will be determined with whole brain and regional brain volume changes from baseline.
Statistical analyses: Associations will be assessed with mixed models, controlling for baseline values and age.

Brief Project Background and Statement of Project Significance:

Brain volume reduction and ventricular enlargement has been observed in several anti-amyloid monoclonal antibodies (Alves et al., 2023). With the licensing of anti-amyloid monoclonal antibodies in some countries worldwide, and ongoing review in many others, there are urgent calls to understand the causes and safety implications of observed brain volume changes (Alves et al., 2023; Liu et al., 2023).
There are limited patient-level analyses of MRI volumetric outcomes in anti-amyloid monoclonal antibody therapy. Verubecestat was found to reduce volumes in amyloid-rich cortical regions (Sur et al., 2020). Limited regional results have been performed for donanemab (A Study of LY3002813 in Participants With Early Symptomatic Alzheimer's Disease (TRAILBLAZER-ALZ), 2022) which found reductions in volume of both grey and white matter. Direct comparison of regional brain volume with amyloid or tau markers have not been performed, nor has correlation of volumetric changes with cognitive changes.
This project aims to assess associations of brain volume changes with imaging and CSF markers of Alzheimer's disease, and clinical markers. Outcomes of this project may provide additional safety information about anti-amyloid monoclonal antibodies which to date has not been provided for highly active medications (i.e., aducanumab, lecanemab, and donanemab). Although bapineuzumab treatment was not associated with clinical change, ventricular enlargement appears to be a class effect (Alves et al., 2023) and so findings may generalise within this drug class.

Specific Aims of the Project:

Aim 1: Determine the associations of amyloid and tau change with regional brain volume change.
Objective: Determine markers of amyloid (PiB Global Cortical Uptake SUVR, CSF Amyloid-Beta) and tau (CSF p-tau and CSF t-tau) on brain volumes across treatment groups.

Hypothesis: Amyloid and tau reduction will be associated with statistically significant increases in ventricle volume and reduction in brain volumes in the pooled treatment group.

Aim 2: Evaluate associations between cognitive and functional measures with brain volume change.
Objective: Evaluate the association between cognitive and functional outcome measures (ADAS-Cog11, DAD, Neuropsychological Test Battery, CDR-sum of boxes, MMSE, Dependence Scale) with MRI volumetric outcomes across treatment groups.
Hypothesis: Cognitive and functional outcomes will have no statistically significant association with volumetric outcomes across treatment groups.

Study Design:

Individual trial analysis

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

New research question to examine treatment safety

Research on clinical trial methods

Research Methods

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

Patient-level data is sought from NCT00574132 and NCT00575055 which will be pooled across all placebo and treatment arms.
All participants will be included; no additional exclusion criteria will be applied.
For neuroimaging data, we request:
- All available scans for T1-weighted sequences, and if available, T2/FLAIR weighted sequences. T1 weighted sequences are required for automatic regional volume processing. Optional T2/FLAIR weighted sequences will allow more accurate automatic processing.
- Electronic data transfer of MRI scans to local secure server. Local secure servers will be used with restricted access (the same which were utilised for the original neuroimaging analysis of boundary-shift integral).
- MRI scans locally to be identified by participant ID and visit only. Output of local volumetric processing to be uploaded to secure online (Safe Harbour) platform and matched to patient-level data for subsequent analysis.

Primary and Secondary Outcome Measure(s) and how they will be categorized/defined for your study:

Both aims will have the same primary and secondary outcomes:

Primary outcome measures:
MRI volumetric measures for whole brain, ventricles, and hippocampus (mean of left and right) at final visit calculated via the boundary-shift integral

Secondary outcome measures:
MRI volumetric measures for lobar brain grey and white matter at all (19, 45, and 71 week) visits. Regional volumes will be computed using Freesurfer (Fischl, 2012) which is a well-established volumetric parcellation pipeline.

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

Aim 1: Determine the associations of amyloid and tau with brain and ventricle volume change
Markers of amyloid: PiB Global Cortical Uptake SUVR, CSF Amyloid-Beta
Markers of tau: CSF p-tau and CSF t-tau
Treatment: Placebo and pooled bapineuzumab treatment group (across APOE4 carriers and non-carriers and doses)

Aim 2: Evaluate associations between cognitive and functional measures with brain volume change.
Cognitive and functional outcome measures: ADAS-Cog11, DAD, Neuropsychological Test Battery, CDR-sum of boxes, MMSE, Dependence Scale).
Treatment: Placebo and pooled bapineuzumab treatment group (across APOE4 carriers and non-carriers and doses)

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

All analyses will include covariate of age.
APOE4 status and bapinezumab dose required to characterise groups.

Statistical Analysis Plan:

Aim 1: Determine the associations of amyloid and tau with brain and ventricle volume change
Mixed models for repeated measures, separate models for each biomarker (PiB, CSF amyloid, CSF, p-tau, CSF t-tau) across each MRI volume
Response variable: MRI volume change from baseline
Predictor variables: Biomarker change from baseline, treatment, and biomarker-by-treatment interaction
Covariate: Age, baseline MRI volume, baseline biomarker value

Aim 2: Evaluate associations between cognitive and functional measures with brain volume change.
Mixed models for repeated measures, separate models for each cognitive and functional outcome measure (ADAS-Cog11, DAD, Neuropsychological Test Battery, CDR-sum of boxes, MMSE, Dependence Scale) across each MRI volume
Response variable: MRI volume change from baseline
Predictor variables: Cognitive or functional scale change from baseline, treatment, and scale-by-treatment interaction
Covariates: Age, baseline MRI volume, baseline cognitive or functional scale score

For primary outcomes, nominal p-values will be used to assess for statistical significance.
For secondary outcomes, p-values adjusted by the false discovery rate will be used to assess for statistical significance.

Software Used:

RStudio

Project Timeline:

September- October 2024: Conduct data processing and analyses
November-December 2024: Manuscript preparation, submission, and reporting to YODA Project.

Dissemination Plan:

Submissions to scientific conferences (e.g., AAIC or CTAD) and/or neurology scientific journals (e.g., Brain, Neurology, Alzheimer's and Dementia).

Bibliography:

A Study of LY3002813 in Participants With Early Symptomatic Alzheimer's Disease (TRAILBLAZER-

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Alves, F., Kalinowski, P., & Ayton, S. (2023). Accelerated Brain Volume Loss Caused by Anti–β-Amyloid Drugs: A Systematic Review and Meta-analysis. *Neurology*, *100*(20). https://doi.org/10.1212/WNL.0000000000207156

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Liu, K. Y., Villain, N., Ayton, S., Ackley, S. F., Planche, V., Howard, R., & Thambisetty, M. (2023). Key questions for the evaluation of anti-amyloid immunotherapies for Alzheimer's disease. *Brain Communications*, *5*(3), fcad175. https://doi.org/10.1093/braincomms/fcad175

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