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Requires Data Access? Yes

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Requires Data Access? Yes

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/2024/11/COI_Matsouaka_YODA.pdf
https://yoda.yale.edu/wp-content/uploads/2024/11/COI_Barnhart.pdf
https://yoda.yale.edu/wp-content/uploads/2024/11/COI_Lokhnygina.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. 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
2. 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

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

Research Proposal

Project Title

Study proposal: Evaluating win statistics in longitudinal studies using data from the Bapineuzumab 302 trial.

Narrative Summary:

In this study, we will use data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) to evaluate the effect of Bapineuzumab on clinical outcomes, which include mortality, Alzheimer's Disease Assessment Scale (ADAS) score and the Disability Assessment for Dementia (DAD) score. Assessment of the treatment effect will be carried and win measures will be estimated (along with the corresponding confidence intervals) at baseline and subsequently every 13 weeks (t = 13, 26, 39, 52, 65, 78 weeks). Then the overall test statistic and global win measures will be evaluated for the whole study duration.

Scientific Abstract:

Background: Alzheimer's disease (AD) is a multifaceted disease, which requires multiples outcomes to ascertain the patient's experience. AD clinical trials collect data on multiple endpoints to comprehensively evaluate treatment efficacy.
Objective: To evaluate treatment efficacy through a hierarchical composite endpoints using win measures. The goal is to provide a combine treatment effect measure that encompasses the whole patient experience and a unique related test statistic that does not require multiplicity adjustments.
Study design: Posthoc observational study involving the original study of the Bapineuzumab Trials (Apolipoprotein E4 Carriers and Non-Carriers)
Participants: Patients enrolled in the Bapineuzumab Trials (NCT 00574132 and NCT 00575055)
Primary outcome: composite of mortality, Alzheimer's Disease Assessment Scale (ADAS) score and the Disability Assessment for Dementia (DAD) score.
Secondary outcome: scores on the Neuropsychological Test Battery, the Clinical Dementia Rating--Sum of Boxes, the MMSE, and the Dependence Scale
Statistical analysis: Summary statistics will be estimated using the outcomes and patients' characteristics. Treatment groups will be compared on outcomes and patients' characteristics using t-test, wilcoxon test, Chi-square test or fisher's exact test accordingly, depending on the nature of the variables (continuous, ordinal, categorical) and their underlying disrtibutions (normal, non-normal, or count). Composite endpoints will be evaluated between treatment groups using the win measures and their confidence intervals.

Brief Project Background and Statement of Project Significance:

Neurodegenerative disorders such as Alzheimer's disease (AD) present a significant global health challenge, characterized by cognitive decline, functional impairment, and other debilitating effects. Current AD clinical trials often assess multiple longitudinal primary endpoints to comprehensively evaluate treatment efficacy. Often, competing risk data arise when non-terminal events are censored by terminal or fatal events. An abundant literature exists on model-based methods to analyze such data. Traditional methods, however, may fail to capture global treatment effects, require larger sample sizes due to multiplicity adjustments, and may not fully exploit multivariate longitudinal data. Specifications of the joint distribution is complex and not easy to provide as the

measured outcomes have different natures, scales, and underlying distributions. To address these limitations, we will develop and promote the use of win statistics (win ratio, net treatment benefit, and win odds) for longitudinal data. The win statistics offer flexibility throughout various data distributions encountered in AD research and maximizes the utilization of longitudinal data. These are nonparametric rank-based measures of treatment effect on additive and multiplicative scale. This will enable a comprehensive assessment of the treatment efficacy across multiple endpoints and time points without the need for multiplicity adjustments, effectively controlling Type I error while enhancing statistical power.

Specific Aims of the Project:

To assess the treatment effect using win measures (along with the corresponding confidence intervals) at baseline and subsequently every 13 weeks (t = 13, 26, 39, 52, 65, 78 weeks). Then the overall test statistic and global win measures will be evaluated for the whole study duration, based on the following aims:
Aims 1: Evaluate win ratio and corresponding confidence intervals;
Aim 2: Calculate the win odds and draw inference;
Aim 3: Estimate the net treatment benefits.
In all of these aims we will use the Bapineuzumab trials data to illustrate the methods.

Our global hypothesis is that patients on Bapineuzumab have better outcomes overall compare to the placebo.

Study Design:

Individual trial analysis

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

Participant-level data meta-analysis

Meta-analysis using only data from the YODA Project

Research Methods

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

Participant inclusion criteria: We will use the same inclusion criteria as the original studies
Participation exclusion criteria: No systematic exclusions will be considered. However, in most of our analyses, the patients with missing outcome(s) measures or those who did not complied with the study treatments, as per the study-specific protocol, will be excluded. Thus, the analysis will be performed in the modified intention-to-treat population, which includes participants who received at least one dose of the study treatment and underwent a baseline and at least one post-baseline evaluation of the co-primary efficacy endpoints.
We do not intend to input missing data.

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

Primary outcome: composite of mortality, Alzheimer's Disease Assessment Scale (ADAS)-Cognitive Subscale/11 score, and the Disability Assessment for Dementia (DAD) score.
Secondary outcome: scores on the Neuropsychological Test Battery, the Clinical Dementia Rating--Sum of Boxes, the Mini-Mental State Examination (MMSE), and the Dependence Scale.
The category will be defined based on the Bapineuzumab treatment versus the placebo.
We will also consider subgroup analyses where the participants will be stratified by age subgroups, race (Black, Whites, Hispanic/Latino) and Sex (Male vs. Female).

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

The predictors will represent the set of baseline patient characteristics defining the study populations and will be used to determine the descriptive statistics of patients. These include characteristics presented in Table 1 of the Bapineuzumab trial publication (N Engl J Med 2014; 370:322-333) and include age, sex, race (White/Black/Hispanic/Latino), APOE status, use of acetylchlolinesterase inhibitor or memantine, MMSE total score, ADAS-cog11 total score, DAD total score, total infusion received.

Particular interest will be reserved to the variables age, sex, race as we also consider to investigate the effect of treatment in these pre-specified subgroups.

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

Additional predictors: APOE epsilon 4 status, use of acetylcholinesterase inhibitor or memantine,

Additional outcomes: Clinical dementia rating scale--Sum of boxes total score, Neuropsychological Test Battery Total Score, Dependance scale, and total infusion received.

All variables will be defined according to the respective definition used in the original trials (as indicated in the Bapineuzumab trial publication (N Engl J Med 2014; 370:322-333))

Statistical Analysis Plan:

we will develop and promote the use of win statistics (win ratio, net treatment benefit, and win odds) for longitudinal data. The win statistics offer flexibility throughout various data distributions encountered in AD research and maximizes the utilization of longitudinal data. These are nonparametric rank-based measures of treatment effect on additive and multiplicative scale. Overall test statistic and global win measures will be evaluated for the whole study duration. We will also extend the assessment of the win measures by also including the findings on positron-emission tomographic amyloid imaging with the use of Pittsburgh compound B (PIB-PET) and cerebrospinal fluid phosphorylated tau concentrations.

Software Used:

R

Project Timeline:

Aim 1: Evaluate win ratio and corresponding confidence intervals (January--March 2025)
Aim 2: calculate the win odds and draw inference (April--June 2025)
Aim 3: estimate the net treatment benefits (July--September 2025)
Analysis completion date: 30 September 2025
Results reported back to the YODA Project: October -- November 2024

Dissemination Plan:

First manuscript writing and publication: March 2025--June 2025;
Publication target journal: Biostatistics, Statistics in Medicine, Journal of Biopharmaceutical statistics.

Second manuscript writing and publication: July 2025--September 2025
Publication target journal: Biostatistics, Statistical Methods in Medical Research, Journal of Biopharmaceutical statistics.

Third manuscript writing and publication: Oct. 2025--December 2025

Publication target journal: Biostatistics, Statistical Methods in Medical Research, Journal of Biopharmaceutical statistics.

Presentation at the Joint Statistical Meetings: August 2025

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