Consistency of Efficacy Assessments Across Various Statistical Methods from the Lecanemab Phase 2 Proof-of-Concept Study, BAN2401-G000-201, in Subjects with Early Alzheimer's Disease

Shobha Dhadda,[1] Michio Kanekiyo,[1] David Li,[1] Chad J. Swanson,[1] Michael Irizarry,[1] **Donald A Berry**,[2,3] Scott Berry,[2] and Lynn D. Kramer[1]

1. Eisai Inc., Woodcliff Lake, NJ, USA
2. Berry Consultants, LLC, Austin, TX, USA
3. Univ. of Texas M.D. Anderson Cancer Center, Houston, TX, USA

Disclosures

Dr. D. Berry is co-owner of Berry Consultants, LLC, a company that designs adaptive Bayesian clinical trials for medical device and pharmaceutical companies (including lecanemab trial 201), NIH cooperative groups, patient advocacy groups, and international consortia.

Design of Bayesian Adaptive Lecanemab 201 Trial

ELSEVIER

Alzheimer's & Dementia: Translational Research & Clinical Interventions 2 (2016) 1-12

Alzheimer's & Dementia

Featured Article

Design of a Bayesian adaptive phase 2 proof-of-concept trial for BAN2401, a putative disease-modifying monoclonal antibody for the treatment of Alzheimer's disease

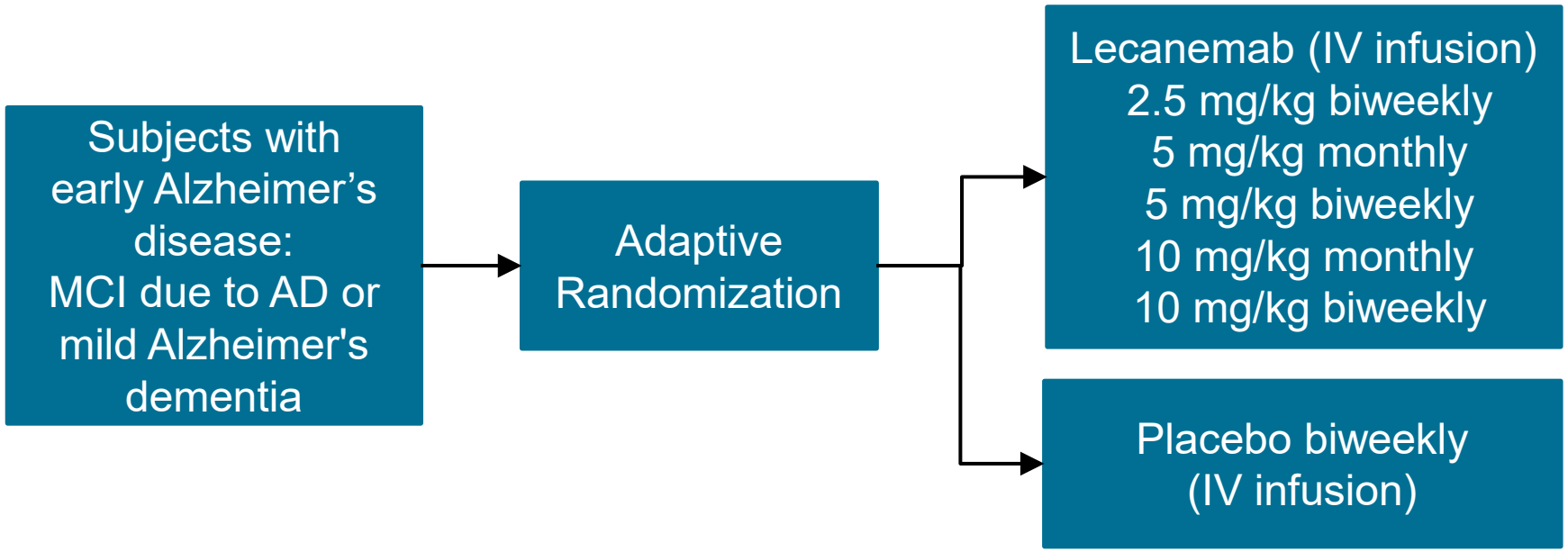
Andrew Satlin[a,*], Jinping Wang[a], Veronika Logovinsky[a], Scott Berry[b], Chad Swanson[a], Shobha Dhadda[a], Donald A. Berry[b]

[a]*Neuroscience & General Medicine, Eisai Inc., Woodcliff Lake, NJ, USA*
[b]*Berry Consultants, LLC, Austin, TX, USA*

Abstract

Introduction: Recent failures in phase 3 clinical trials in Alzheimer's disease (AD) suggest that novel approaches to drug development are urgently needed. Phase 3 risk can be mitigated by ensuring

Design of Lecanemab Phase 2b Trial 201



- A goal of the design was to efficiently determine the ED90, smallest dose that achieves ≥90% of maximum treatment effect.
- Adaptive randomization begins after a fixed allocation period.
- At each IA, the adaptive randomization probability for each of the five active doses changes based on the probability of each being the ED90.
- The adaptive randomization probability for placebo mirrors probability for most likely ED90.

Analyses of Results of Lecanemab 201 Trial

Swanson *et al. Alzheimer's Research & Therapy* (2021) 13:80
https://doi.org/10.1186/s13195-021-00813-8

Alzheimer's Research & Therapy

RESEARCH Open Access

A randomized, double-blind, phase 2b proof-of-concept clinical trial in early Alzheimer's disease with lecanemab, an anti-Aβ protofibril antibody

Chad J. Swanson[1], Yong Zhang[1], Shobha Dhadda[1], Jinping Wang[1], June Kaplow[1], Robert Y. K. Lai[2], Lars Lannfelt[3,4], Heather Bradley[1], Martin Rabe[1], Akihiko Koyama[1], Larisa Reyderman[1], Donald A. Berry[5], Scott Berry[5], Robert Gordon[2], Lynn D. Kramer[1] and Jeffrey L. Cummings[6*]

Lecanemab 201 Trial: Primary Endpoint Method of Analyses

From Swanson et al.

- Methods:
  - Primary endpoint was Bayesian analysis of 12-month clinical change on ADCOMS for the ED90 dose, with goal of identifying most efficacious dose.
  - Primary analysis was super-superiority over placebo by ≥25%: goal was 80% probability of ≥25% reduction in decline versus placebo.
- Results:
  - 856 subjects randomized.
  - Study achieved goal of identifying smallest dose that achieved ≥90% of maximum treatment effect (10 mg/kg biweekly), identifying ED90 dose.
  - At 12 months, ED90 dose had 64% probability super-superior to placebo.
  - At 12 months, ED90 dose had 98% probability superior to placebo.

Allocation of Subjects Based on Response Adaptive Randomization:

Number of Subjects Randomized by Dose

Placebo	2.5 mg/kg Bi-weekly	5 mg/kg Monthly	5 mg/kg Bi-weekly	10 mg/kg Monthly	10 mg/kg Bi-weekly	Total
247	52	51	92	**253**	**161**	856
				414		

What Is This Thing Called Bayes?

Phase 3 (registration) Trial Precedents

- **Eli Lilly's Trulicity AWARD-5 trial in Type II diabetes**
  - Fully Bayesian design developed within FDA's Critical Path Initiative
  - Adaptively randomized to 7 positive doses plus 2 controls (similar to Study 201)
  - Clinical Utility Index components: HbA1c, weight loss, heart rate, DBP
  - Longitudinal modeling, dose-response modeling
  - Design picked 2 doses → small confirmatory stage & 2 other phase 3 trials
  - Trulicity now $5B+/year drug at these doses
- **Platform trials in FDA's Complex Innovative Design (CID) initiative**
  - GBM AGILE in glioblastoma (NCT03970447)
  - Precision Promise in pancreatic cancer (NCT04229004)

This Thing Called Bayes Is Here to Stay

Interacting with the FDA on Complex Innovative Trial Designs for Drugs and Biological Products

---

Guidance for Industry

December 2020

II. SCOPE

Although CID has been considered to refer to complex adaptive, Bayesian, and other novel clinical trial designs, there is no fixed definition of CID because what is considered innovative or novel can change over time. For the purposes of this guidance, CID includes trial designs that have rarely or never been used to date to provide substantial evidence of effectiveness in new drug applications or biologics license applications.

Were Efficacy Results in Lecanemab Trial 201 Robust?

What endpoint?

ADCOMS: Alzheimer's Disease Composite Score
CDR-SB: Clinical Dementia Rating—Sum-of-Boxes
ADAS-Cog14: Alzheimer's Disease Assessment Scale-Cognitive Subscale

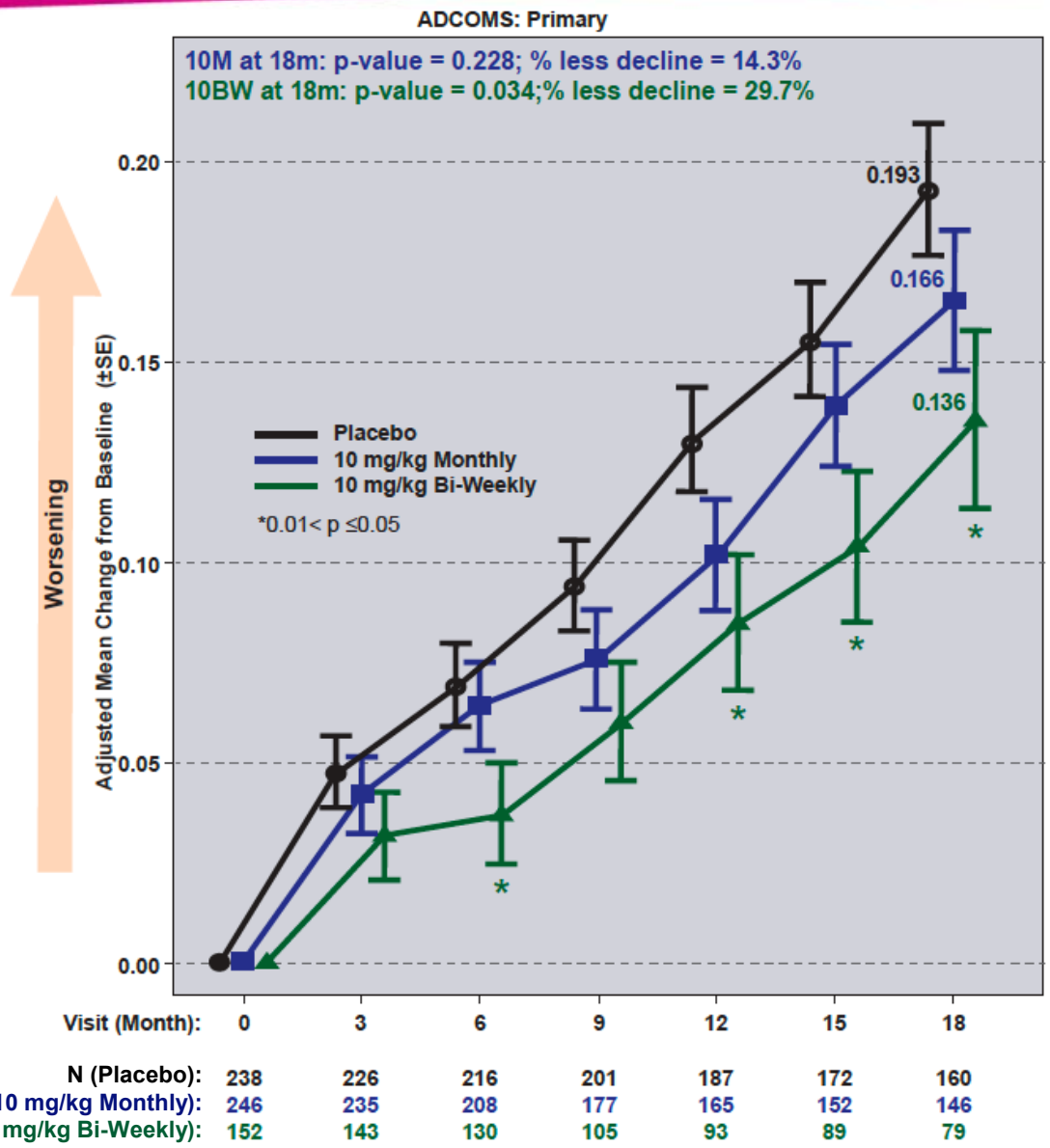
What statistical method?

MMRM (Primary): Mixed Model for Repeated Measures
DPM: Disease Progression Model
NCS2: Natural Cubic Spline
QMM: Quadratic Mixed Model
MMRM + Base*visit
MMRM + Base*visit, trt*apoe4+visit*apoe4+3-way

Definitions of Analysis Methods

- MMRM used these factors: dose, visit, MCI vs Mild AD, ongoing AD treatment, APOE4, region, & dose-by-visit interaction, with baseline value as covariate.
- DPM is proportion of disease progression comparing dose with placebo.
- NCS used MMRM terms but spline basis functions in place of visit.
- QMM used MMRM terms but “week” in place of visit & quadratic term week*week.

ADCOMS: Primary Endpoint



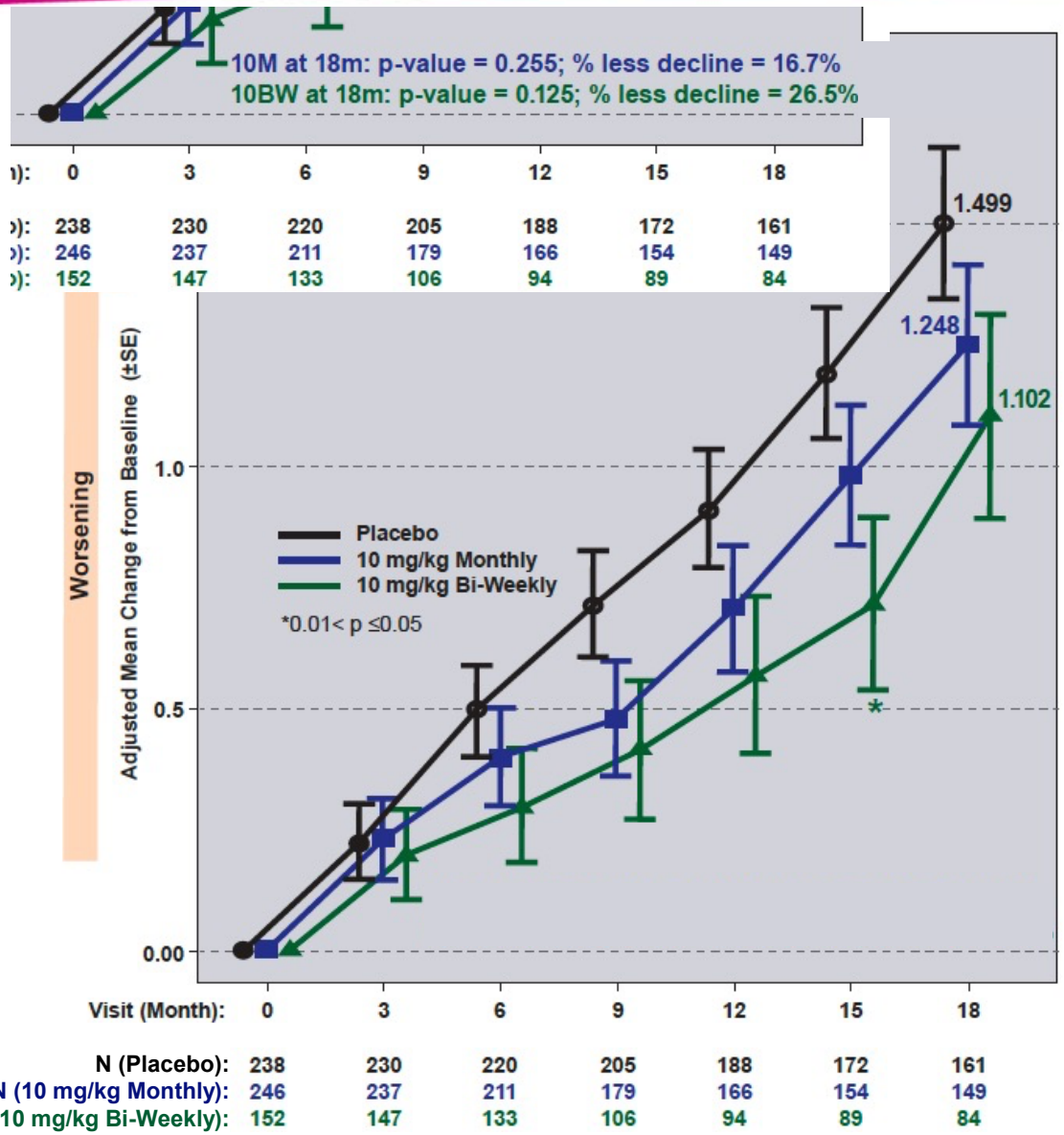
Results at 18 months

10 mg/kg Bi-weekly vs PBO		
Method	Percent reduction	Nominal P-value
Primary: MMRM#	29.7	0.034
DPM	29.1	0.044
NCS2	34.8	0.013
QMM	32.6	0.013
MMRM + Base*visit	32.5	0.015
MMRM + Base*visit, trt*apoe4+visit*apoe4+3-way	37.4	0.036

Note:

- **For this table, * shows interaction term between two variables**
- **# = pre-specified analyses in the protocol**

CDR-SB



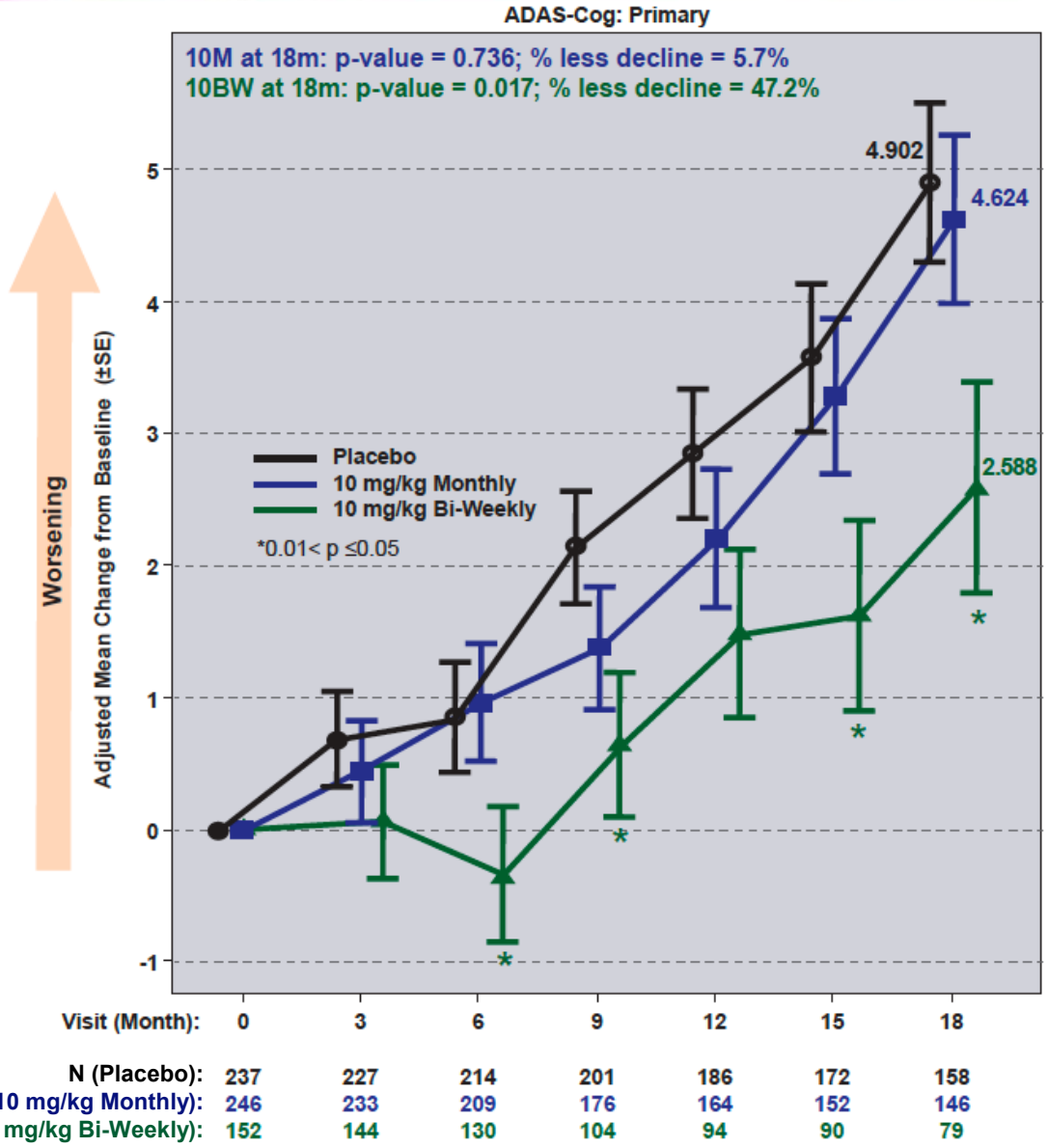
Results at 18 months

10 mg/kg Bi-weekly vs PBO		
Method	Percent reduction	Nominal P-value
Primary: MMRM#	26.5	0.125
DPM	28.2	0.030
NCS2	34.8	0.042
QMM	32.9	0.048
MMRM + Base*visit	31.2	0.062
MMRM + Base*visit, trt*apoe4+visit*apoe4+3-way	32.1	0.169

Note:

- **For this table, * shows interaction term between two variables**
- **# = pre-specified analyses in the protocol**

ADAS-Cog



Results at 18 months

10 mg/kg Bi-weekly vs PBO		
Method	Percent reduction	Nominal P-value
Primary: MMRM#	47.2	0.017
DPM	37.4	0.005
NCS2	51.7	0.014
QMM	48.8	0.009
MMRM + Base*visit	49.4	0.009
MMRM + Base*visit, trt*apoe4+visit*apoe4+3-way	55.9	0.018

Note:

- **For this table, * shows interaction term between two variables**
- **# = pre-specified analyses in the protocol**

Conclusions

- Lecanemab Phase 2 trial 201 clinical efficacy results are consistent across endpoints and statistical methodology, including with the primary Bayesian analyses.
- Two phase 3 studies of lecanemab are underway to confirm efficacy and safety:
  - Clarity AD (NCT03887455) in early Alzheimer's
  - AHEAD (NCT04468659) in preclinical Alzheimer's

Acknowledgments

We thank the patients, their families, and the sites participating in this study.

Funding for the studies and analyses was provided by Eisai Inc. and Biogen Inc.

Editorial support, funded by Eisai Inc, was provided by Mayville Medical Communications.