Treatment of Early AD Subjects With BAN2401, an Anti-Aβ Protofibril Monoclonal Antibody, Significantly Clears Amyloid Plaque and Significantly Reduces Clinical Decline

Chad J. Swanson, PhD; Yong Zhang, MS; Shobha Dhadda, PhD; Jinping Wang, PhD; June Kaplow, PhD; Robert Lai, MA, MB, Bchir; Lars Lannfelt, MD, PhD; **Lynn D. Kramer, MD, FAAN;** Johan Luthman, DDS, PhD

hhc
human health care

BAN2401 Study 201 Positioning in the Overall Development Program

Efficient, Rapid Development Program Despite Chronic and Slowly Progressing Disease

Considerations for Trial Design to Achieve Overall Goal

- Shift toward Early AD
- Obtain strong clinical proof-of-concept
- Evaluate dose ranging effect and subgroups
- Account for duration of study and magnitude of treatment effect
- Potential for early decision-making (12-month) while preserving 18-month disease modification data

Innovations Required to Achieve Overall Goal

- Clinical response driving adaptive randomization (Bayesian design)
- Clinical assessment allowing earlier detection of clinical change over time (ADCOMS*) for Early AD

*ADCOMS: Alzheimer's Disease Composite Score.

BAN2401-G000-201: Global* Phase 2b

Population

Early AD: MCI due to AD or mild Alzheimer's dementia (NIA-AA Criteria)

- Amyloid pathology confirmed by amyloid PET or CSF
- MMSE range: 22-30
- CDR global range: 0.5 (MCI); 0.5-1.0 (mAD)

Design

- Duration and Size: **18 months** and approximately 800 subjects
- Treatment: 6 arms (1 Pbo, 5 dose arms, 2 regimens)
  - All subjects received bi-weekly infusions to maintain the blind
  - All subjects remained on the same randomized dose throughout dosing
  - Active dose arms/regimen: 2.5 mg/kg bi-weekly, 5 mg/kg monthly, 5 mg/kg bi-weekly, 10 mg/kg monthly, 10 mg/kg bi-weekly
- Periodic IAs for efficacy/futility
  - Computer generated algorithm allocates more subjects to the best dose(s) at each IA based on ADCOMS
- Primary clinical outcome assessment
  - **ADCOMS** assessed every 3 months
- Key secondary clinical outcome assessments
  - **ADAS-cog**, **CDR-SB** assessed every 3 months
- Longitudinal biomarkers
  - **Amyloid PET sub study** – Baseline, 12, and 18 months
  - **CSF sub study** – Baseline, 12, and 18 months
  - Volumetric MRI – Baseline, 6, 12, and 18 months
- Safety
  - All ARIA-E discontinued permanently from study drug per protocol (MRI-based)

*NA, EU, Asia Pacific regions.

Clinical Measure Allowing Earlier Detection of Clinical Change: ADCOMS

APPROACH

ADCOMS is a Statistically Derived Score Designed to Measure Cognition and Function Longitudinally in Early AD

- 4 MCI study datasets
- 4 mAD dementia study datasets
- ADAS-Cog, MMSE, CDR-SB, NTB, ADLs

PERFORMANCE

ADCOMS Predicted 20% or More Improvement in Responsiveness Over Existing Clinical Outcome Measures

- Now replicated in 3 settings (Roche SCarlett RoAD; Elenbecestat Poster #: P4-389, AAIC 2018; BAN2401 Study 201)

ELEMENTS

Modeling was Performed to Maximize Responsiveness to Clinical Progression and Treatment in Early AD

- Total of 12 items identified from CDR-SB (6), ADAS-cog (4), and MMSE (2)

ADCOMS Items		
CDR	**ADAS-cog**	**MMSE**
Personal Care	Delayed Word Recall	Orientation to Time
Community Affairs	Orientation	Drawing
Home and Hobbies	Word Recognition	
Memory	Word Finding Difficulty	
Orientation		
Judgement and Problem Solving		

Wang J, Logovinsky V., et al. *J Neurol Neurosurg Psychiatry.* 2016;87:993–999. doi:10.1136/jnnp-2015-312383.

BAN2401 Analyses

Primary Endpoint
(Interim Analysis)

ADCOMS as clinical outcome assessment using longitudinal data through **12 months** with **Bayesian analysis**

Secondary Endpoints
(12- and 18-month Final Analysis)

Change from baseline in PET SUVr (amyloid load)

Conversion from amyloid positive to negative (visual read)

Change from baseline in ADCOMS

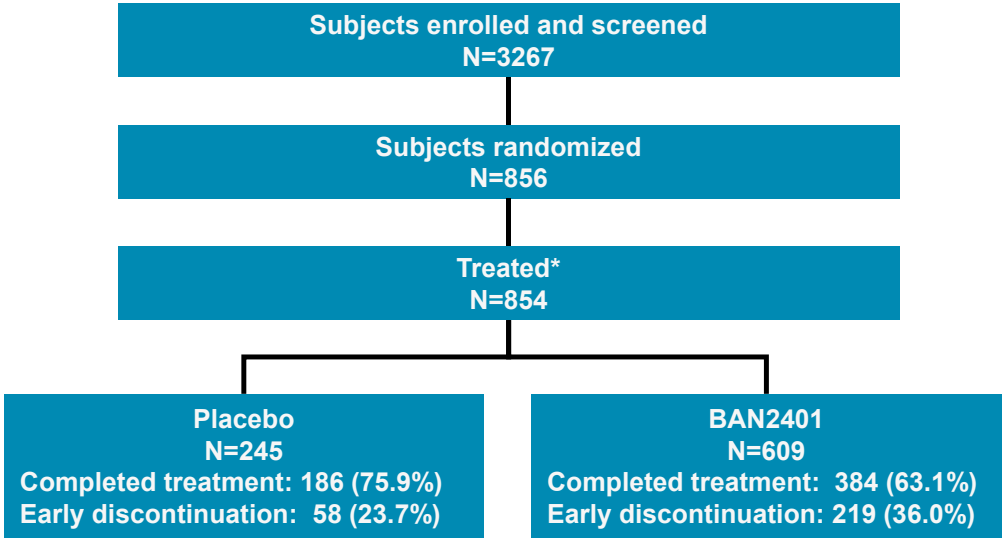
Change from baseline in ADAS-cog

Change from baseline in CDR-SB

Change from baseline in CSF measures ($A\beta_{1\text{-}42}$, total-Tau, etc.)

Subgroup Analyses Using Similar Methodologies

Subject Disposition



Primary Reason for Discontinuation	
Non-ARIA-E AE	13 (5.3%)
ARIA-E AE	2 (0.8%)
per protocol	
Subject choice	23 (9.4%)
Inadequate therapeutic effect	1 (0.4%)
Other	19 (7.8%)

Primary Reason for Discontinuation	
Non-ARIA-E AE	34 (5.6%)
ARIA-E AE	46 (7.5%)
per protocol	
Subject choice	77 (12.6%)
Inadequate therapeutic effect	2 (0.3%)
Other	32 (5.3%)
Forced discontinuation	26 (4.3%)

Discontinuations due to non-ARIA-E AEs were similar between placebo and BAN2401

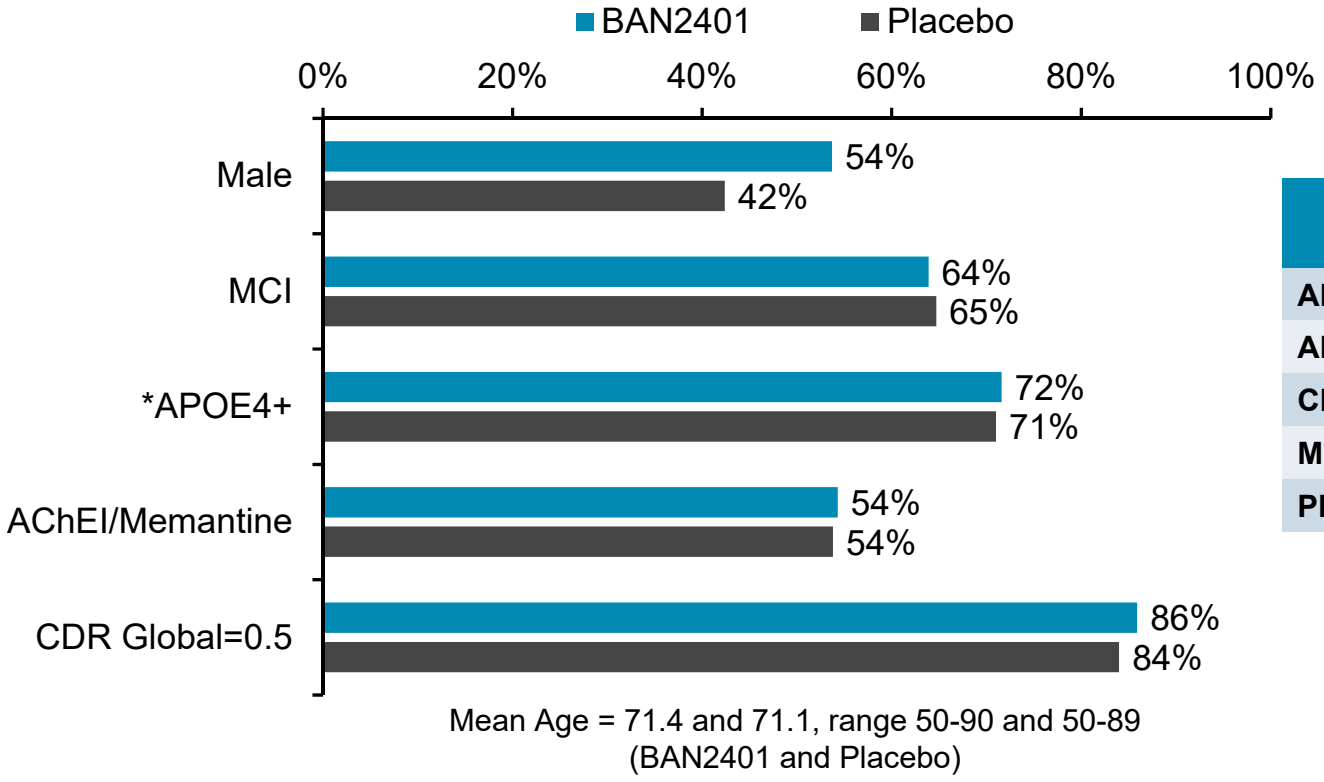
Subject choice and inadequate treatment effect were similar between placebo and BAN2401

Ex US Health Authority Requested (July 2014)

- **APOE4+ subjects no longer be randomized to 10 mg/kg bi-weekly**
- **Discontinue APOE4+ subjects on 10 mg/kg bi-weekly who had not reached 6 months treatment**
  - **26 asymptomatic subjects without ARIA-E**

*Not treated N=2 (both in placebo arm).

Demographic and Baseline Characteristics Similar Between Placebo and BAN2401 Treatment Groups



Mean Age = 71.4 and 71.1, range 50-90 and 50-89 (BAN2401 and Placebo)

(Mean±SD)

	BAN2401 (N=587)	Placebo (N=238)
ADCOMS	0.378±0.158	0.370±0.166
ADAS-cog#	22.2±7.4	22.6±7.7
CDR-SB	2.95±1.37	2.89±1.45
MMSE	25.6±2.4	26.0±2.3
PET SUVr*	1.41±0.16	1.40±0.16

#N=586 in BAN2401, N=237 in Placebo
*PET sub study; N=214 in BAN2401, N=98 in Placebo

BAN2401 has more male subjects (53.7% vs 42.4%).
*Proportion of APOE4+ subjects is general for clinical studies in this population.

Bayesian Results for Change From Baseline in ADCOMS

Top Two Doses Identified Early as Meaningful – Thus Received Most Subjects

Number Randomized Per 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		

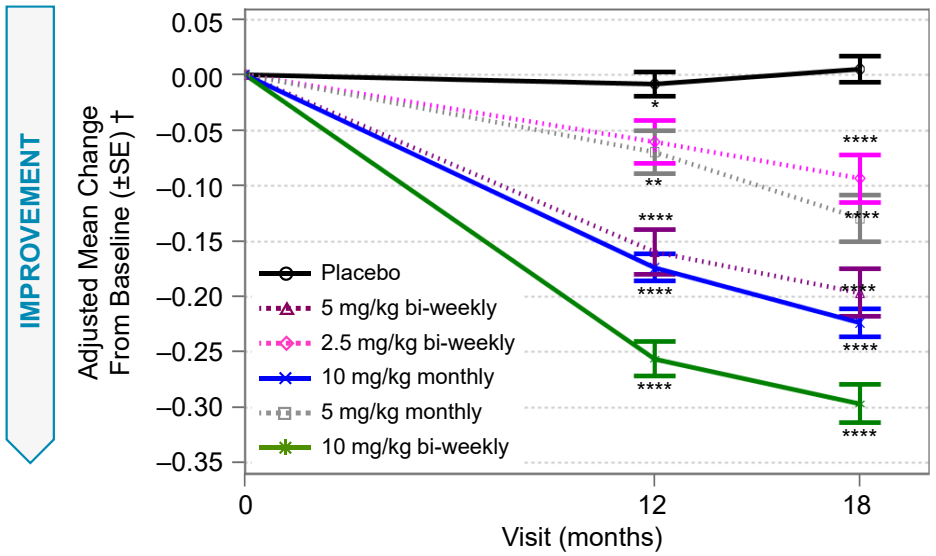
- 12-month Bayesian model identified 10 mg/kg bi-weekly as the best dose (ED90*)
  - This time point had 98% probability of being superior to placebo
- Threshold for success at 12-month (primary endpoint)
  - Pre-specified: 80% probability of being superior to placebo by 25% reduction
  - Actual results: 64% probability of being superior to placebo by 25% reduction
- Bayesian results and conventional statistics are consistent at the end of the study

*ED90: dose producing 90% of maximum treatment effect.

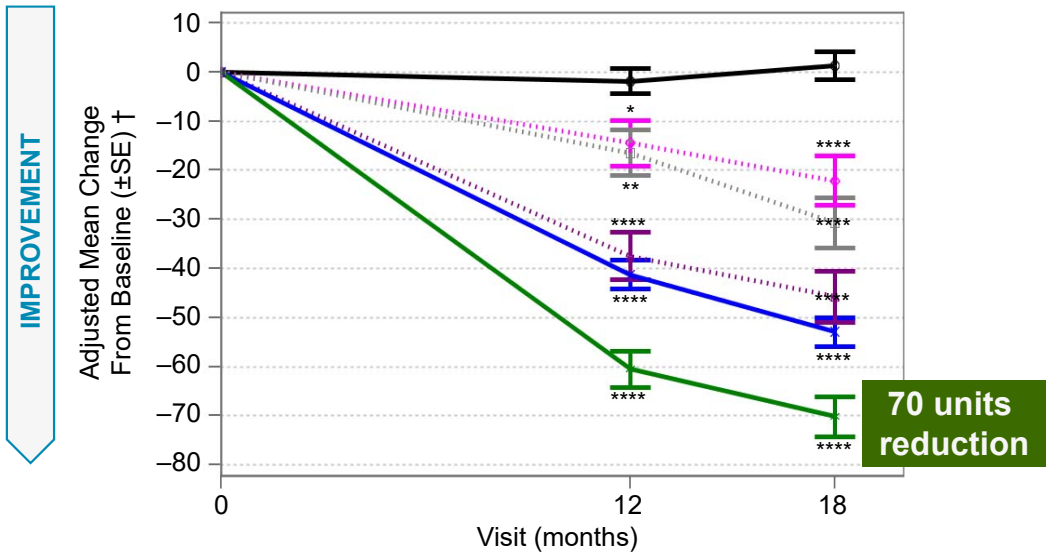
BAN2401 Reduces Amyloid Burden

- **Dose dependent reduction in amyloid PET values (Florbetapir tracer)**
- **BAN2401 significantly reduced amyloid PET values across all doses**
- **Similar results with SUVr and Centiloid measures across all reference regions analyzed**
  - **Reference regions analyzed: SWM, WC mask, WC derived, WC/WM correction, CG, Composite**
- **Top dose: observed baseline mean (74.5), observed 18-month mean (5.5)**

PET SUVr



Centiloid



Global Cortical Average versus Whole Cerebellum Reference

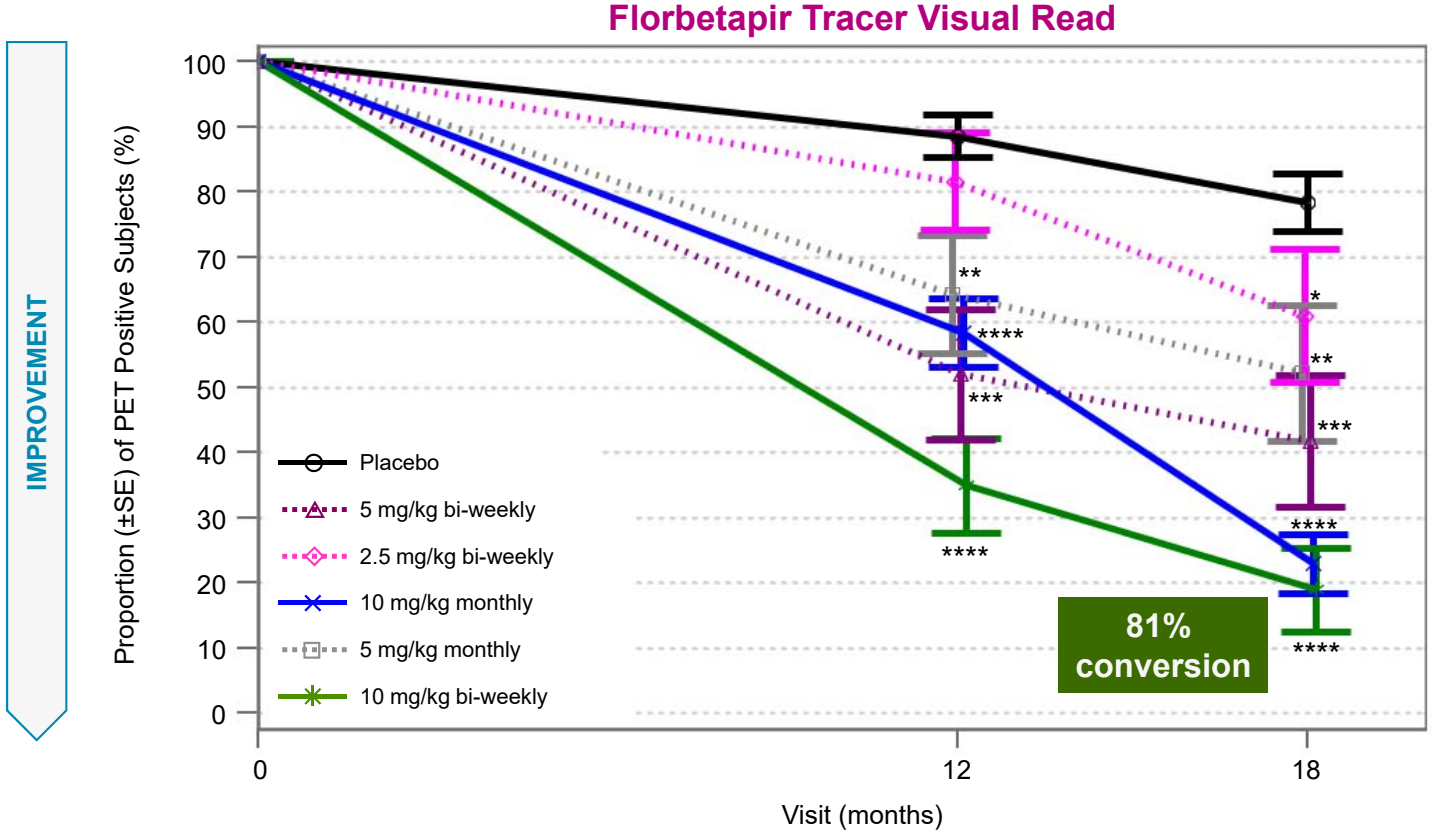
*P<0.05, **P<0.01, ***P<0.001, ****P<0.0001. †Adjusted mean change from baseline by Mixed Model Repeated Measures (MMRM).

The Mixed Model Repeated Measures (MMRM) uses treatment group, visit, clinical subgroup (MCI due to AD, Mild AD), the presence or absence of ongoing AD treatment at baseline, APOE4 status (positive, negative), region, treatment group-by-visit interaction as factors, and baseline value as covariate.

For PET analysis N=306 at 12 months and N=277 at 18 months.

Significant Conversion of Amyloid Positive to Negative With Visual Read

- Dose dependent conversion from amyloid positive to negative vs placebo
- BAN2401 significantly converted subjects from amyloid positive to negative across most doses

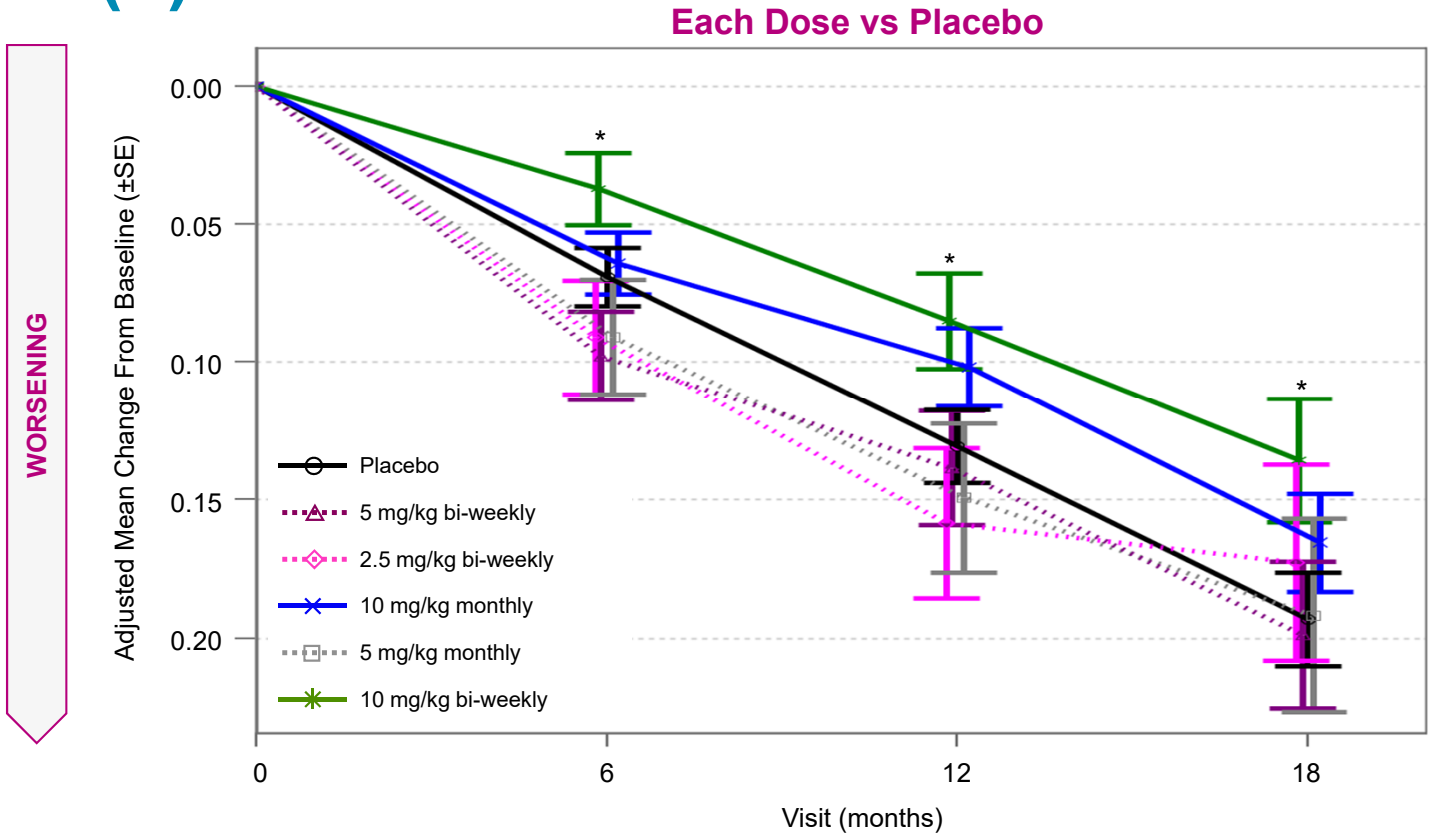


*P<0.05, **P<0.01, ***P<0.001, ****P<0.0001.

Baseline images were read at time of inclusion; longitudinal 12 and 18 month reads were conducted after all subjects completed 18 months of treatment. Fisher's exact test was used to compare each dose vs placebo.

BAN2401 Slowed Cognitive Decline on ADCOMS Over 18 Months (1)

- Dose dependent reduction in decline on ADCOMS over time; starting at 6 months of treatment

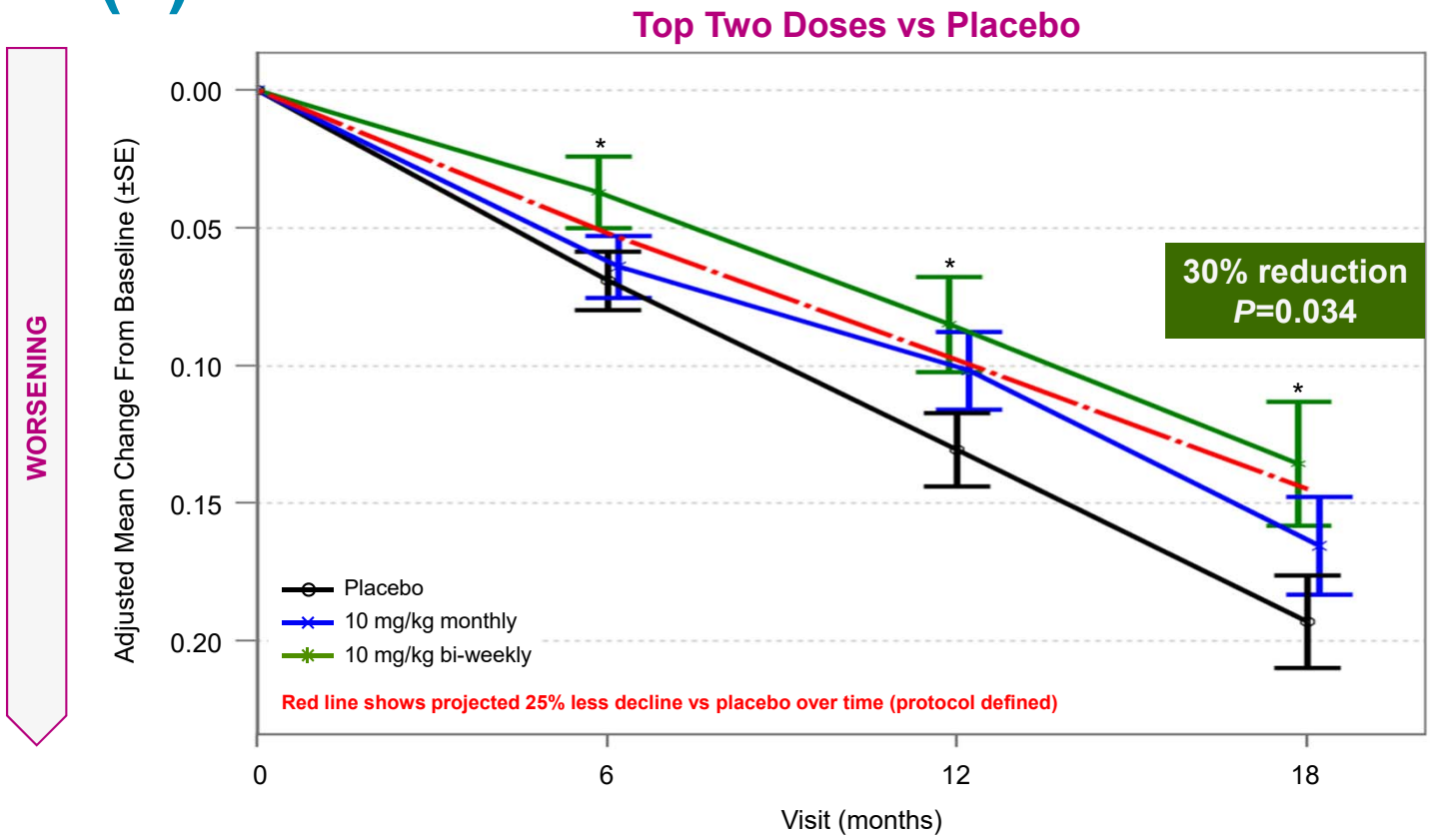


*P<0.05.

The Mixed Model Repeated Measures (MMRM) uses treatment group, visit, clinical subgroup (MCI due to AD, Mild AD), the presence or absence of ongoing AD treatment at baseline, APOE4 status (positive, negative), region, treatment group-by-visit interaction as factors, and baseline value as covariate.

BAN2401 Slowed Cognitive Decline on ADCOMS Over 18 Months (2)

- Less decline on ADCOMS for 10 mg/kg bi-weekly dose (**green**) vs placebo (**black**) across all time points

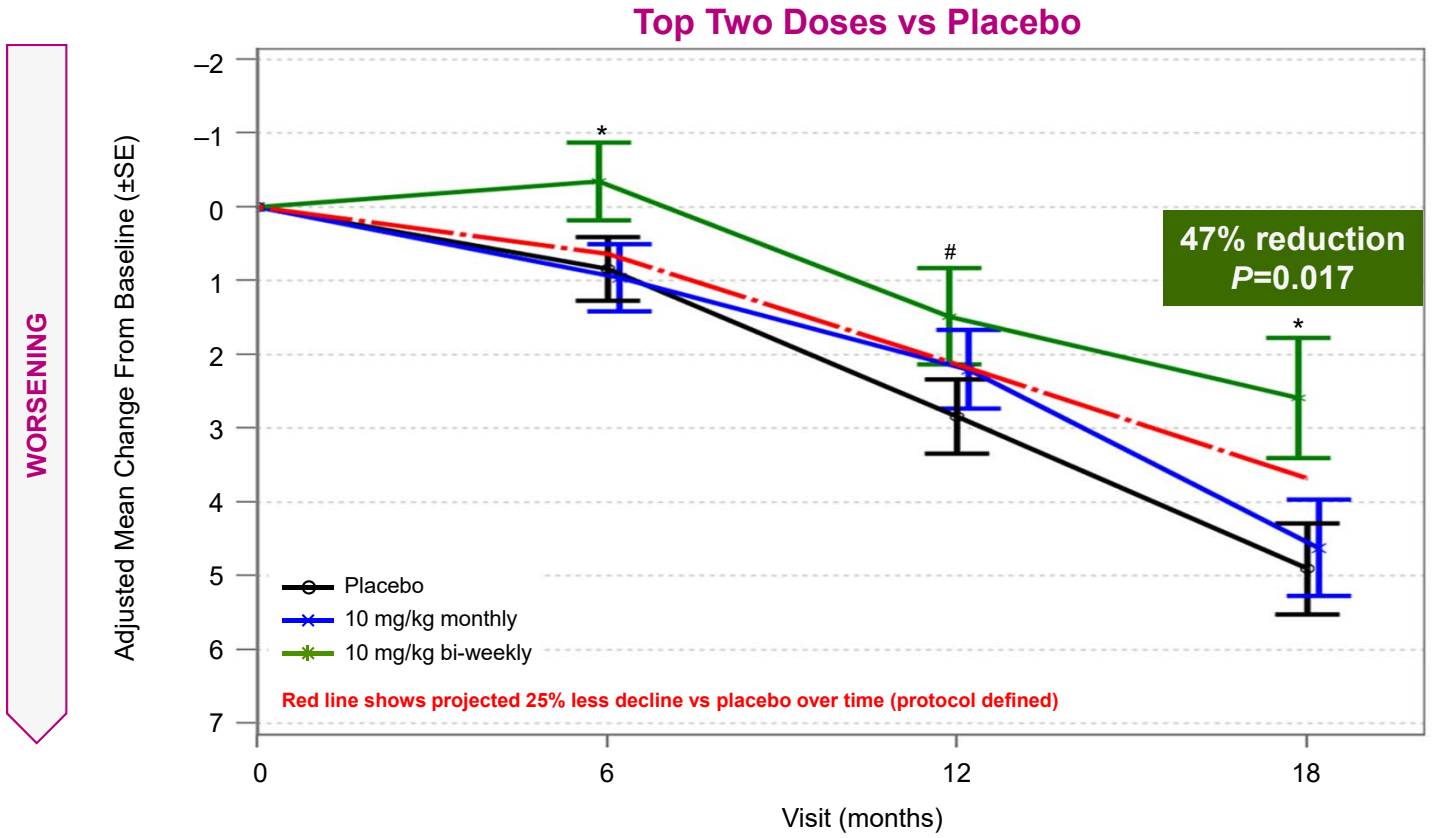


*P<0.05.

The Mixed Model Repeated Measures (MMRM) uses treatment group, visit, clinical subgroup (MCI due to AD, Mild AD), the presence or absence of ongoing AD treatment at baseline, APOE4 status (positive, negative), region, treatment group-by-visit interaction as factors, and baseline value as covariate.

BAN2401 Slowed Cognitive Decline on ADAS-cog Over 18 Months

- Dose dependent reduction in decline on ADAS-cog over time; starting at 6 months
- Slower decline on ADAS-cog 10 mg/kg bi-weekly dose (**green**) vs placebo (**black**) across all time points

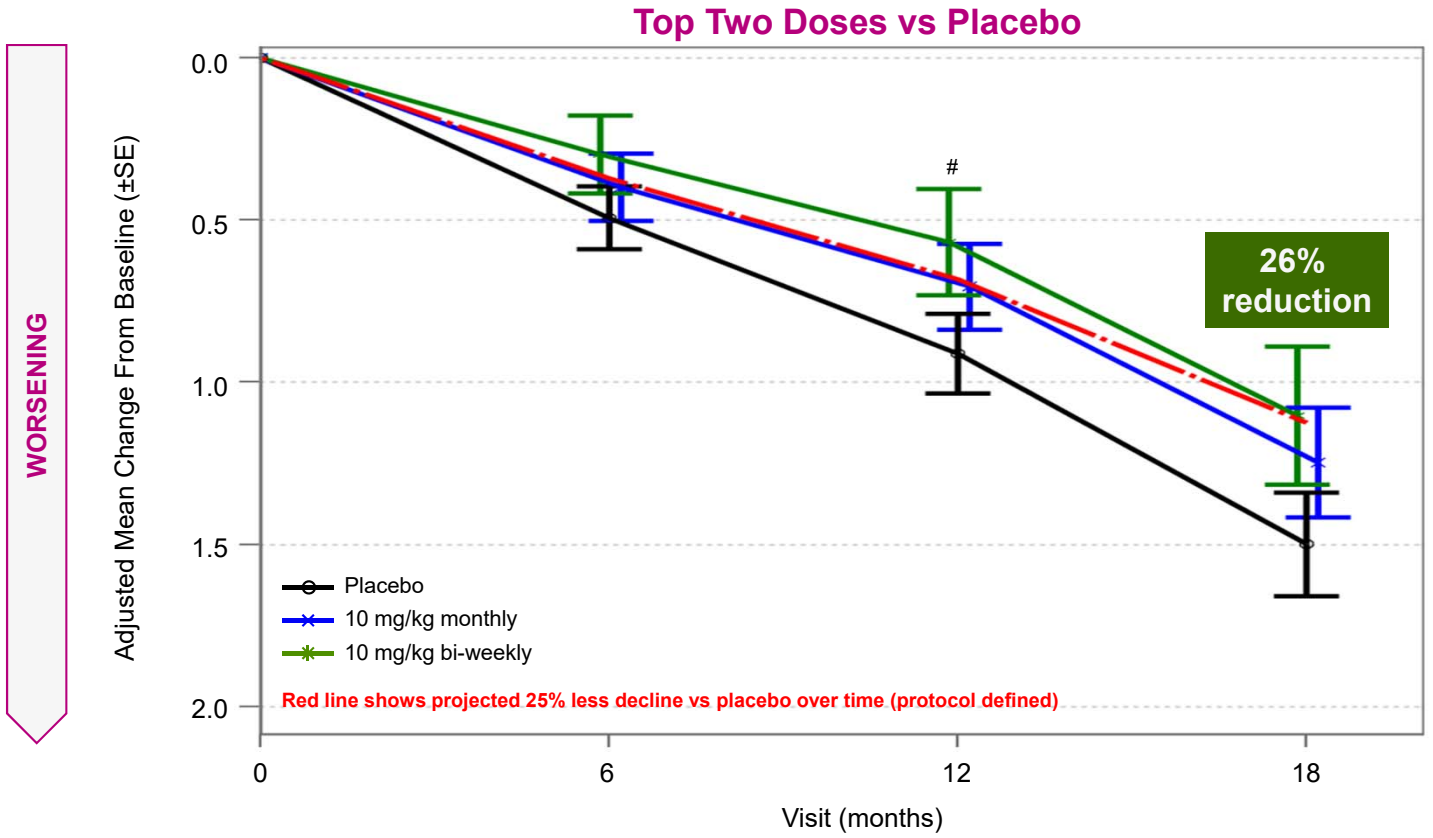


#*P*<0.1 (*P*=0.073), **P*<0.05.

The Mixed Model Repeated Measures (MMRM) uses treatment group, visit, clinical subgroup (MCI due to AD, Mild AD), the presence or absence of ongoing AD treatment at baseline, APOE4 status (positive, negative), region, treatment group-by-visit interaction as factors, and baseline value as covariate.

BAN2401 Slowed Cognitive Decline on CDR-SB Over 18 Months

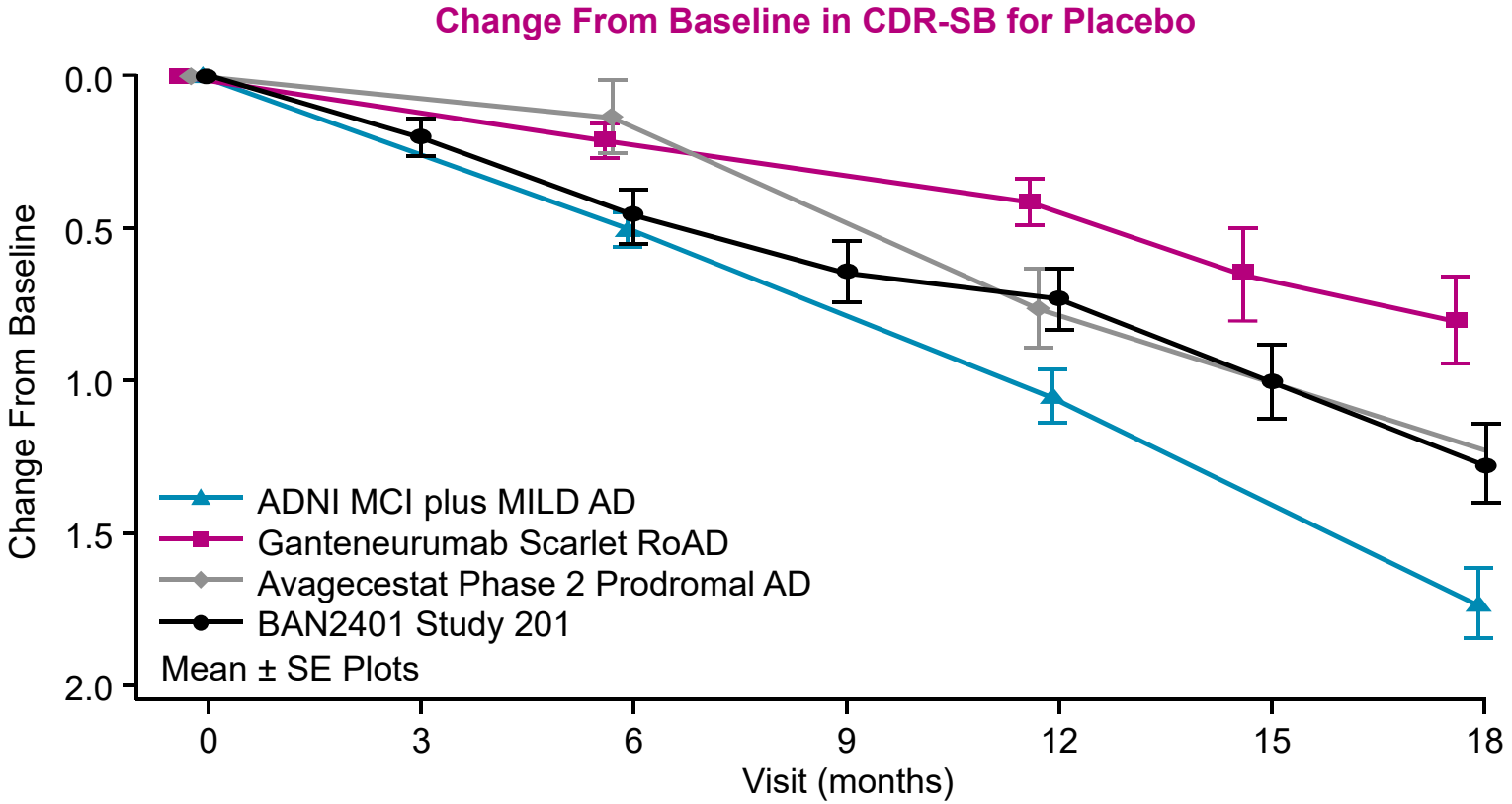
- Dose dependent reduction in decline on CDR-SB over time; starting at 6 months of treatment
- Slower decline (>25%) on CDR-SB for 10 mg/kg bi-weekly dose (**green**) vs placebo (**black**) across all time points



#*P*<0.1 (*P*=0.077).

The Mixed Model Repeated Measures (MMRM) uses treatment group, visit, clinical subgroup (MCI due to AD, Mild AD), the presence or absence of ongoing AD treatment at baseline, APOE4 status (positive, negative), region, treatment group-by-visit interaction as factors, and baseline value as covariate.

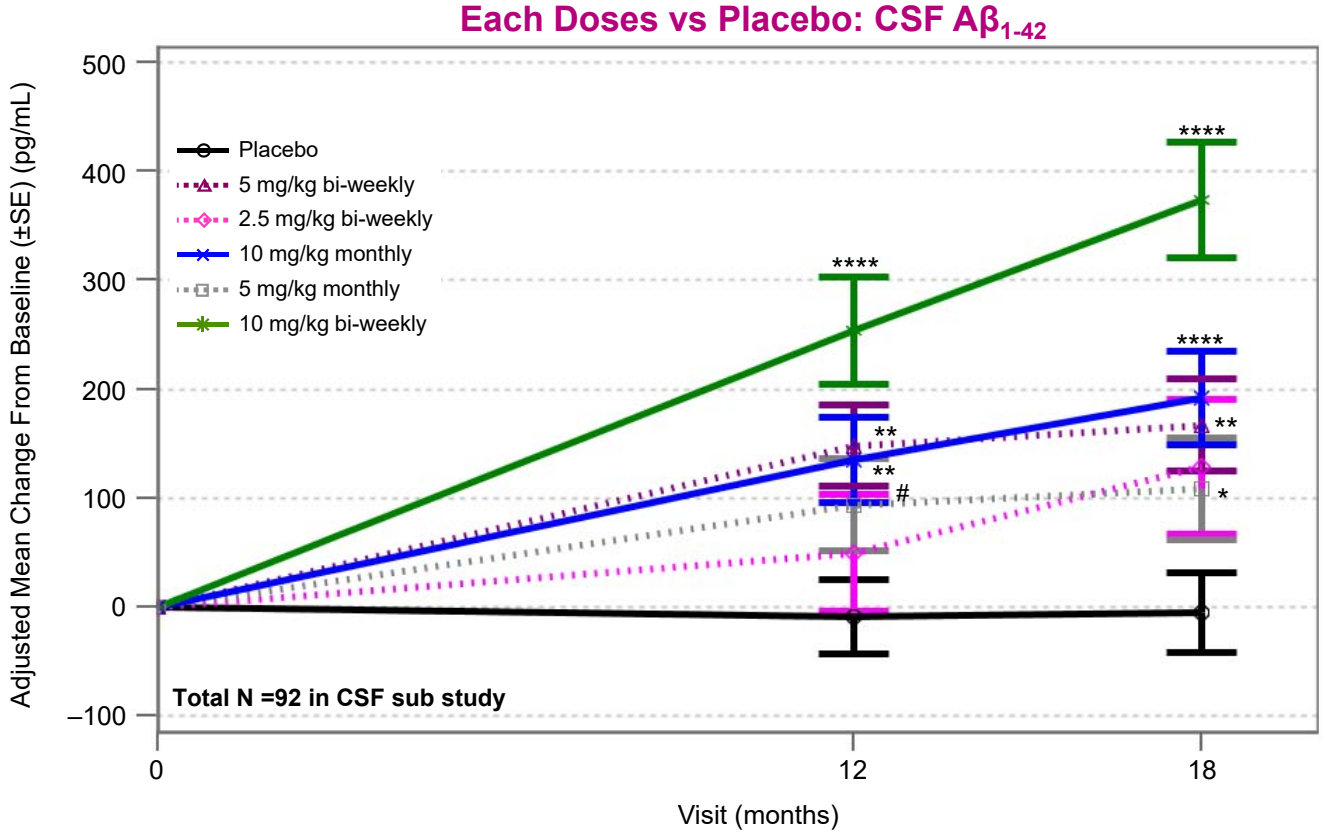
Placebo Decline Similar to Other Larger AD Trials in Similar Populations



1. ADNI analysis on matched population on file in house.
2. Suanne Ostrowitzki, et al. A phase III randomized trial of gantenerumab in prodromal Alzheimer's disease, *Alzheimer's Research & Therapy*. 2017;9:95.
3. Coric V., et al. Targeting Prodromal Alzheimer Disease With Avagacestat: A Randomized Clinical Trial, *JAMA Neurology.* 2015;72:1324–33.

Cerebrospinal Fluid (CSF) Aβ1-42 Demonstrates Target Engagement

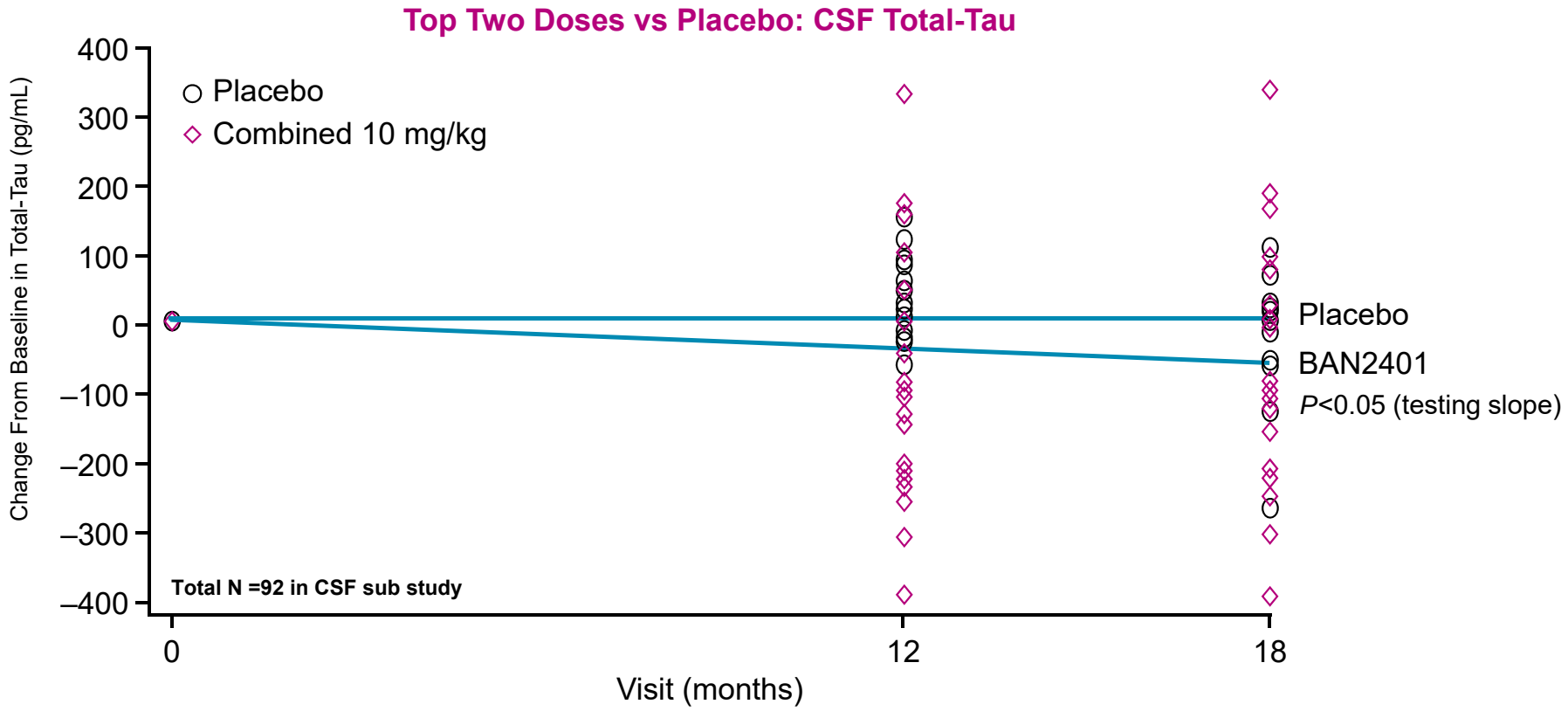
- Dose dependent increase in Aβ1-42
  - Increase expected due to antibody binding prolonging half-life of Aβ1-42 species
  - Investigation ongoing to determine free and bound versus total fractions



#*P*<0.1 (*P*=0.067), **P*<0.05. ***P*<0.01, ****P*<0.001, *****P*<0.0001.

The Mixed Model Repeated Measures (MMRM) uses treatment group, visit, clinical subgroup (MCI due to AD, Mild AD), the presence or absence of ongoing AD treatment at baseline, APOE4 status (positive, negative), region, treatment group-by-visit interaction as factors, and baseline value as covariate.

Significant Reduction in Cerebrospinal Fluid (CSF) Total-Tau Over Time at the Combined Top Two Doses



Based on linear regression model testing the slope of change from baseline; post-hoc statistical analysis utilized due to small sample size.

Pre-specified Subgroup Analyses are Ongoing

- Clinical subgroup (MCI due to AD, Mild AD)
- Presence or absence of ongoing AD treatment at baseline
- APOE4 status (positive, negative)
- Age
- Region
- Gender
- Ethnicity
- Race
- Anti-drug antibody

Eisai's initial priority has been to conduct and communicate these topline analyses contained in this presentation to the scientific community here at AAIC. Further, we are working to conduct subgroup analyses to ensure a thorough understanding of this rich dataset.

Treatment Emergent Adverse Events

Category	Placebo (N=245) n (%)	BAN2401 2.5 mg/kg Bi-weekly (N=52) n (%)	BAN2401 5 mg/kg Monthly (N=51) n (%)	BAN2401 5 mg/kg Bi-weekly (N=92) n (%)	BAN2401 10 mg/kg Monthly (N=253) n (%)	BAN2401 10 mg/kg Bi-weekly (N=161) n (%)
Any TEAE	216 (88.2)	46 (88.5)	48 (94.1)	81 (88.0)	238 (94.1)	139 (86.3)
Treatment-related TEAE	65 (26.5)	23 (44.2)	25 (49.0)	31 (33.7)	135 (53.4)	76 (47.2)
Serious Adverse Event	43 (17.6)	10 (19.2)	4 (7.8)	16 (17.4)	31 (12.3)	25 (15.5)
Deaths	2 (0.8)	2 (3.8)	0	1 (1.1)	2 (0.8)	0
AE leading to discontinuation	15 (6.1)	7 (13.5)	4 (7.8)	10 (10.9)	47 (18.6)	24 (14.9)
Infusion reaction leading to discontinuation*	2 (0.8)	0	0	0	5 (2.0)	4 (2.5)

- Incidence rates of AE, SAE and TEAE consistent with patient population and balanced across placebo and BAN2401 treatment groups
- Most common TEAE were infusion reaction and ARIA (amyloid-related imaging abnormality)
- No changes in labs, ECGs, or vital signs

*Events included in AEs leading to discontinuation.

Amyloid-Related Imaging Abnormalities-Edema (ARIA-E) Summary

Category	Placebo (N=245) n (%)	BAN2401 2.5 mg/kg Bi-weekly (N=52) n (%)	BAN2401 5 mg/kg Monthly (N=51) n (%)	BAN2401 5 mg/kg Bi-weekly (N=92) n (%)	BAN2401 10 mg/kg Monthly (N=253) n (%)	BAN2401 10 mg/kg Bi-weekly (N=161) n (%)
ARIA-E	2 (0.8)	1 (1.9)	1 (2.0)	3 (3.3)	25 (9.9)	16 (9.9)
APOE4+	2/173 (1.2%)	1/38 (2.6%)	1/40 (2.5%)	3/84 (3.6%)	23/225 (10.2%)	7/48 (14.6%)
APOE4-	0/72	0/14	0/11	0/8	2/28 (7.1%)	9/113 (8%)

Most ARIA-E occurred within first 3 months of treatment

Mostly mild to moderate in severity (radiographic)

MRI findings typically resolved within 4-12 weeks

5/48 (~10%) Cases of Symptomatic ARIA-E

Included headache, visual disturbances, or confusion

- (1) Severe at 2.5 mg/kg bi-weekly; Non serious AE
- (1) Mild at 10 mg/kg monthly; SAE
- (1) Moderate at 10 mg/kg bi-weekly; SAE
- (2) Severe at 10 mg/kg bi-weekly; both SAE

Severity represents radiographic findings.

Overall Summary of BAN2401 Study 201

- First large clinical trial to support the amyloid hypothesis
- Response adaptive randomization identified top two doses early with 10 mg/kg bi-weekly as the best dose
- Dose-dependent, statistically significant reduction in brain amyloid by 70 units in Centiloid analysis on top dose [observed baseline mean (74.5), observed 18-month mean (5.5)]
- Majority of subjects at top dose became amyloid negative on visual read with statistical significant conversion of 81%
- Dose-dependent, clinically meaningful and statistically significant slower decline on clinical outcome measures of cognition and function at 18 months on ADCOMS with 30% less decline on top dose and ADAS-cog with 47% less decline on top dose; and dose-dependent, clinically meaningful slower decline at 18 months on CDR-SB with 26% less decline on top dose
- Dose-dependent, statistically significant effect on CSF $A\beta_{1-42}$ and statistically significant longitudinal reduction in CSF total-Tau
- Generally well-tolerated with ARIA-E incidence <10% at highest dose

Acknowledgements

We thank all the patients and their family members participating in the BAN2401-201 study as well as the investigators and their staff conducting the study

BAN2401-201 CORE TEAM

Chad J. Swanson

Heather Bradley
Shobha Dhadda
Gordon Espie
Robert Gordon
Marin Hsuan
June Kaplow
Robert Lai
Johan Luthman
Kiran Putti
Martin Rabe
Cheryl Ruburiano
Kenchiro Totsuka
Kate Tranotti
Jinping Wang
Yong Zhang

**Eisai and Biogen are in a collaboration to jointly develop and commercialize BAN2401.
BAN2401 is a result of a strategic research alliance between Eisai and BioArctic.
Berry Consultants helped with design and implementation of the study.**