Clinical and Biomarker Updates from BAN2401 Study 201 in Early AD

Chad J. Swanson, PhD; Yong Zhang, MS; Shobha Dhadda, PhD; Jinping Wang, PhD; **Akihiko Koyama, PhD**; June Kaplow, PhD; Robert Lai, MA, MB, Bchir; Heather Bradley, MPH; Martin Rabe, MSc; Robert Gordon; Lars Lannfelt, MD, PhD; Lynn D. Kramer, MD, FAAN; Johan Luthman, DDS, PhD

hhc
human health care

Disclosures

- Chad J. Swanson, Yong Zhang, Shobha Dhadda, Jinping Wang, Akihiko Koyama, June Kaplow, Robert Lai, Heather Bradley, Martin Rabe, Robert Gordon, Lynn D. Kramer, and Johan Luthman are employees of Eisai Inc.
- Lars Lannfelt is affiliated with BioArctic and Uppsala University
- Jeffrey Cummings is affiliated with Cleveland Clinic

Presented at the 11th Clinical Trials on Alzheimer's Disease (CTAD) Conference October 24-27, 2018

Agenda for Today

1. BAN2401 Study 201 Study Design and Topline Results
   – *Professor Jeffrey Cummings, Cleveland Clinic*
2. Pre-specified Subgroup Analysis in BAN2401 Study 201
   – *Dr. Chad Swanson, Eisai Inc.*
3. Effect of BAN2401 on Underlying AD Pathophysiology
   – *Dr. Chad Swanson, Eisai Inc.*
4. Totality of Results from BAN2401 Study 201 (Clinical Outcome Measures, Amyloid PET, CSF Biomarkers)
   – *Professor Jeffrey Cummings, Cleveland Clinic*
5. Q&A
   – *Professor Jeffrey Cummings, Cleveland Clinic; Dr. Chad Swanson and Dr. Akihiko Koyama, Eisai Inc.*

Communication 1

BAN2401 Study 201 Design and Topline Results

Professor Jeffrey Cummings, MD, ScD
Center for Neurodegeneration and Translational Neuroscience
Cleveland Clinic Lou Ruvo Center for Brain Health
Las Vegas, Nevada, USA

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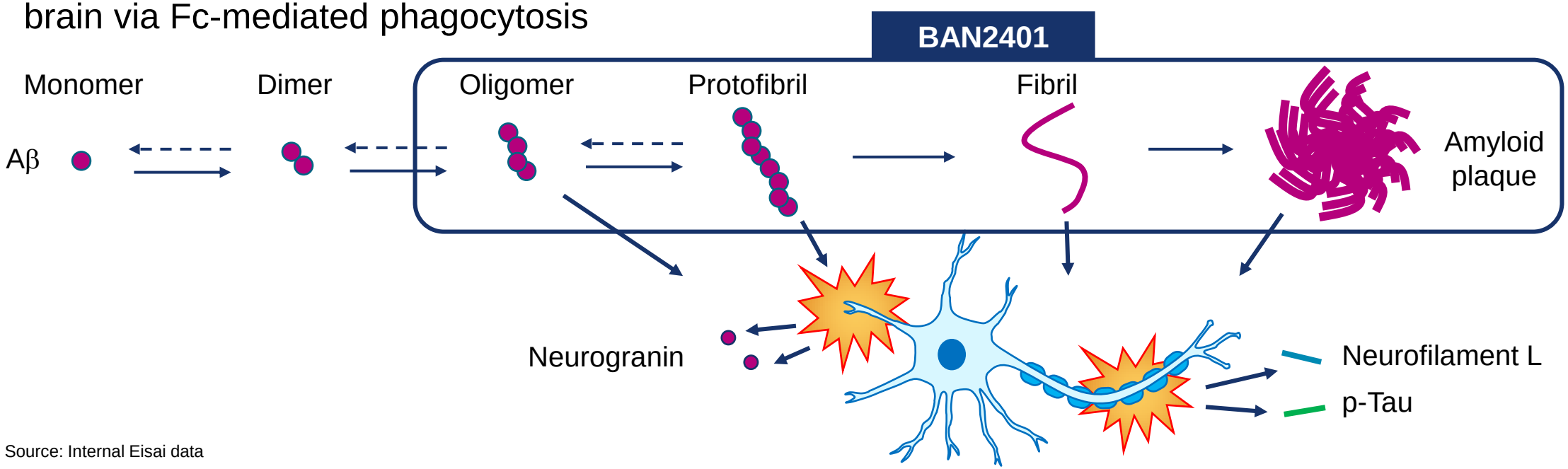
What is BAN2401?

- BAN2401 is an antibody with a low affinity for Aβ monomers and high affinity for aggregated Aβ species (>1000x)
  - This is in contrast to many of the other anti-Aβ mAbs, which have generally had higher affinity for monomers in addition to affinity for aggregated Aβ species
  - High concentration of monomers in CNS/plasma limits antibody engagement with aggregated Aβ species
- Among aggregated species, BAN2401 shows preferential activity for Aβ protofibrils over fibrils (>10x)
- BAN2401 both neutralizes the large soluble aggregates and clears aggregated Aβ species from the brain via Fc-mediated phagocytosis



Source: Internal Eisai data

Bayesian Design Selected for BAN2401 Study 201 in Early Alzheimer's Disease Population

- There were multiple questions to be addressed in the Phase 2 study for BAN2401
  - Dose regimen and response
  - Treatment effect size
  - Sample size required
  - Duration of therapy required to show disease-modifying effect

- Bayesian adaptive design uses ongoing analysis of existing blinded study data
  - FDA draft guidance[1] entitled "Adaptive Designs for Clinical Trials of Drugs and Biologics" issued on September 28, 2018 highlights use of adaptive trial designs
  - Adaptive trial designs are often used in oncology[2,3], previously used in Alzheimer's disease[4,5], and recently used for an approval in diabetes[6, 7]

Source: [1]FDA Guidance. Adaptive design for clinical trials of dugs and biologics. 2018; [2]Berry D. Nat Rev Clin Oncology 2011; 9: 199-207; [3]Berry S et al. Clin Trials 2010; 7: 121-135; [4]Lenz R et al. Alz Dis Assoc Dis 2015; 29: 192-199; [5]Finger E et al. Alz Res & Therapy 2018: 10; 102-110.; [6]FDA Summary Review for Trulicity; [7]Diabetes Obes Metab. 2014 Aug;16(8):748-56.

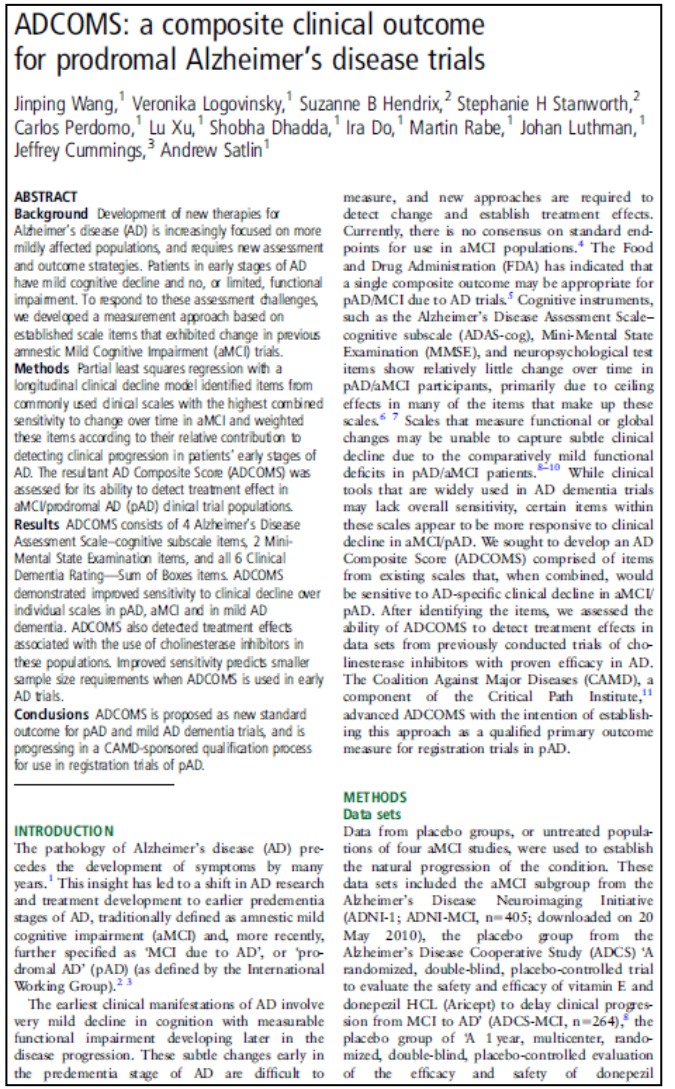
Bayesian Design Allowed Flexible Allocation of Subjects to Most Meaningful Doses Based on Robust Ongoing Assessments of Treatment Effects, with Conventional Analysis at End of Study

- Conventional and Bayesian approaches are both rigorous statistical methods
- Bayesian analysis allowed for early decision making through rapid detection of treatment effect by using accumulated data to make timely and appropriate subject to dose allocations
  - The primary endpoint of Study 201 was set at 12 months with super superiority to placebo needed to potentially accelerate time to Phase 3 with frequent interim Bayesian analyses to identify proof-of-concept as early as possible
  - Study 201 satisfies the key principles of September 2018 FDA draft guidance on adaptive trials[1]
  - Allowed efficient utilization of accumulating data in allocating new subjects to doses that work best
  - The study maintained integrity and allowed interpretability by using pre-defined design, with limited access of comparative interim results (only to external experts) and well controlled Type I error contributing to reproducible treatment effects
- Conventional (per protocol) statistical analysis was used to assess the observed data at the end of the double-blinded treatment period (18 months) and identify magnitude of treatment effects after the study was unblinded

Source: [1]FDA Guidance. Adaptive design for clinical trials of dugs and biologics. 2018

ADCOMS* Utilized to Detect Changes in Earlier AD Population

- Mild disease requires strategies with the ability to detect changes in cognition and function in an early patient population
- ADCOMS combines data from recognized endpoints (CDR-SB, MMSE, ADAS-Cog) and leverages specific items that are more likely to be impacted earlier in the disease
  - Based on analysis of MCI trials to identify items that were most sensitive to progression
  - Incorporates all six components of CDR-SB plus select cognitive components of MMSE and ADAS-Cog



ADCOMS: a composite clinical outcome for prodromal Alzheimer's disease trials

Jinping Wang,[1] Veronika Logovinsky,[1] Suzanne B Hendrix,[2] Stephanie H Stanworth,[2] Carlos Perdomo,[1] Lu Xu,[1] Shobha Dhadda,[1] Ira Do,[1] Martin Rabe,[1] Johan Luthman,[1] Jeffrey Cummings,[3] Andrew Satlin[1]

ABSTRACT

Background Development of new therapies for Alzheimer's disease (AD) is increasingly focused on more mildly affected populations, and requires new assessment and outcome strategies. Patients in early stages of AD have mild cognitive decline and no, or limited, functional impairment. To respond to these assessment challenges, we developed a measurement approach based on established scale items that exhibited change in previous amnestic Mild Cognitive Impairment (aMCI) trials.

Methods Partial least squares regression with a longitudinal clinical decline model identified items from commonly used clinical scales with the highest combined sensitivity to change over time in aMCI and weighted these items according to their relative contribution to detecting clinical progression in patients' early stages of AD. The resultant AD Composite Score (ADCOMS) was assessed for its ability to detect treatment effect in aMCI/prodromal AD (pAD) clinical trial populations.

Results ADCOMS consists of 4 Alzheimer's Disease Assessment Scale–cognitive subscale items, 2 Mini-Mental State Examination items, and all 6 Clinical Dementia Rating—Sum of Boxes items. ADCOMS demonstrated improved sensitivity to clinical decline over individual scales in pAD, aMCI and in mild AD dementia. ADCOMS also detected treatment effects associated with the use of cholinesterase inhibitors in these populations. Improved sensitivity predicts smaller sample size requirements when ADCOMS is used in early AD trials.

Conclusions ADCOMS is proposed as new standard outcome for pAD and mild AD dementia trials, and is progressing in a CAMD-sponsored qualification process for use in registration trials of pAD.

INTRODUCTION

The pathology of Alzheimer's disease (AD) precedes the development of symptoms by many years.[1] This insight has led to a shift in AD research and treatment development to earlier predementia stages of AD, traditionally defined as amnestic mild cognitive impairment (aMCI) and, more recently, further specified as 'MCI due to AD', or 'prodromal AD' (pAD) (as defined by the International Working Group).[2 3]

The earliest clinical manifestations of AD involve very mild decline in cognition with measurable functional impairment developing later in the disease progression. These subtle changes early in the predementia stage of AD are difficult to measure, and new approaches are required to detect change and establish treatment effects. Currently, there is no consensus on standard endpoints for use in aMCI populations.[4] The Food and Drug Administration (FDA) has indicated that a single composite outcome may be appropriate for pAD/MCI due to AD trials.[5] Cognitive instruments, such as the Alzheimer's Disease Assessment Scale–cognitive subscale (ADAS-cog), Mini-Mental State Examination (MMSE), and neuropsychological test items show relatively little change over time in pAD/aMCI participants, primarily due to ceiling effects in many of the items that make up these scales.[6 7] Scales that measure functional or global changes may be unable to capture subtle clinical decline due to the comparatively mild functional deficits in pAD/aMCI patients.[8–10] While clinical tools that are widely used in AD dementia trials may lack overall sensitivity, certain items within these scales appear to be more responsive to clinical decline in aMCI/pAD. We sought to develop an AD Composite Score (ADCOMS) comprised of items from existing scales that, when combined, would be sensitive to AD-specific clinical decline in aMCI/pAD. After identifying the items, we assessed the ability of ADCOMS to detect treatment effects in data sets from previously conducted trials of cholinesterase inhibitors with proven efficacy in AD. The Coalition Against Major Diseases (CAMD), a component of the Critical Path Institute,[11] advanced ADCOMS with the intention of establishing this approach as a qualified primary outcome measure for registration trials in pAD.

METHODS

Data sets

Data from placebo groups, or untreated populations of four aMCI studies, were used to establish the natural progression of the condition. These data sets included the aMCI subgroup from the Alzheimer's Disease Neuroimaging Initiative (ADNI-1; ADNI-MCI, n=405; downloaded on 20 May 2010), the placebo group from the Alzheimer's Disease Cooperative Study (ADCS) 'A randomized, double-blind, placebo-controlled trial to evaluate the safety and efficacy of vitamin E and donepezil HCL (Aricept) to delay clinical progression from MCI to AD' (ADCS-MCI, n=264),[8] the placebo group of 'A 1 year, multicenter, randomized, double-blind, placebo-controlled evaluation of the efficacy and safety of donepezil

J Neurol Neurosurg Psychiatry. 2016 Sep; 87(9): 993–999.

*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)

Assessments

- 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)

Endpoints

Primary Endpoint
(Interim Analysis)

ADCOMS as clinical outcome assessment

Secondary Endpoints
(18-month Final Analysis Using Conventional Statistics [MMRM])

- 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

*NA, EU, Asia Pacific regions

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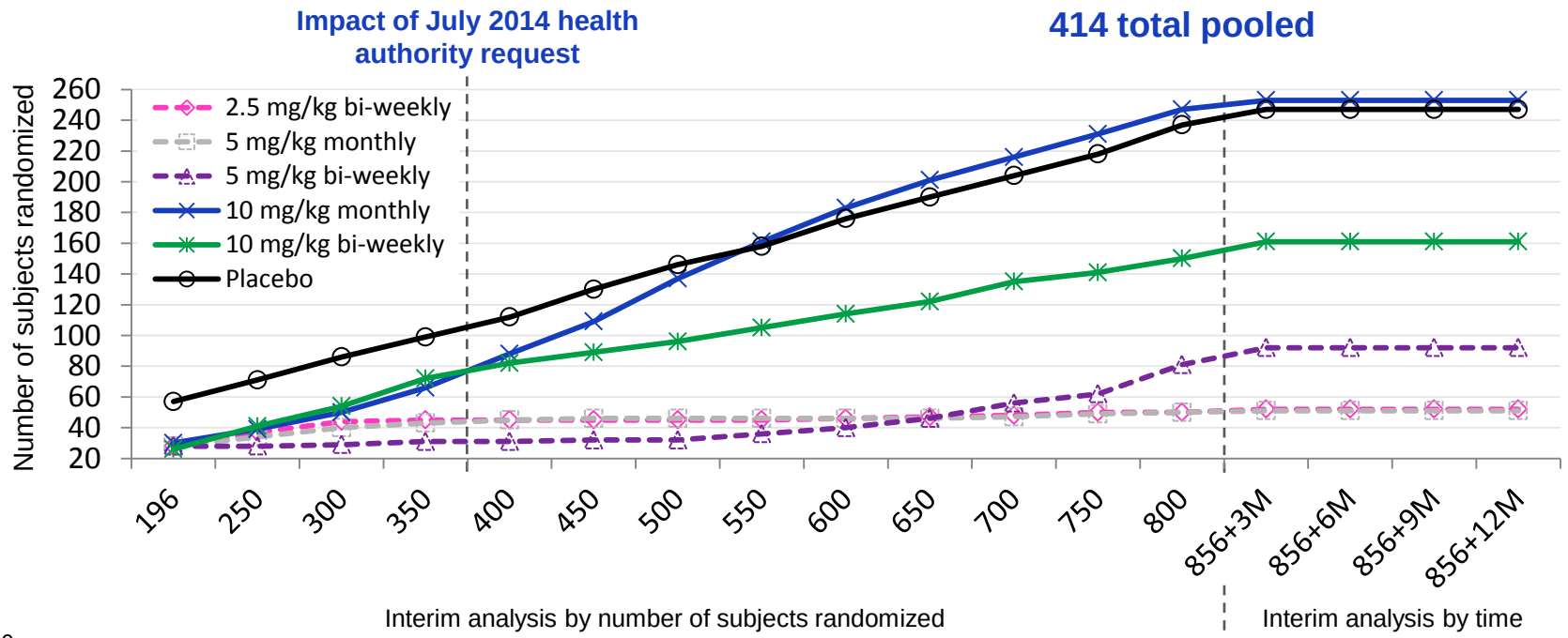
Allocation of Subjects According to Response Adaptive Randomization

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

Number of Subjects Randomized Per Dose

APOE4 Status	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
All	**247**	52	51	92	**253**	**161**	**856**
+	**175**	38	40	84	**225**	**48**	**610**
-	**72**	14	11	8	**28**	**113**	**246**

414 total pooled



- A health authority requested in July 2014 that:
  - APOE4 carriers no longer be randomized to 10 mg/kg bi-weekly
  - APOE4 carriers on 10 mg/kg bi-weekly who had not reached 6 months treatment be discontinued
- Implementation of this request resulted in an imbalance of APOE4 carriers at 10 mg/kg monthly and bi-weekly doses

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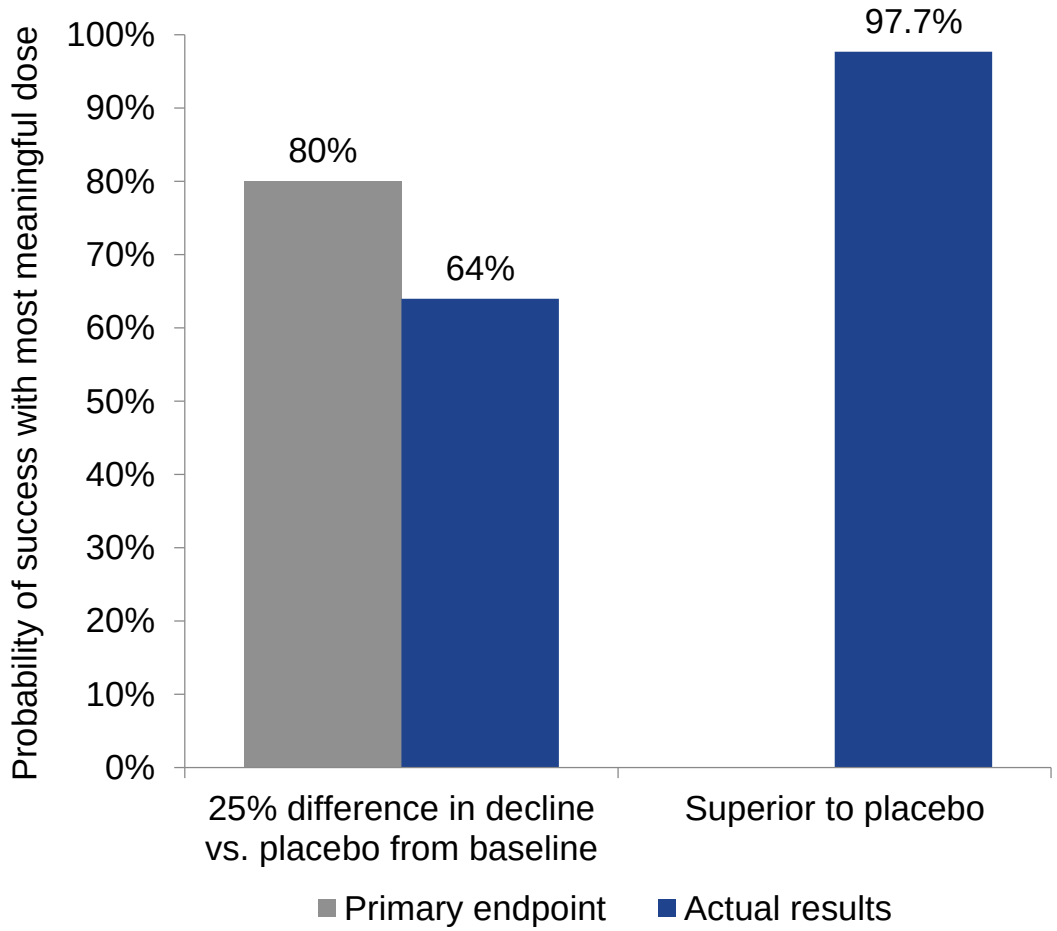
Probability of Success on ADCOMS at 12 Months Under Bayesian Statistical Models

- 12-month Bayesian model identified 10 mg/kg bi-weekly as the most meaningful dose
- Bayesian model defined “success” as an at least 25% difference in disease progression from baseline versus placebo at 12 months on ADCOMS
  - Pre-specified primary endpoint was an 80% probability of success at 12 months
  - Bayesian results at 12 months showed a 64% probability of success
- Using the Study 201 Bayesian model, the 10 mg/kg bi-weekly dose had a 97.7% probability of being superior to placebo by any magnitude
- The study continued in a blinded fashion through 18 months; no unblinding occurred with the 12 month analysis

Probability of Achieving Threshold Levels of Success at 12 Months



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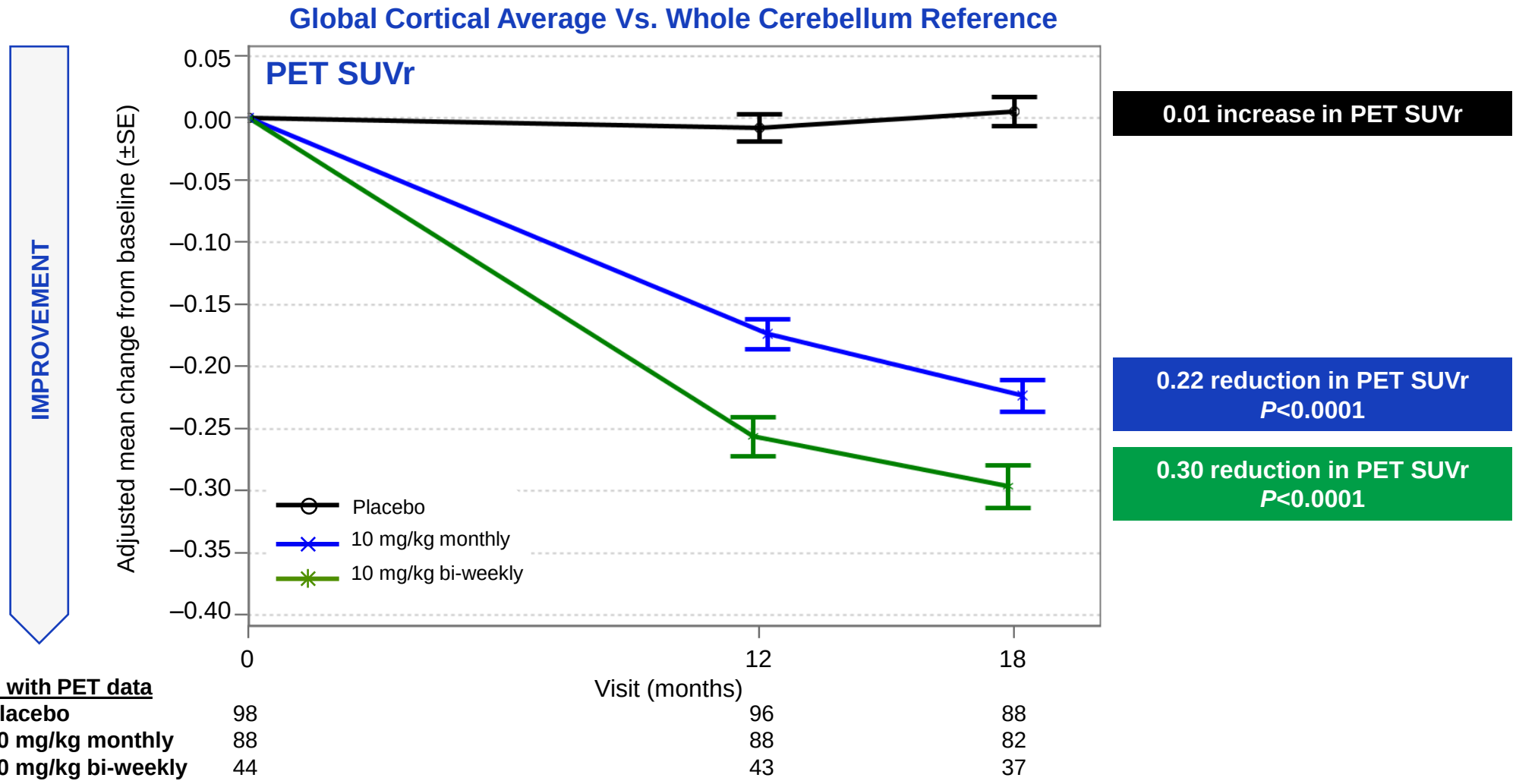
BAN2401 Reduces Amyloid Burden Over 18 Months



N with PET data			
Placebo	98	96	88
10 mg/kg monthly	88	88	82
10 mg/kg bi-weekly	44	43	37

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.

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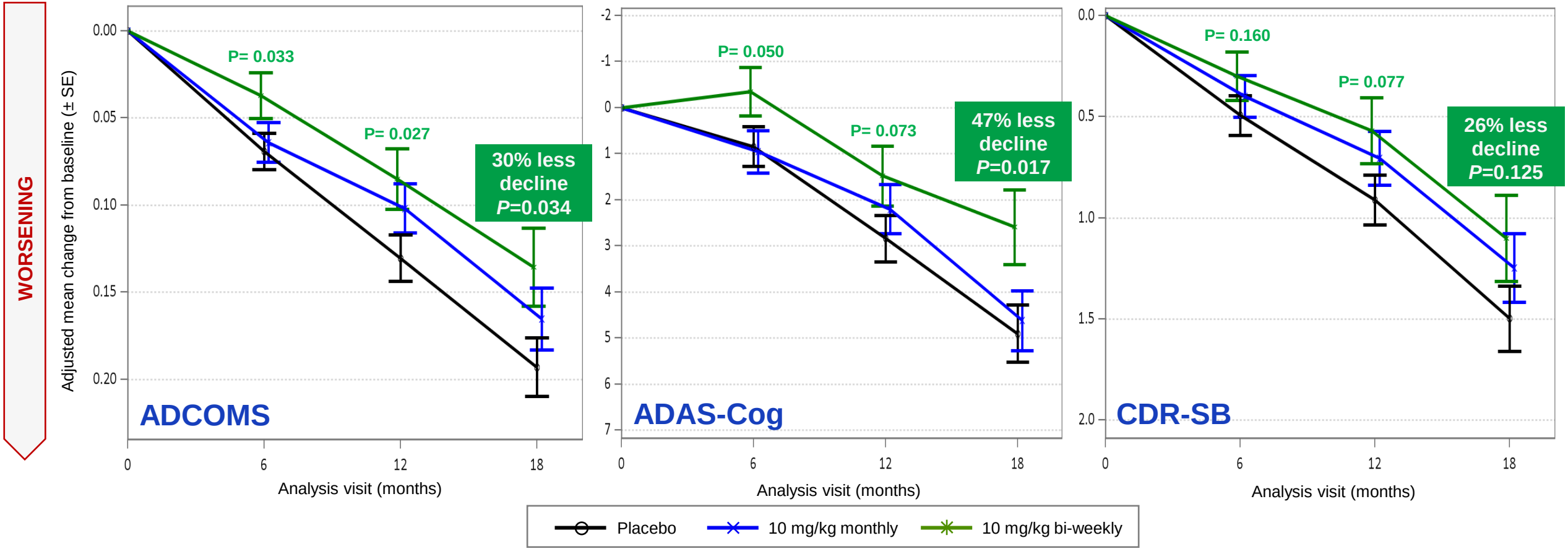
BAN2401 Slows Disease Progression on Clinical Outcome Measures Over 18 Months



N with data	0 mo.	6 mo.	12 mo.	18 mo.
Placebo	238	216	187	160
10 mg/kg monthly	246	208	165	146
10 mg/kg bi-weekly	152	130	93	79

Analyses were based on protocol-specified Mixed Model Repeated Measures (MMRM) models.

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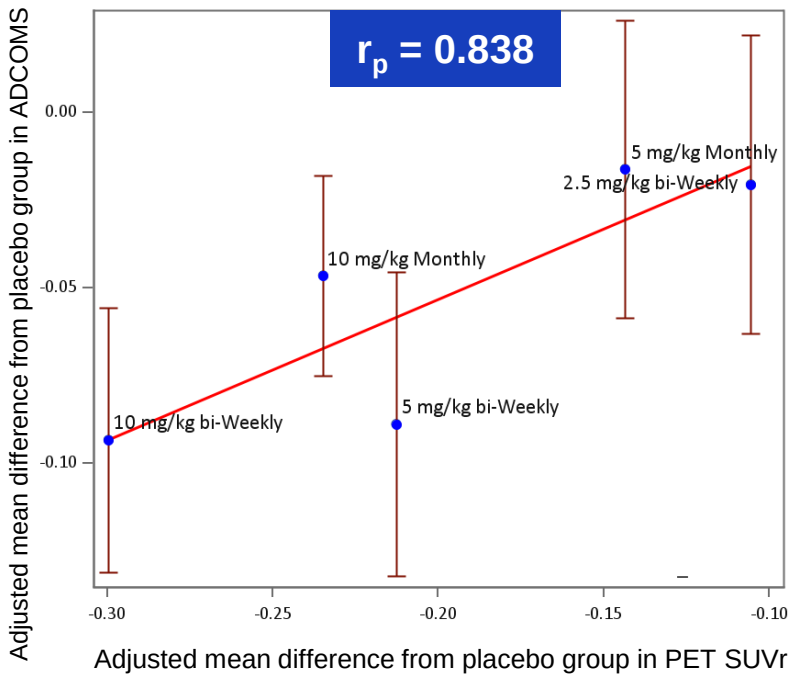
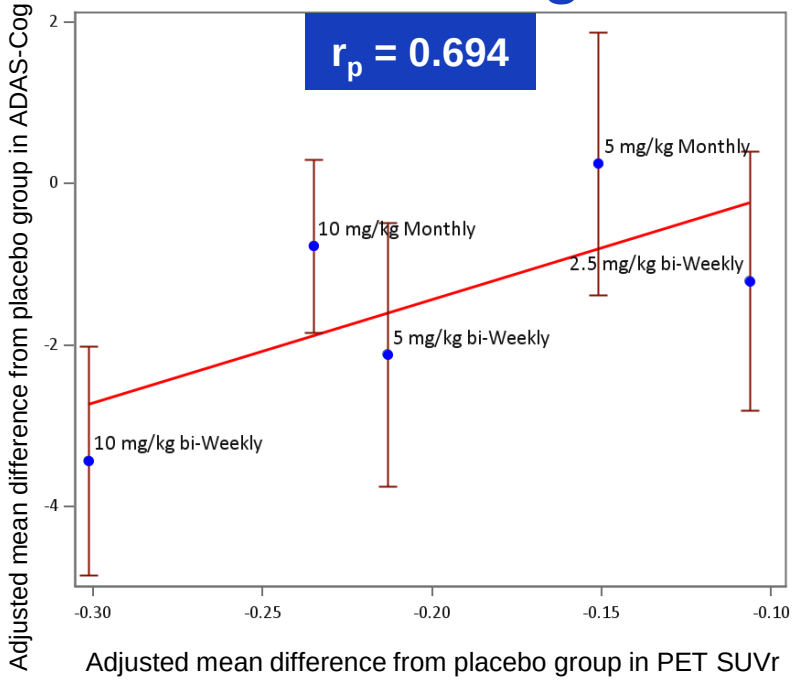
Amyloid Clearance (PET SUVr) Correlates with Clinical Efficacy

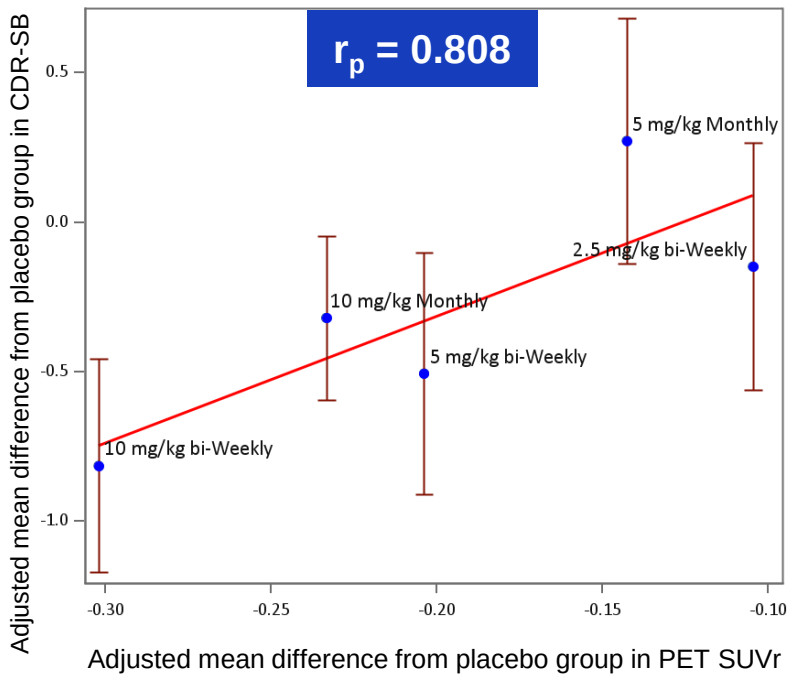
ADCOMS



ADAS-Cog



CDR-SB



CLINICAL IMPROVEMENT

AMYLOID CLEARANCE

	2.5 mg/kg bi-weekly	5 mg/kg monthly	5 mg/kg bi-weekly	10 mg/kg monthly	10 mg/kg bi-weekly
N with 18 mo. PET data	23	23	24	82	37

Note: r_p is Pearson's correlation coefficient

Adjusted mean was based on a protocol-specified mixed effects model with repeated measures (MMRM). The MMRM model included baseline as a covariate, with treatment group, visit, region, randomization stratification variables (clinical stage, concurrent AD medication, APOE4 status), and treatment group-by-visit interaction as fixed effects. Data shown are for subjects enrolled in the PET sub-study with PET SUVr and clinical data at 12 or 18 months (N=288).

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BAN2401-G000-201 Safety Summary

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

- 5/48 (~10%) cases of symptomatic ARIA-E
  - Included headache, visual disturbances, or confusion
- 60% of ARIA-E occurred within first 3 months of treatment
- ~89% of cases were mild to moderate in severity (radiographic)
- MRI findings typically resolved within 4-12 weeks

		BAN2401				
Category	**Placebo (N=245) n (%)**	**2.5 mg/kg bi-weekly (N=52) n (%)**	**5 mg/kg monthly (N=51) n (%)**	**5 mg/kg bi-weekly (N=92) n (%)**	**10 mg/kg monthly (N=253) n (%)**	**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%)

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Overall Summary of Study 201

- BAN2401 showed statistically meaningful differences on the primary outcome (ADCOMS) at 18 months
- BAN2401 showed efficacy at reducing brain amyloid at 18 months
- The effect of BAN2401 on amyloid PET clearance correlates with clinical efficacy
- Outstanding questions from topline data presentation will be addressed today, including:
  - Impact of APOE4 status allocation and pre-specified subgroup analyses
  - Biomarker analyses related to neurodegeneration

Communication 2

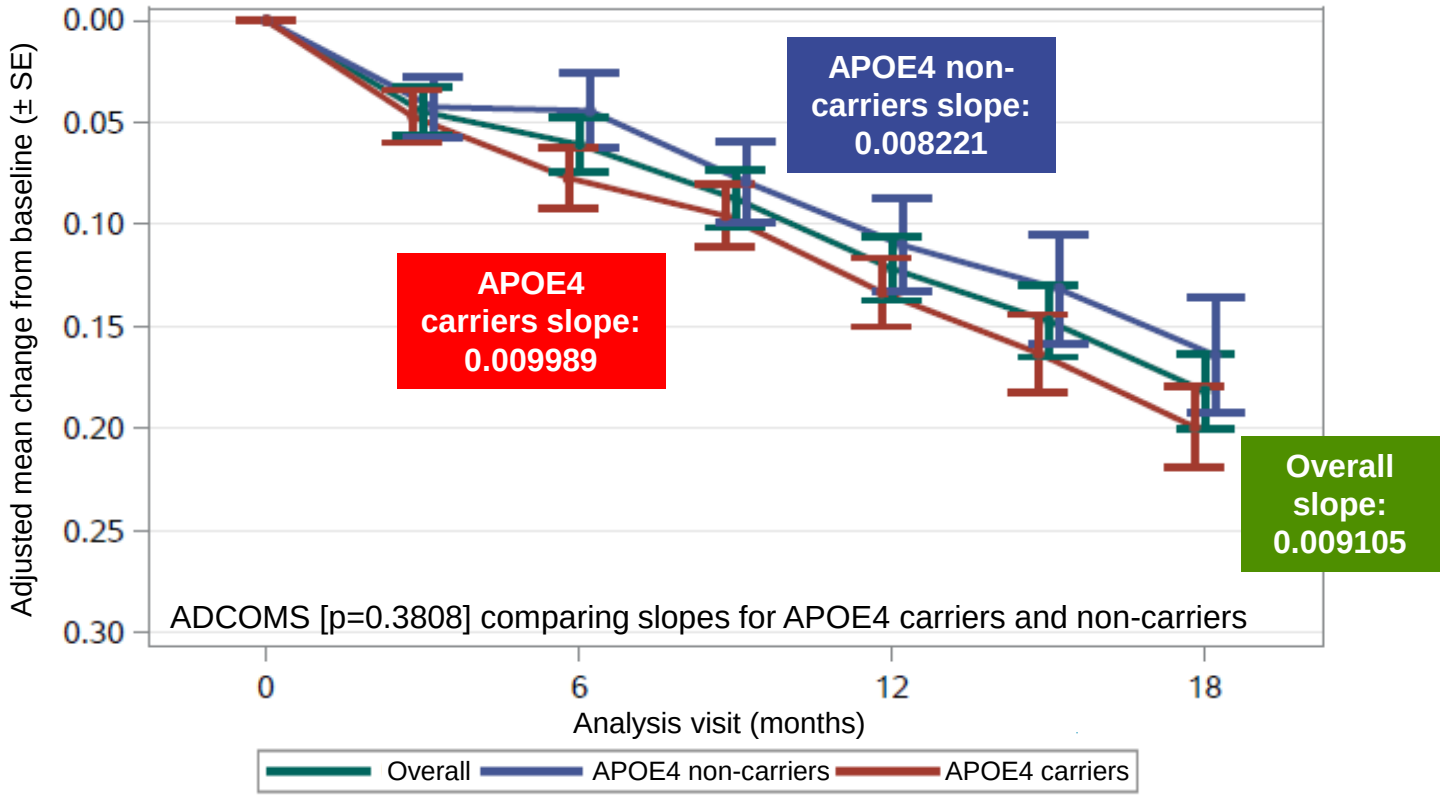
Pre-specified Subgroup Analysis in BAN2401 Study 201

Chad J. Swanson, PhD
Senior Director, Clinical Research, Neurology Business Group
Eisai Inc.
Woodcliff Lake, NJ, USA

Presented at the 11th Clinical Trials on Alzheimer's Disease (CTAD) Conference October 24-27, 2018

Placebo Data Show that APOE4 Carriers and Non-Carriers in Study 201 Progressed at a Similar Rate

Placebo Data on ADCOMS by APOE4 Status and Overall



N with data							
Placebo overall	238	226	216	201	187	172	160
APOE4 carriers	168	161	150	141	134	124	113
APOE4 non-carriers	70	65	66	60	53	48	47

- APOE4 status is a risk factor for age of onset of disease[1], but has limited effect on disease progression at this stage of disease in amyloid positive subjects[2]
- Clinical decline for APOE4 carrier and non-carrier placebo groups aligned around that of the overall placebo group and were not statistically different from each other on ADCOMS, ADAS-Cog, or CDR-SB

Source: [1]Liu, et. al., 2013; [2]Steenland, et. al., 2018
Analyses were based on protocol-specified Mixed Model Repeated Measures (MMRM) models. Slopes shown represent change in ADCOMS per month.

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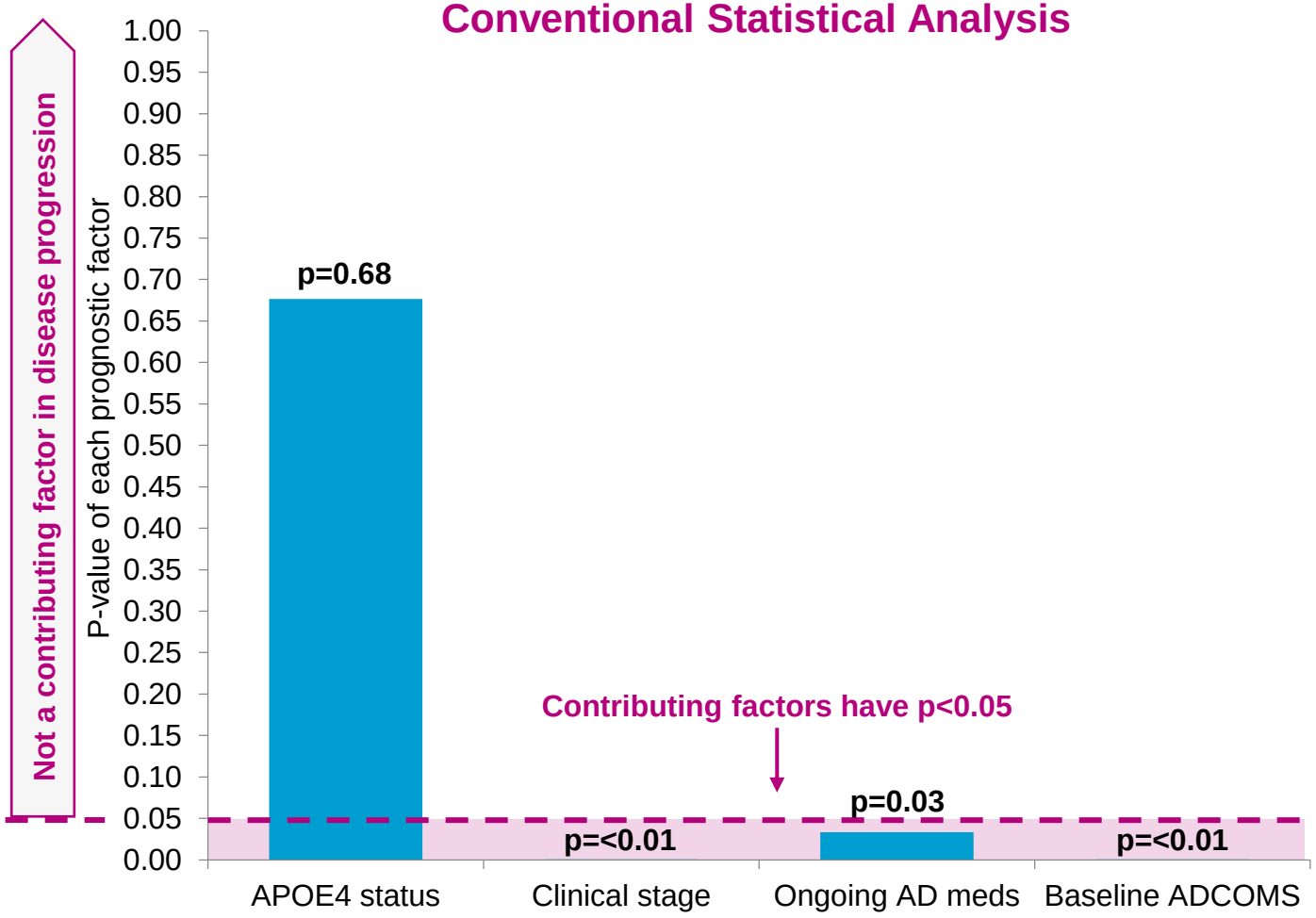
Disease Progression at 18 Months is Not Driven by APOE4 Status

Impact of Key Factors on Disease Progression as Measured by ADCOMS in Protocol-specified Conventional Statistical Analysis



- According to the protocol-specified conventional statistical analysis:
  - APOE4 status was not a contributing factor in driving disease progression while clinical stage, concomitant AD medication, and baseline ADCOMS were
- Additional statistical analyses were run to evaluate the contribution of key factors by themselves or in combination, to disease progression
  - APOE4 status was not a significant contributor in any analysis tested
- Results are consistent across ADCOMS, ADAS-Cog, and CDR-SB
- Thus, effect of 10 mg/kg bi-weekly was driven by treatment with BAN2401 and not an imbalance in subject allocation by APOE4 status

Analyses were based on protocol-specified Mixed Model Repeated Measures (MMRM) models.

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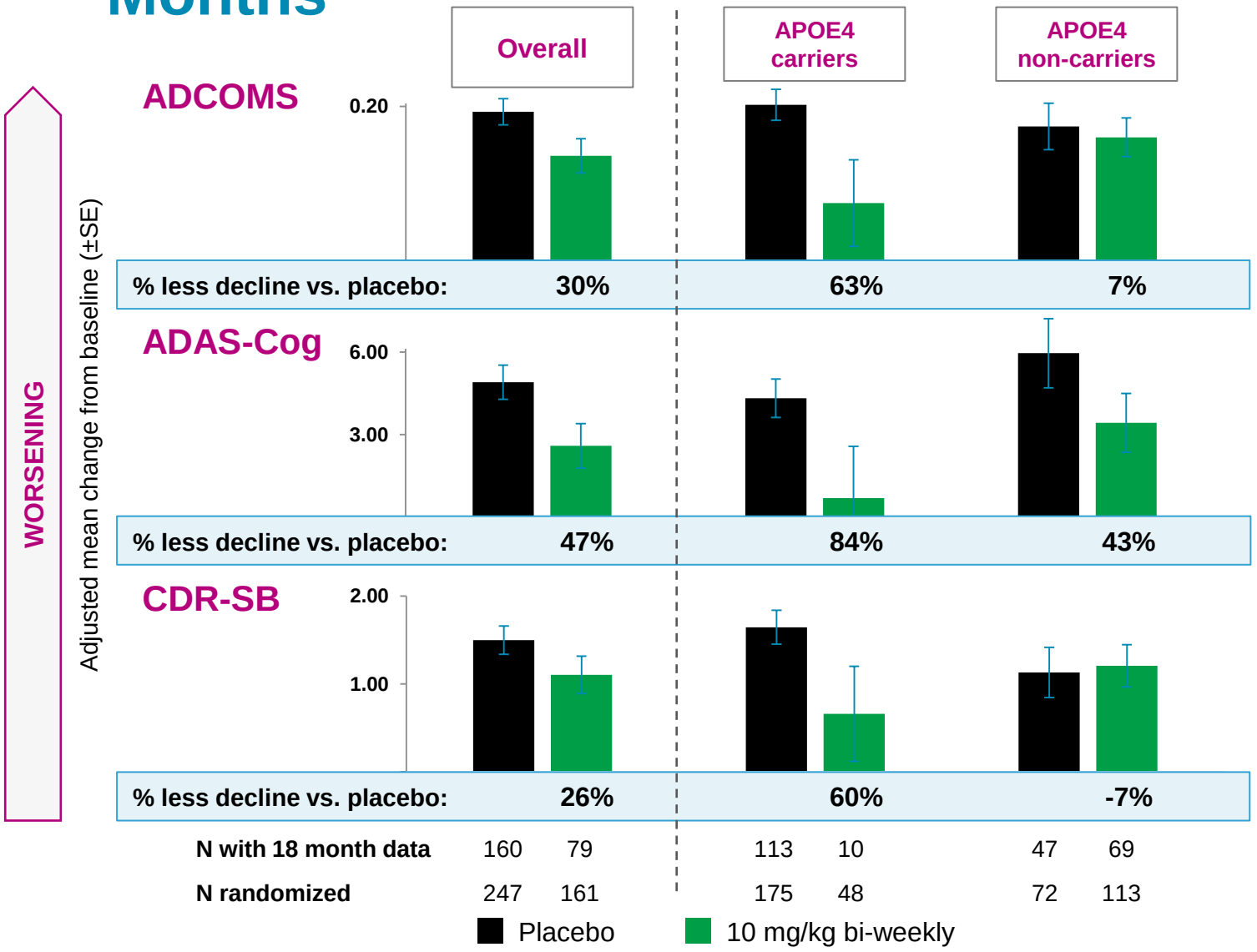
Clinical Effects in APOE4 Carriers and Non-carriers at 18 Months



- Treatment effect for the 10 mg/kg bi-weekly dose was not due to an imbalance in subject allocation by APOE4 status, and the imbalance may have underestimated the overall BAN2401 treatment effect
- Pooling the 10 mg/kg bi-weekly and 10 mg/kg monthly doses corrects APOE4 imbalance and results in less decline on ADCOMS vs. placebo at 18 months of:
  - 21% overall (n*=414)
  - 25% for APOE4 carriers (n*=273)
  - 6% for APOE4 non-carriers (n*=141)
  - PK modeling suggests that C_{avg} is a key driver of dose response between 10 mg/kg bi-weekly and monthly

*n = number of subjects randomized to 10 mg/kg bi-weekly and 10 mg/kg monthly dose groups combined
Analyses were based on protocol-specified Mixed Model Repeated Measures (MMRM) models with longitudinal assessment of data for all subjects.

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Clinical Effects in Both MCI and Mild AD Subjects at 18 Months

- Treatment effect did not differ between MCI and mild AD on ADCOMS and was comparable on ADAS-Cog
- Effect on CDR-SB seen in both MCI and mild AD subjects, though, as expected, treatment effect in mild AD subjects was numerically larger

Analyses were based on protocol-specified Mixed Model Repeated Measures (MMRM) models with longitudinal assessment of data for all subjects.

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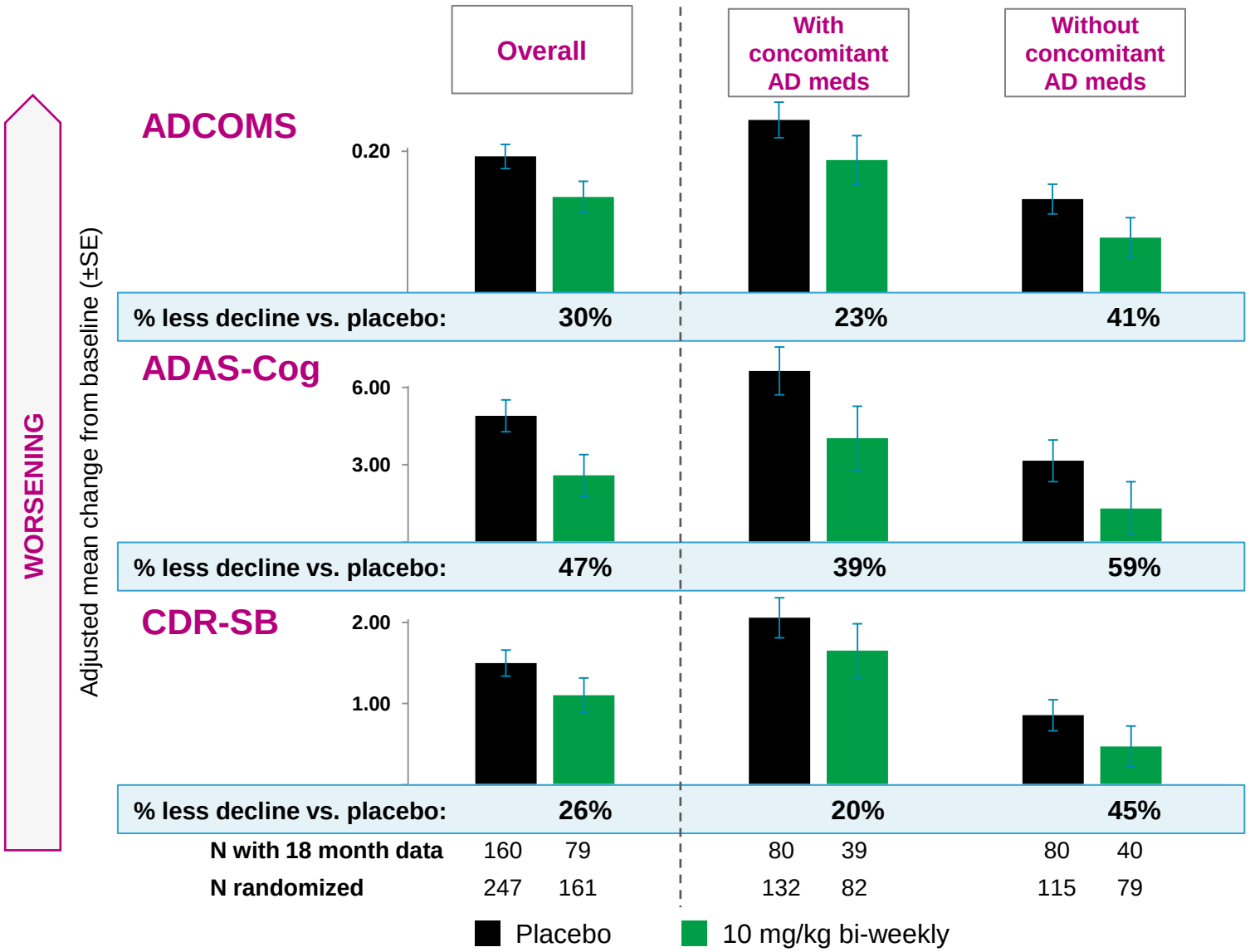
Clinical Effects in Subjects Who Began the Study with and Without Concomitant AD Medications



- Treatment effect was meaningful regardless of whether subjects started the study with or without concomitant AD medications

Analyses were based on protocol-specified Mixed Model Repeated Measures (MMRM) models with longitudinal assessment of data for all subjects.

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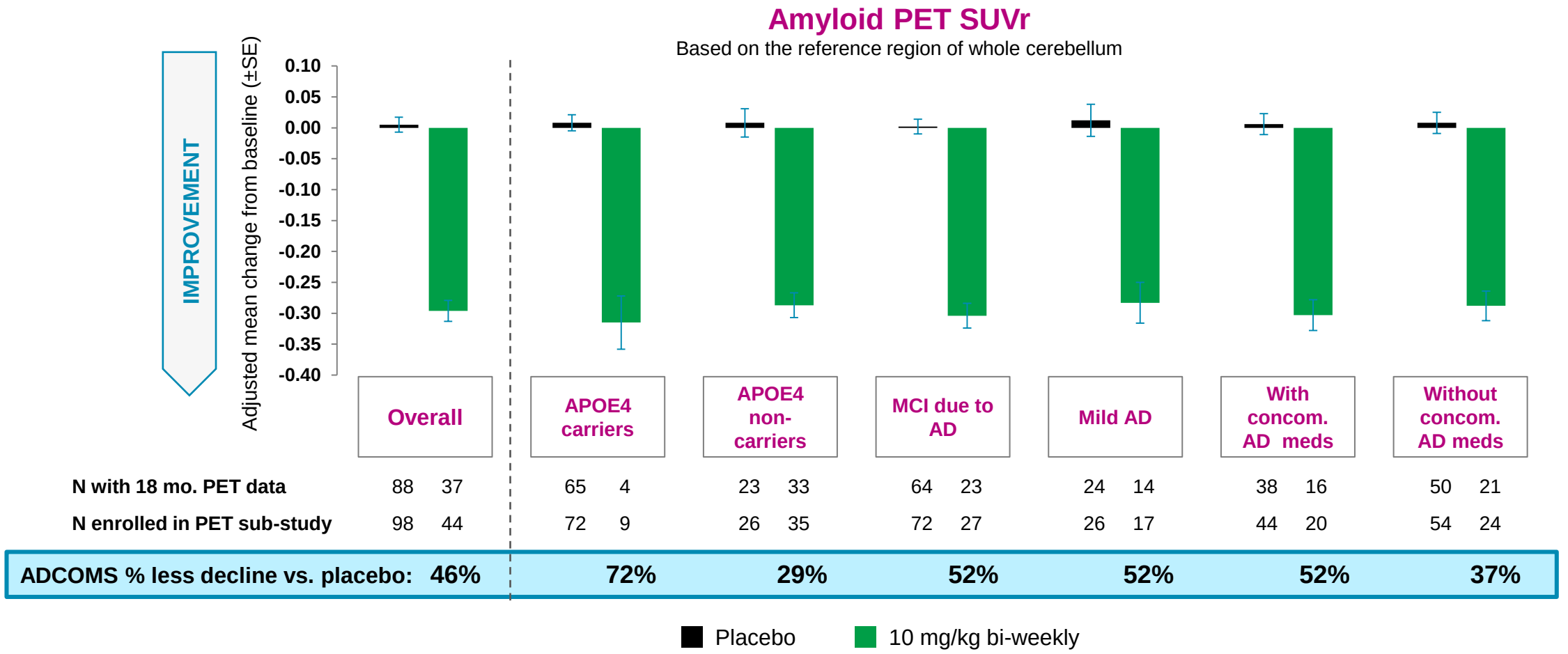
Significant Brain Amyloid Clearance Across Pre-specified Subgroups



- ADCOMS data for subjects in the PET sub-study are consistent and meaningful across subgroups

Analyses for the overall population were based on protocol-specified Mixed Model Repeated Measures (MMRM) models with factors of treatment, visit, clinical stage, the presence of ongoing AD treatment at baseline, ApoE ε4 status, region, treatment-by-visit interaction and baseline value. The corresponding stratification factor was removed in the subgroup analyses.
SE=standard error.

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BAN2401 Study 201 Subgroup Analysis Summary

- Statistically meaningful effect of 30% less decline in disease progression seen for 10 mg/kg bi-weekly dose versus placebo at 18 months on ADCOMS was driven by BAN2401 treatment effect and not an imbalance in subject allocation by APOE4 status
  - Placebo disease progression was similar in amyloid positive APOE4 carriers and non-carriers
  - APOE4 status was not a contributing factor to change from baseline in disease progression
  - Imbalance of APOE4 carriers in the 10 mg/kg bi-weekly dose group may have actually underestimated the overall treatment effect
- Effect on disease progression at 18 months was meaningful across subgroups of clinical stage and concomitant AD medication
- Impact on brain amyloid was significant across subgroups

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Communication 3

Effect of BAN2401 on Underlying AD Pathophysiology

Chad J. Swanson, PhD
Senior Director, Clinical Research, Neurology Business Group
Eisai Inc.
Woodcliff Lake, NJ, USA

Presented at the 11th Clinical Trials on Alzheimer's Disease (CTAD) Conference October 24-27, 2018

Change of CSF Biomarkers in Combined 10 mg/kg Groups Compared to Placebo Suggest Impact on Neurodegeneration

- CSF collected at baseline, 12 months, and 18 months in biomarker subgroup
- CSF biomarkers were measured by ELISA
  - Synaptic damage: Neurogranin
  - Downstream tau pathway: Phosphorylated Tau_{181} (p-Tau)
  - Axonal degeneration: Neurofilament Light Chain (NfL)
- 10 mg/kg bi-weekly and 10 mg/kg monthly groups were combined to increase the sample size in CSF subgroup

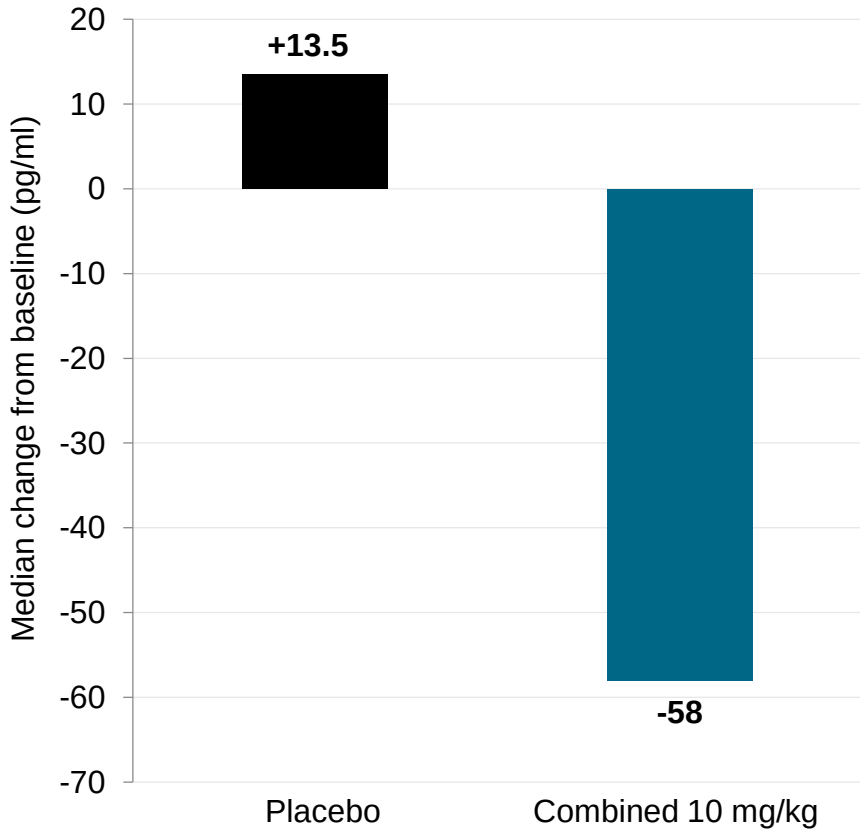
Presented at the 11th Clinical Trials on Alzheimer's Disease (CTAD) Conference October 24-27, 2018

BAN2401 Reduces Neurogranin in CSF

- Neurogranin is a synaptic protein and a CSF marker of synaptic damage
- CSF neurogranin levels are elevated in subjects with early AD[1]
  - Baseline for control subjects is reported[2] to be ~236-496 pg/ml
  - Overall baseline for all subjects in CSF sub-study was 530 pg/ml (median)
- BAN2401 reduces CSF neurogranin levels by 11% (58 pg/ml median reduction from baseline) over 18 months

Combined 10 mg/kg Vs. Placebo: CSF Neurogranin

Median change from baseline at 18m in neurogranin, all subjects



	Placebo	Combined 10 mg/kg
N with 18 mo. data	16	23
Interquartile range (Q1, Q3)	(-91, 32)	(-97, 8)

Source: [1]Kvartsberg H et al. Alzheimer's Dementia 2015; 11(10):1180-90; [2]Willemse EAJ et al. Clin Chem. 2018;64(6):927-937.; Analysis conducted using same assay as Study 201 data. Neurogranin ELISA assay (ADx/Euroimmun) was measured by in Vrije Universiteit Amsterdam (CV = 6.7%).
For regression analysis over time, the slope difference via a Robust Wald Test, $p<0.0001$.

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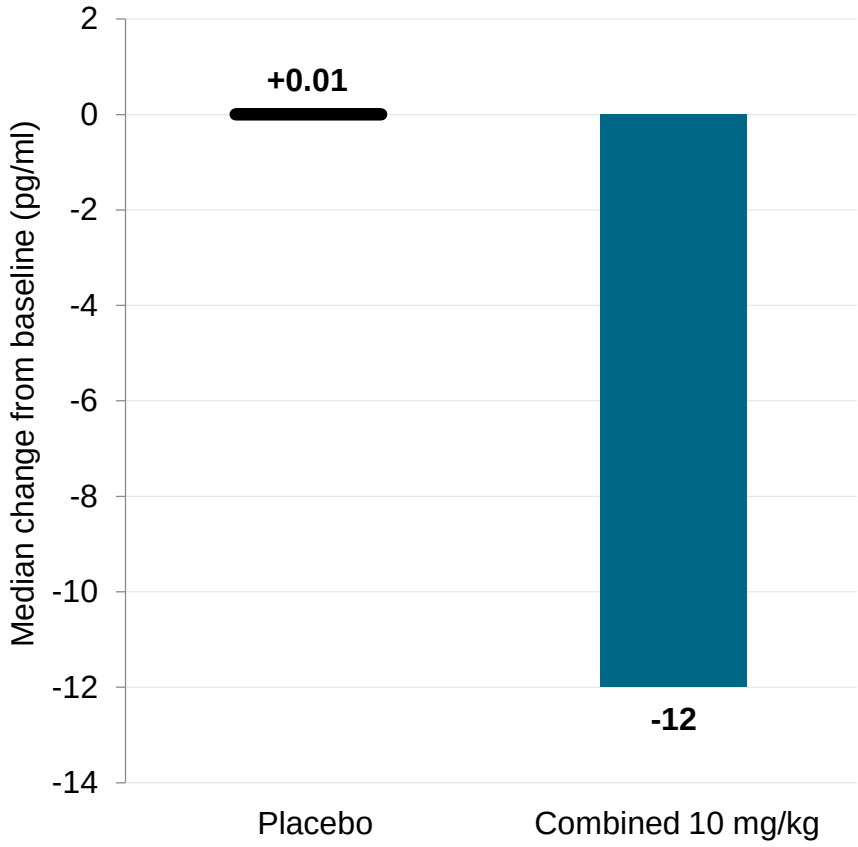
BAN2401 Reduces Phospho-Tau (p-Tau) in CSF

- Phospho-Tau$_{181}$ (p-Tau) is a CSF marker that correlates with tau pathology
- CSF p-Tau level is elevated in subjects with AD[1]
  - Baseline for control subjects is reported[2] to be ~35-48 pg/ml
  - Overall baseline for all subjects in CSF sub-study was 89 pg/ml (median)
- BAN2401 significantly reduces CSF p-Tau levels by 13% (12 pg/ml median reduction from baseline) over 18 months

Combined 10 mg/kg Vs. Placebo: CSF p-Tau

Median change from baseline at 18m in p-Tau, all subjects



	Placebo	Combined 10 mg/kg
N with 18 mo. data	16	23
Interquartile range (Q1, Q3)	(-2, 12)	(-20, 1)

Source: [1]Zetterberg H et al. J Alzheimers Dis. 2007 Nov;12(3):255-60; [2]Hampel et al. Alzheimers Dement. 2018:492-501.; Analysis conducted using same assay as Study 201 data. INNOTEST® PHOSPHO-TAU(181P) was measured by Laboratoire CERBA/BARC, Saint-Ouen-l'Aumône (CV = 2.7%).
For statistical analyses at 18 months performed via Wilcoxon Test, p=0.0124. For regression analysis over time, the slope difference via a Robust Wald Test, p<0.0001.

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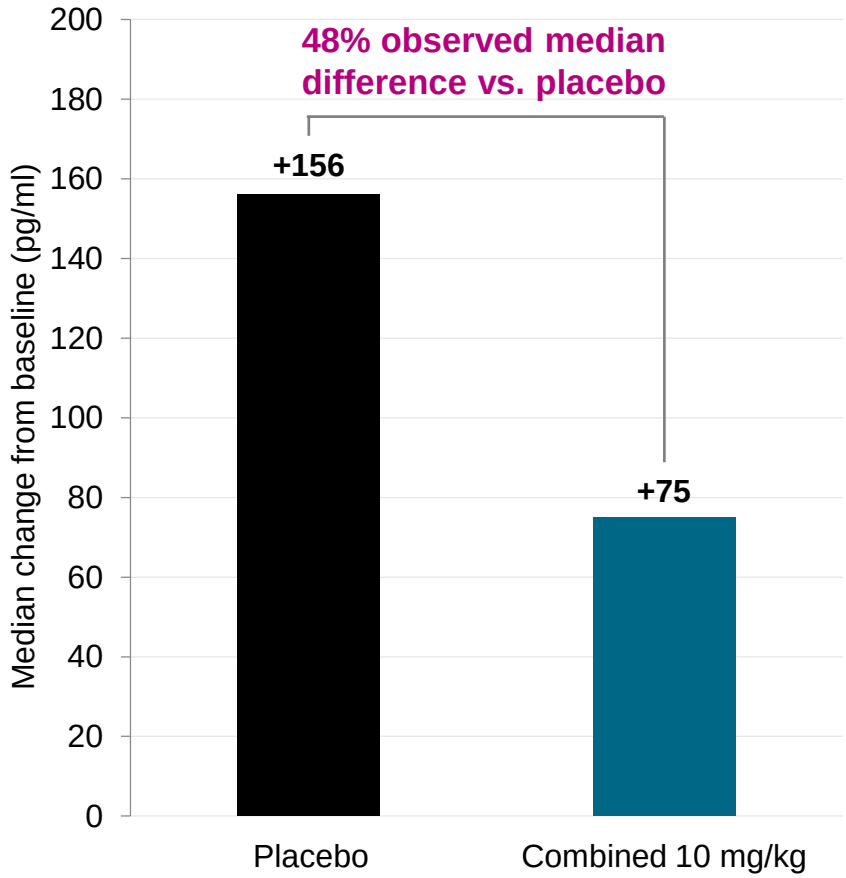
BAN2401 Slows Increase of Neurofilament Light Chain (NfL) from Baseline

- Neurofilament light chain (NfL) is a neuronal structural scaffold protein and a CSF marker of axonal degeneration[1]
- CSF NfL levels are elevated in subjects with AD
  - Baseline for control subjects is reported[2] to be ~516-773 pg/ml
  - Overall baseline for all subjects in CSF sub-study was 1094 pg/ml (median)
- BAN2401 slows increase in NfL in the CSF by 48% (median difference) compared to placebo over 18 months

Combined 10 mg/kg Vs. Placebo: CSF NfL

Median change from baseline at 18m in NfL, all subjects



	Placebo	Combined 10 mg/kg
N with 18 mo. data	16	23
Interquartile range (Q1, Q3)	(92, 195)	(16, 188)

Source: [1]Khali M et al. Nat Rev Neurol. 2018; 14(10):577-589; [2]Hampel et al. Alzheimers Dement. 2018:492-501.; Analysis conducted using same assay as Study 201 data.
NF-light® ELISA assay (UmanDiagnostics AB) was measured by Vrije Universiteit Amsterdam (CV = 6.3%).
For regression analysis over time, the slope difference via a Robust Wald Test, $p<0.001$.

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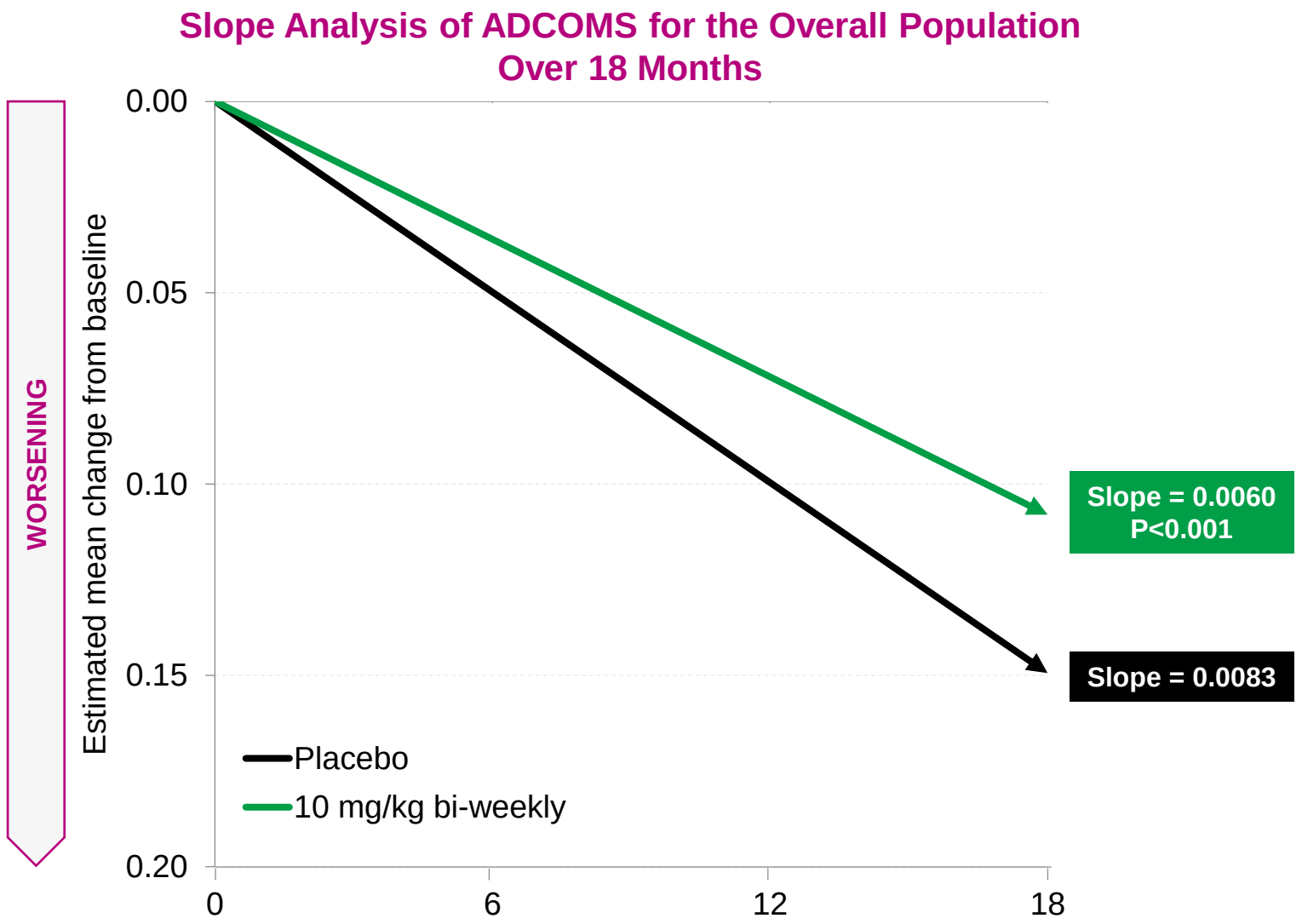
BAN2401 Significantly Slows Rate of Disease Progression Over 18 Months at 10 mg/kg Bi-weekly Dose

- Significant slope difference for 10 mg/kg bi-weekly dose group compared to placebo (p<0.001)
- ADCOMS measured every 3 months



Linear regression model testing the slope of change from baseline. Slopes shown represent change in ADCOMS per month.

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Summary of the Effects of BAN2401 on Underlying AD Pathophysiology

- CSF biomarkers are consistent in showing treatment of underlying disease pathophysiology
  - Reduction in synaptic damage (neurogranin)
  - Reduction in downstream tau pathway (p-Tau)
  - Reduction in increase of axonal degeneration (NfL)

- BAN2401 treatment at the 10 mg/kg bi-weekly dose significantly slows the rate of disease progression over time

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Communication 4

Totality of Results from BAN2401 Study 201

Professor Jeffrey Cummings, MD, ScD
Center for Neurodegeneration and Translational Neuroscience
Cleveland Clinic Lou Ruvo Center for Brain Health
Las Vegas, Nevada, USA

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Study 201 Satisfied Key Principles of FDA Guidance on Adaptive Trials and Study Result was Driven by BAN2401 Treatment Effect

- Bayesian analysis allowed for early decision making through rapid detection of treatment effect by using accumulated data to make timely and appropriate subject to dose allocations while conventional statistical analysis was used, per protocol, to analyze actual observed magnitude of treatment effect after the study was unblinded at 18 months

- Effect observed in 10 mg/kg bi-weekly dose was driven by treatment with BAN2401 and not an imbalance in subject allocation by APOE4 status, and, the required randomization adjustment that impacted APOE4 carrier allocation to that dose may have actually underestimated the treatment effect for BAN2401

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Consistency of Data on Clinical Outcome Measures, Brain Amyloid, and CSF Biomarkers Supports Treatment Effect

BAN2401
Treatment Effect in Early AD

1 Clinical Outcome Measures

- Slowing of disease progression over time observed across clinical outcome measures at the highest dose, including 30% on ADCOMS
- Slowing of disease progression observed across subgroups

2 Brain Amyloid

- Significant amyloid clearance on PET overall
- Over 80% of subjects at highest dose converted from positive to negative on amyloid PET
- Amyloid PET data significant across subgroups

3 CSF Biomarkers

- All CSF biomarkers demonstrate beneficial impact on AD pathophysiology
  - Synaptic damage (neurogranin)
  - Downstream tau pathway (p-Tau)
  - Axonal degeneration (NfL)

Targeting Aggregated Aβ Species with Low Affinity to Monomers

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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 STUDY SITES

Abington Neurological Associates
Advanced Memory Research Institute of NJ, PC
Akademiska Sjukhuset
Alexian Brothers Medical Center - Neuroscience Research Institute
Alzheimer's Research and Treatment Center
American Neuropsychiatric Research Institute Inc
ANI Neurology, PLLC d/b/a Alzheimer's Memory Center
Asan Medical Center
ASCLEPES Research Centers, P.C.
Atlanta Center for Medical Research
Axiom Clinical Research of Florida
Azienda Ospedaliera di Perugia Ospedale S. Maria della Misericordia
Azienda Ospedaliero Universitaria di Parma
Azienda Ospedaliero Universitaria Pisana
Azienda Ospedaliero Universitaria San Martino
Berma Research Group
Bezirkskrankenhaus Guenzburg
Bioclinica Orlando
Bioclinica The Villages
Boston University School of Medicine
Bradenton Research Center, Inc.
Brain Matters Research
Brain Research Center
Brigham and Women's Hospital
CCM Clinical Research Group, Inc.
CHU Strasbourg - Hôpital Hautepierre
CHU Toulouse - Hôpital Casselardit
Clinical Trial Network
Clinical Trials of Texas, Inc.
Collaborative Neuroscience Network, LLC
Columbus Regional Medical Center
Cutting Edge Research Group, Inc.
Dent Neurologic Institute
Diakoniekrankenhaus Henriettenstiftung gGmbH
Dong-A University Hospital
Elkhart Clinic
Emory University Cognitive Neurology Clinic & ADRC
Empire Neurology, PC
Florida Atlantic University
Fondazione IRCCS CA' Granda Ospedale Maggiore Policlinico
Fondazione Santa Lucia IRCCS
Fukuoka University Hospital
Fundacio ACE
FutureSearch Trials of Dallas, LP
Galiz Research, LLC
Gesundheitszentrum Hoppegarten
Glasgow Memory Clinic Ltd
Great Lakes Clinical Trials
Groupe hospitalier Broca - La Rochefoucauld - La Collégiale
Henry Ford Hospital
Hospital de Cruces
Hospital General de Catalunya
Hospital San Vicente
Hospital Universitario Clinico San Carlos
Hospital Universitario Virgen Macarena
Hotel Dieu Hospital
Hyogo Brain and Heart Center
Hyogo College of Medicine Hospital
INACTIVE Margolin Brain Institute
Indiana University School of Medicine
Infinity Clinical Research, LLC
Innovative Clinical Trials
Institute for Neurodegenerative Disorders
IRCCS Centro San Giovanni di Dio Fatebenefratelli
Ishikawa Clinic
JEM Research Institute
Katayama Medical Clinic
Kawartha Centre - Redefining Healthy Aging
Klinikum rechts der Isar der TU Muenchen
Kobe University Hospital
Konkuk University Medical Center
Kotobukikai Tominaga Hopital
Lahey Clinic Inc.
Lynn Health Science Institute
MD Clinical
Medical College of Wisconsin, Inc.
Memory Enhancement Center of America, Inc.
Miami Jewish Health Systems
Michigan State University
Misael Gonzalez, MD
National Clinical Research Inc.-Richmond
Neuro Rive Sud Clinic/Center for Diagnosis & Research on Alzheimer's Disease
Neurocare, Inc., dba Neurocare Center for Research
Neuropsychiatric Research Center of Southwest Florida
NeuroStudies.net, LLC
New Orleans Center for Clinical Research / Volunteer Research Group, an AMR company
New York University Medical Center
NHO Hiroshima-Nishi Medical Center
Oregon Health & Science University
Osaka Saiseikai Nakatsu Hospital
Osaka University Hospital
Pacific Institute of Medical Research
Pacific Neuroscience Medical Group
Palm Beach Neurological Center
Parkinson's and Neurodegenerative Disorders Clinic
Parkinson's Disease and Movement Disorders Center
Pharmacology Research Institute
Pharmakologisches Studienzentrum Chemnitz GmbH
Policlinica Guipuzcoa
Praxis Dr. med. Peter Franz
Praxis Dr. med. Volker Schumann
Praxis Dres. Bittkau
Psychiatry and Alzheimer's Care of Rochester. PLLC
Quantum Laboratories Inc.
Quest Research Institute
Renstar Medical Research
Rhode Island Mood & Memory Research Institute
Sahlgrenska Universitetssjukhuset, Mölndal Sjukhus
Saneikai Tsukazaki Hospital
Senior Adult Specialty Research
Seoul National University Bundang Hospital
Seoul National University Hospital
Severence Hospital, Yonsei University
Sharp Mesa Vista Hospital
Shinjuku Research Park Clinic
Skånes Universitetssjukhus
St. Joseph's HC- Parkwood Institute
Stedman Clinical Trials, LLC
Summit Research Network (Oregon) Inc.
Suncoast Neuroscience and Associates, Inc.
Synapse Saitama Neuropsychiatry Center
Synexus Clinical Research US, Inc.
Texas Neurology, PA
The Clinical Trial Center, LLC
The Memory Clinic
The National Hospital for Neurology & Neurosurgery
The Neurology Group, LLP
The Regents Of The University Of California
The University of Texas Health Science Center at San Antonio
Tokyo Medical University Hospital
Tokyo Metropolitan Geriatric Hospital
Toronto Memory Program (Neurology Research Inc.)
Torrance Clinical Research Institute, Inc.
Umberto I Pol. di Roma-Università di Roma La Sapienza
University of Alabama at Birmingham
University of Arizona
University of Kansas Medical Center Research Institute, Inc. - Master
University of Kentucky Medical Center
University of Michigan
University of Rochester
USF Suncoast Gerontology Center
Valley Medical Primary Care
Weill Cornell Medical College New York Presbyterian Hospital
West London Cognitive Disorders Treatment and Research Unit
Xenoscience Inc.
Yale University School Of Medicine

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Acknowledgements

BAN2401-201 CORE TEAM

Heather Bradley
Shobha Dhadda
Cindy Dobrinski
Gordon Espie
Robert Gordon
Marin Hsuan
June Kaplow
Akihiko Koyama
Robert Lai
Johan Luthman
Kiran Putti
Martin Rabe
Cheryl Ruburiano
Chad Swanson
Keiichiro Totsuka
Kate Tranotti
Jinping Wang
Yong Zhang

COLLABORATORS

Lars Lannfelt, BioArctic and Uppsala University

Vrije Universiteit Amsterdam

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

Communication 5

Q&A

Professor Jeffrey Cummings, MD, ScD
Cleveland Clinic

Chad J. Swanson, PhD
Senior Director, Clinical Research, Neurology Business Group
Eisai Inc.

Akihiko Koyama, PhD
Executive Director, Global Head of Translational Science
Eisai Inc.

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