Key Trial Design Aspects and Clinical Outcomes of the Lecanemab Phase 2 Trial and Open-Label Extension in Early Alzheimer's Disease

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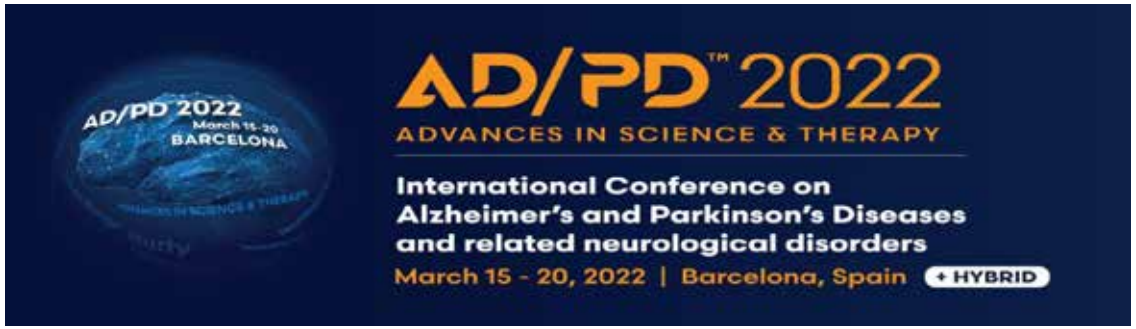
Abstract 2128 | 2022 AD PD Annual Meeting | March 15-20, 2022| Barcelona, Spain. HYBRID

Presenter Disclosures



	No, Nothing to disclose
X	Yes, please specify

Company / Name	Honoraria / Expense	Consulting / Advisory Board	Funded Research	Royalties / Patent	Stock Options	Ownership / Equity Position	Employee	Other (Please specify)
Alzheon, Biogen, Cortexyme, Roche-Genentech, Eisai, KeifeRx, Lilly, Qynapse, Synaptogenix, NeuroTherapia, T3D, Signant Health, Novo Nordisk		X						
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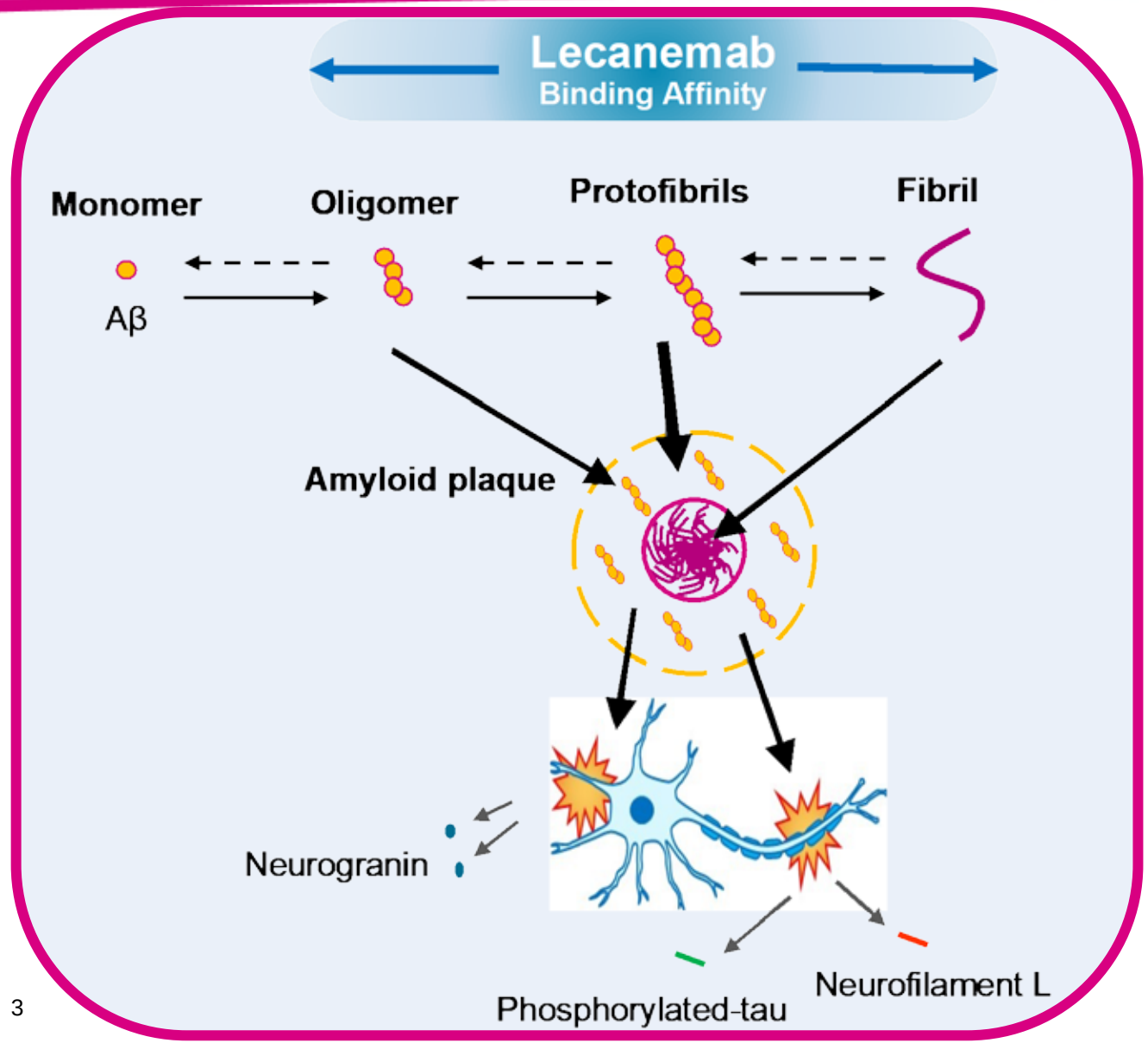
Lecanemab: Anti-Aβ Protofibril Monoclonal Antibody

Selectively Targets Aβ Protofibrils



- Humanized immunoglobulin G1 (IgG1) monoclonal antibody
- Selectively binds to soluble Aβ aggregate species
  - >1000-fold selectivity for protofibrils over Aβ monomers (low affinity for Aβ monomer[1])
  - Preferential activity for Aβ protofibrils over fibrils (>10x) [2-5]

Aβ, amyloid-beta.

1. Tucker S, et al. J Alzheimers Dis. 2015;43(2):575-88. 2. Lord A, et al. *Neurobiol Dis*. 2009;36:425–34. 3. Sehlin D, et al. *PLoS One*. 2012;7:e32014. 4. Sehlin D, et al. *Neurodegener Dis*. 2011;8:117–23. 5. Logovinsky V, et al. *Alzheimer's Research & Therapy*. 2016;8:14.

Lecanemab Study 201 in the Overall Development Program

Efficient, Rapid Development Program Despite Chronic and Slowly Progressing Disease

Study Design Questions and Considerations:

Questions to be Answered through study design in 2012

- Dose regimen and response
- Estimate of Treatment-effect size by best dose(s)
- Bayesian design allowed for max Sample size
- Duration of therapy required to show disease-modifying effect

Considerations for Design

- Shift toward Early AD (may allow larger effect size)
- Obtain strong clinical proof-of-concept
- Evaluate dose ranging effect and subgroups
- Account for study duration & magnitude of treatment effect
- Potential for early decision-making (12-mo) while preserving 18-mo 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
- FDA draft guidance[1] titled “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 AD,[4,5] and recently used for an approval in diabetes[6,7]

AD, Alzheimer’s disease; ADCOMS, Alzheimer’s Disease Composite Score.

1. FDA Guidance. Adaptive design for clinical trials of dugs and biologics. 2018. 2. Berry D. *Nat Rev Clin Oncol.* 2011;9(4):199-207. 3. Berry S et al. *Clin Trials.* 2010;7(2):121-135.
4. Lenz R et al. *Alzheimer Dis Assoc Dis*. 2015;29(3):192-199. 5. Finger E et al. *Alzheimers Res Ther*. 2018;10(1):102-110. 6. FDA Summary Review for Trulicity. 7. Skrivanek Z et al. *Diabetes Obes Metab.* 2014;16(8):748-756.

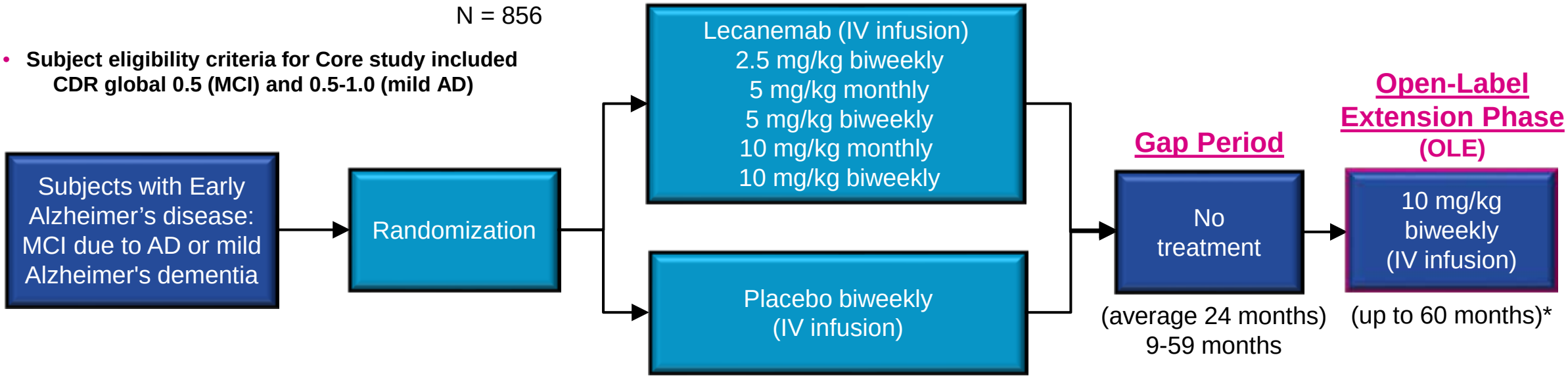
Lecanemab (BAN2401) Phase 2b Trial Design

A Global, Placebo-controlled, Double-blind, Parallel-group, Randomized Trial with Open-label Extension

Core Randomization Phase†

N = 856

- **Subject eligibility criteria for Core study included CDR global 0.5 (MCI) and 0.5-1.0 (mild AD)**



Core Primary Endpoint (Bayesian):
ADCOMS at 12 months

Select Key Secondary Endpoints:
Amyloid PET at 18 months
ADCOMS at 18 months
CDR-SB at 18 months
ADAS-cog at 18 months
Fluid biomarkers at 18 months

- **The 18-month, proof-of-concept study explored the dose response of lecanemab with the objective to establish the most effective (ED90) dose of lecanemab based on ADCOMS**

OLE Primary Endpoint:
Long-term Safety & Tolerability

Select Secondary/Exploratory Endpoints:
Amyloid PET
ADCOMS
CDR-SB
ADAS-cog
Fluid biomarkers

Aβ, amyloid-beta; AD, Alzheimer's disease; ADAS-cog, Alzheimer's Disease Assessment Scale-cognitive subscale; ADCOMS, Alzheimer's Disease Composite Score; CDR, clinical dementia rating; CDR-SB, Clinical Dementia Rating Scale sum of boxes; IV, intravenous; MCI, mild cognitive impairment; OLE, open label extension; PET, positron emission tomography.

*Any subject who completed study treatment (Visit 42 [Week 79] of the Core Study) and fulfilled the Extension Phase eligibility criteria had the option to participate in the Extension Phase. Subjects who previously completed the Core Study (through the Follow-Up Visit, Visit 43) at any time before implementation of the Extension Phase and/or fulfilled the Extension Phase eligibility criteria were eligible to participate. Any subject who had discontinued the Core Study but fulfilled the Extension Phase eligibility criteria were eligible to participate in the Extension Phase (subjects who discontinued due to ARIA were allowed to enroll if they were otherwise eligible). All subjects had a Follow-Up Visit 3 months after the last dose of study drug in the Core. Eisai Inc. Data on file. 2019. †Randomization assignment was determined by Bayesian Adaptive Design methodology.

Key Features of Bayesian Adaptive Study Design

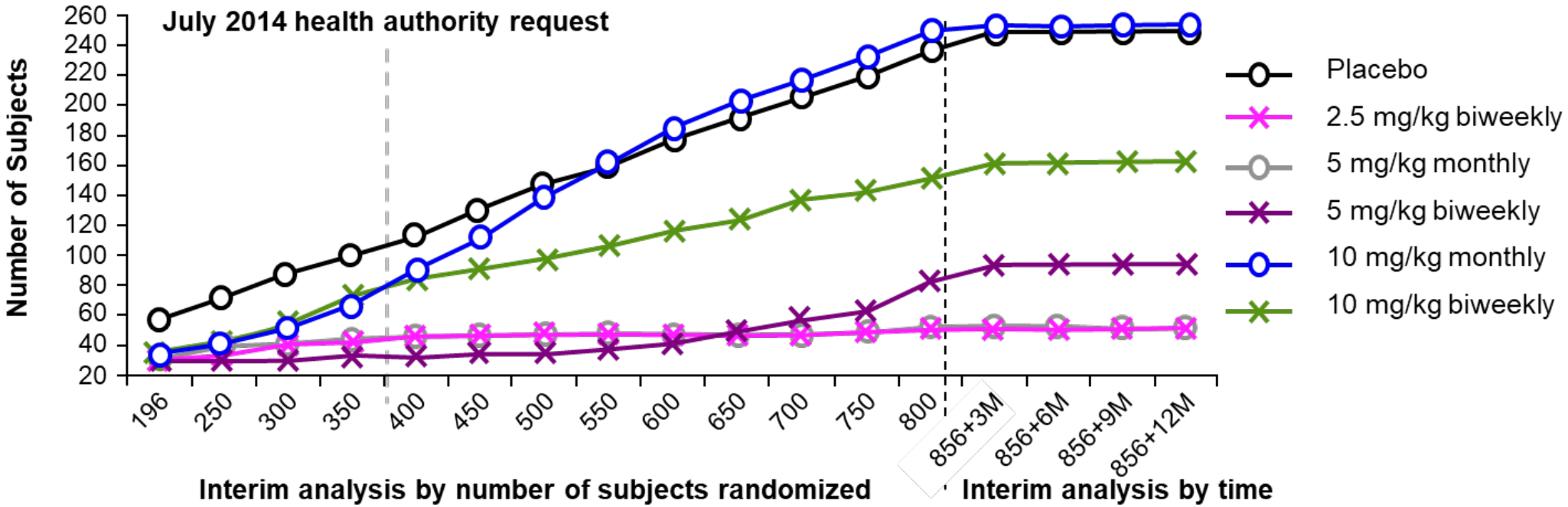
- Study 201 employed a Bayesian adaptive design with response adaptive randomization
  - Frequent blinded interim analyses assessed for early success or futility
  - Subject allocation probabilities were updated based on the predicted 12-month ADCOMS outcomes
- A computer algorithm assessed accumulating ADCOMS data to allocate more subjects to a dose or doses that were most likely to be the ED90 target dose
  - ED90 = the simplest treatment group that achieves at least 90% of the modeled maximum treatment effect
- The study design allowed for rapid decision making and the need to establish clinical proof-of-concept
  - The use of Bayesian methodology with a 12-month primary endpoint in an 18-month study allowed for:
    - Opportunity to move into phase 3 if an early success criterion was met
    - Study completion at 18 months if this condition was not met
- All randomized subjects were to complete the full 18 months of treatment
- 18-month results were analyzed with Bayesian and frequentist (conventional) statistics

ADCOMS, Alzheimer's Disease Composite Score, ED90, effective dose 90%.

Randomization Allocations by Treatment Group Per Protocol-Defined Interim Analyses

NUMBER OF SUBJECTS RANDOMIZED PER DOSE

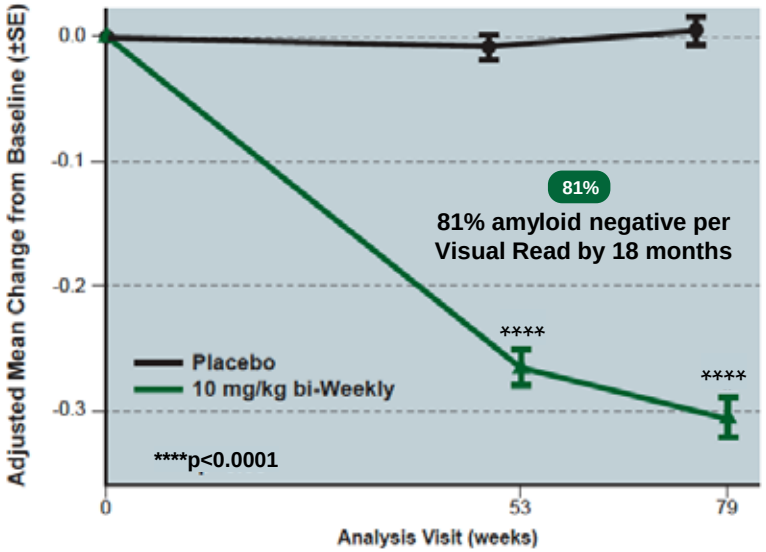
APOE4 STATUS	PLACEBO	2.5 mg/kg BIWEEKLY	5 mg/kg MONTHLY	5 mg/kg BIWEEKLY	10 mg/kg MONTHLY	10 mg/kg BIWEEKLY	TOTAL
All	**247**	52	51	92	**253**	**161**	**856**
+	**175**	38	40	84	**225**	**48**	**610**
-	**72**	14	11	8	**28**	**113**	**246**
					414 total pooled		



Lecanemab Cleared Amyloid Plaques and Slowed Cognitive Decline in Core Study

Significant Amyloid Reduction

Amyloid PET SUVr

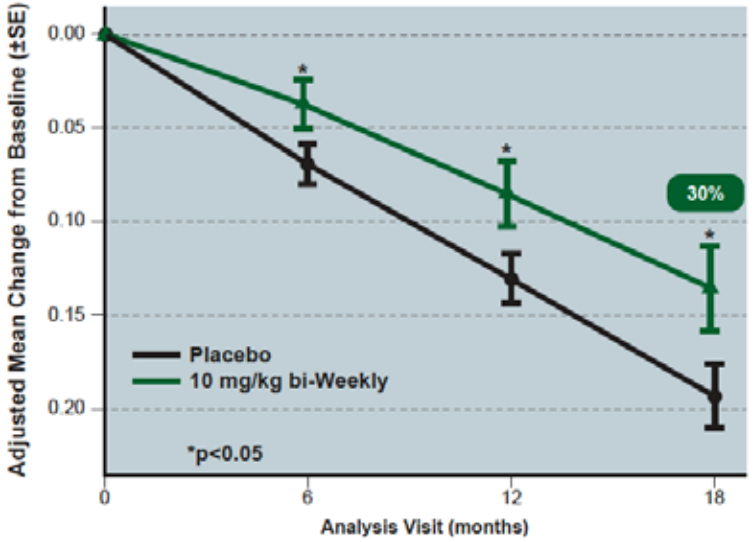


N	BL	12m	18m
Placebo	98	96	88
10BW	44	43	37

Slowing of Cognitive Decline

ADCOMS

Similar results for CDR-SB and ADAS-cog



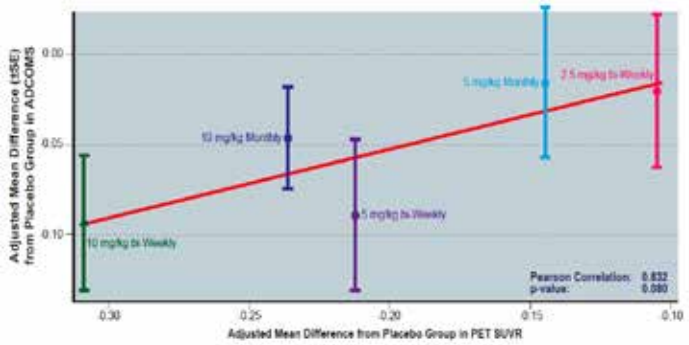
N	BL	6m	12m	18m
Placebo	238	216	187	160
10BW	152	130	93	79

Correlation

ADCOMS vs. PET SUVr

Population Correlation

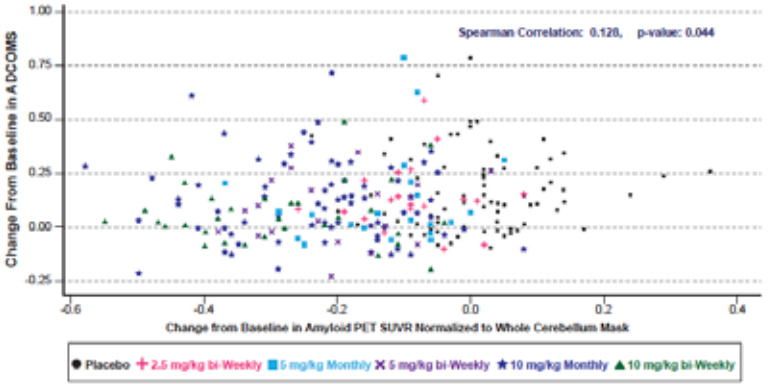
Corr. Coeff=0.832, p-value=0.080



ADCOMS vs. PET SUVr

Subject Level Correlation

Slope=0.128, p=0.044



OLE: rapid **reduction** in brain amyloid as early as 3 months - **43% conversion** to amyloid negative

Aβ, amyloid-beta; ADAS-cog, Alzheimer's Disease Assessment Scale-cognitive subscale; ADCOMS, Alzheimer's Disease Composite Score; BL, baseline; CDR-SB, Clinical Dementia Rating Scale sum of boxes; OLE, open-label extension; PET, positron emission tomography; SUVr, standardized uptake value ratio.

10BW = 10 mg/kg biweekly lecanemab. Each analysis population: All randomized subjects with the relevant endpoint at Core baseline and at least one post-baseline visit in Core Study. Adjusted mean was based on a mixed model for repeated measures (MMRM) with treatment group, visit, clinical subgroup, the presence or absence of ongoing AD treatment, APOE4 status, region, treatment group-by-visit interaction as factors, and baseline value as covariate. Y-axis was inverted for plasma Aβ42/40 Ratio. Increase in plasma Aβ42/40 Ratio reflects decrease in brain amyloid levels for this inverted figure.

Lecanemab ARIA-E Events:

Low Incidence Overall and by APOE Genotype

CORE: Multiple Doses; No titration

- ~10% ARIA-E on 10 mg/kg biweekly
- Incidence of ARIA-E is dose dependent & highest in ApoE4 carriers
- ~2% symptomatic ARIA-E rate on 10 mg/kg biweekly
- Most ARIA-E occurred ≤3 months; MRI findings resolved within 4-16 weeks
- Mostly (90%) mild to moderate in severity (radiographic)
  - 71% mild to moderate in severity in ApoE4 carriers

OLE: All 10 mg/kg biweekly; No titration

- 7.8 % ARIA-E (14/180) overall in OLE
- 4/45 (8.9%) core placebo subjects with ARIA-E
- ~2% symptomatic ARIA-E rate on highest dose
- Most ARIA-E occurred ≤3 months of treatment
- Mostly (70%, 10/14) mild to moderate in severity (radiographic)
  - 50% (2/4) mild to moderate in newly treated ApoE4 carriers

	CORE*						OLE	
		BAN2401					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 (%)	Newly treated Core Placebo (N=45) *(APOE4+=70%)*	All treated in OLE (N=180) *(APOE4+=69%)*
ARIA-E	2 (0.8)	1 (1.9)	1 (2.0)	3 (3.3)	25 (9.9)	16 (9.9)	4/45 (8.9%)	14/180 (7.8%)
APOE4+	2/174 (1.1%)	1/38 (2.6%)	1/40 (2.5%)	3/84 (3.6%)	23/225(10.2%)	7/49 (14.3%)	4/31 (12.9%)	13/125 (10.4%)
Homo	1/40 (2.5%)	0/5	1/12 (8.3%)	1/14 (7.1%)	11/60 (18.3%)	5/10 (50.0%)	1/4 (25.0%)	4/28 (14.3%)
Hetero	1/134 (0.7%)	1/33 (3.0%)	0/28	2/70 (2.9%)	12/165 (7.3%)	2/39 (5.1%)	3/27 (11.1%)	9/97 (9.3%)
APOE4-	0/71	0/14	0/11	0/8	2/28 (7.1%)	9/112 (8.0%)	0/14 (0%)	1/55 (1.8%)

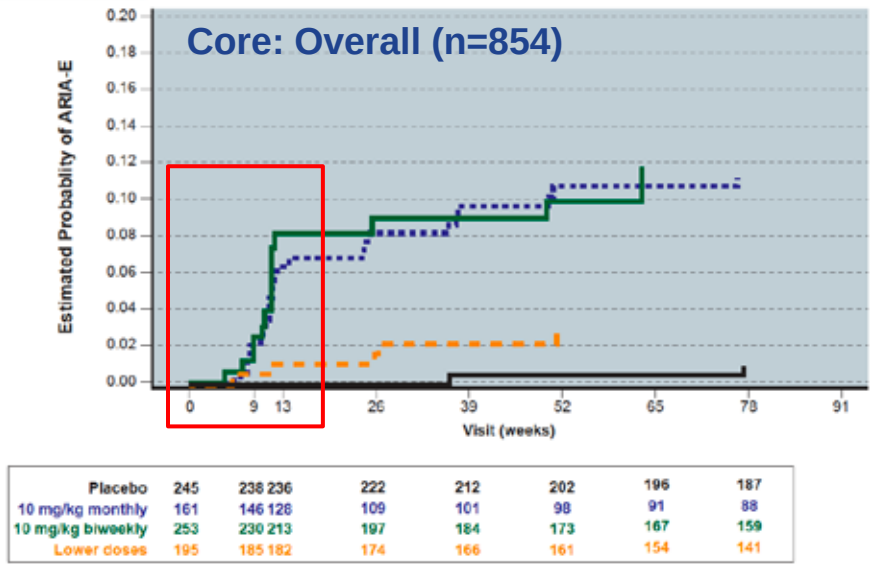
Note: **Core**: 1 hetero on 2.5B, 1 hetero on 10 M and 3 homo on 10 BW had symptomatic ARIA. **OLE**: 1 homo newly treated, 1 hetero & 1 ApoE4 non carrier had symptomatic ARIA

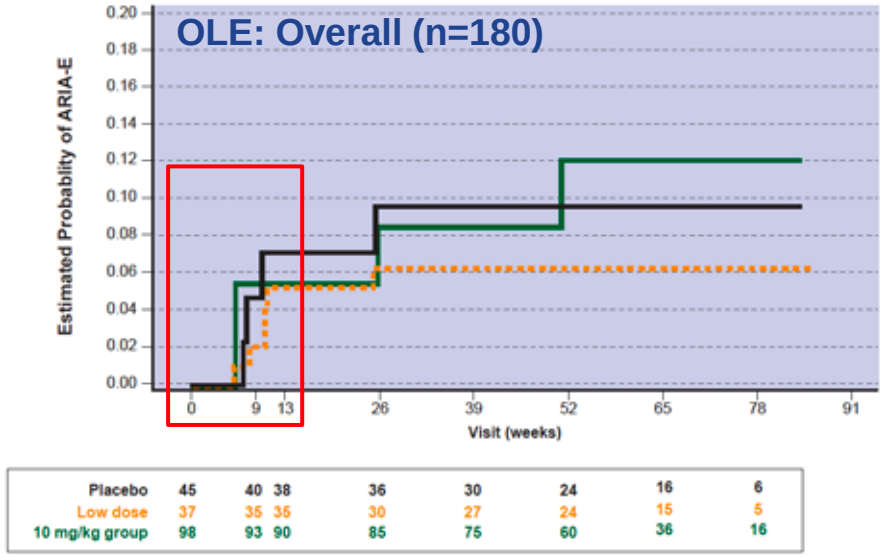
Reference: Swanson et al. (2021) Alzheimers Res Ther. & Swanson et al. (2021) CTAD2021. *APOE4+ percentages provided in Slide 7.

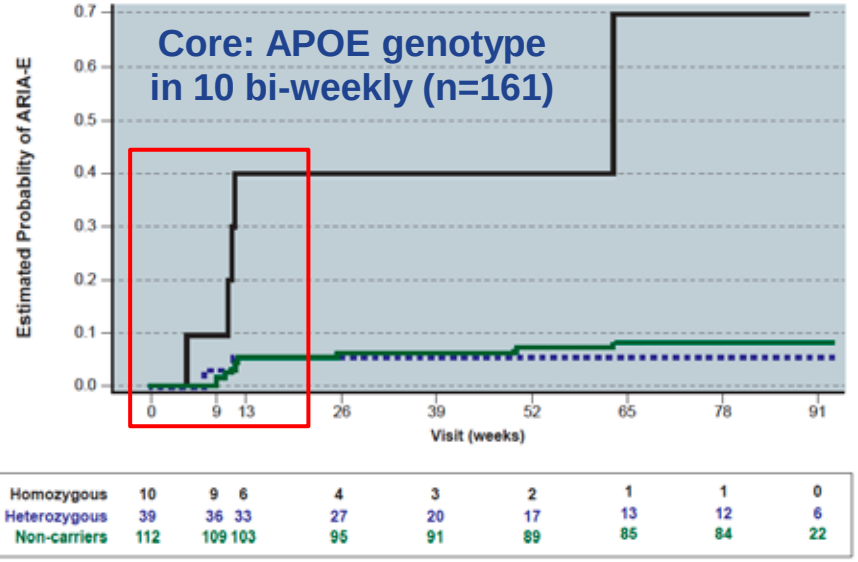
APOE, apolipoprotein E; ARIA-E, Amyloid-related imaging abnormality-edema; OLE, open-label extension.

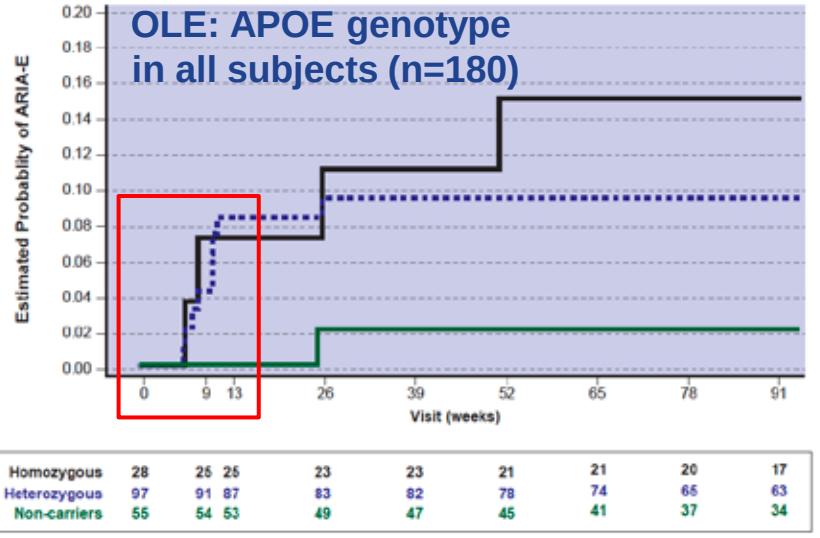
Timing of ARIA-E Events

Most ARIA-E Events Occur within First 3 Months









Kaplan-Meier estimate for ARIA-E:

~10% on 10 mg/kg biweekly in Core and OLE

APOE, apolipoprotein E; ARIA-E, Amyloid-related imaging abnormality-edema; OLE, open-label extension.

Lecanemab ARIA-E Events:

Severity Overall and by APOE Genotype for 10 mg/kg Biweekly

- 9.7% ARIA-E (20/206) overall (consistent with 9.9% in Core)
- ~2% (4/206) symptomatic ARIA-E rate on highest dose
- Most ARIA-E occurred within first 3 months of treatment
- MRI findings resolved within 4-16 weeks
- Mostly (80%, 16/20) mild to moderate in severity (radiographic) in overall
  - 64% (7/11) mild to moderate in severity (radiographic) in ApoE4 carriers

CORE 10 BW + OLE Newly Treated 10 BW (core placebo)

Category	Core 10 m/kg biweekly + Newly Treated core placebo (N=206=161+45)	Radiographic severity (mild/moderate / severe)	Total LEC exposure (subject-years)	Symptomatic - Clinical Severity (mild/moderate/ severe)
ARIA-E	20/206 (9.7%)	8 / 8 / 4	238.5	0/1/3
APOE4+	11/80 (13.8%)	3 / 4 / 4	79.4	0/1/3
Homo	6 /14 (42.9%)	1 / 2 / 3	10.5	0/0/3
Hetero	5/66 (7.6%)	2 / 2 / 1	68.9	0/1/0
APOE4-	9/126 (7.1%)	5 / 4 / 0	159.2	0/0/0

ApoE4+ are underrepresented in Core 10 mg/kg due to regulatory request and some early administrative terminations, however:

(1) Rates are consistent in OLE where all received 10 mg/kg

(2) KM estimates take into account administrative terminations in estimating rate

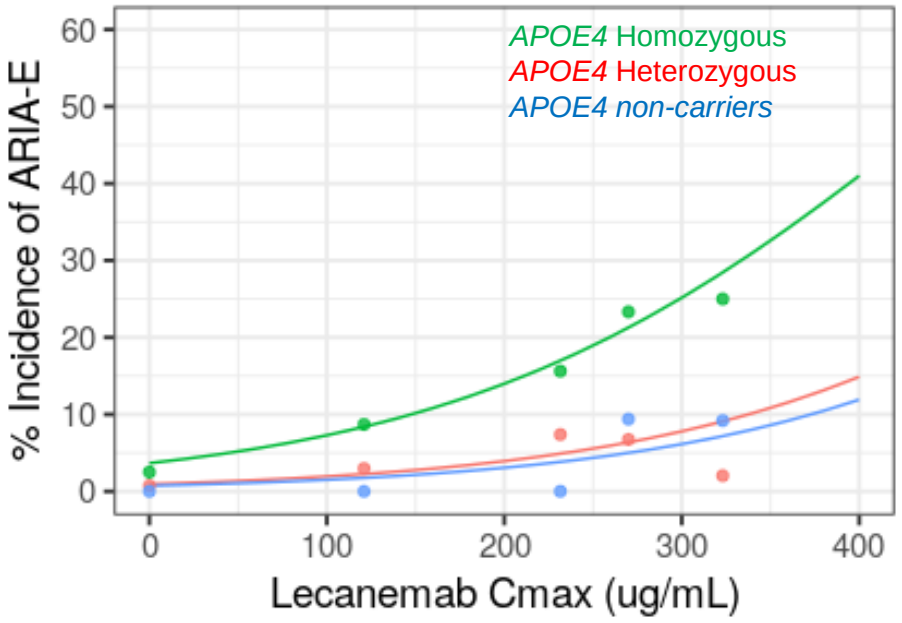
(3) DSMB reviews in Clarity AD and would require informing sponsor/FDA if greater risk

APOE, apolipoprotein E; ARIA-E, amyloid related imaging abnormalities – edema; BW, biweekly; DSMB, Data Monitoring Safety Board; FDA, Food & Drug Administration; KM, Kaplan-Meier; OLE, open-label extension.

ARIA-E Exposure-Response Model:

Effect of APOE4 genotype

Model Predicted and Observed ARIA-E vs. Cmax



Filled circles represent the CORE observed proportion of subject with ARIA-E for each Cmax quartile (1Q-4Q) and placebo, plotted at the median Cmax of each group. Solid line represents the model predicted line.

Observed ARIA-E is correlated by Cmax quartiles across all doses

- PK/PD **Exposure-ARIA-E** model developed from CORE *using data from all doses* and demonstrated that:
  - **ARIA-E is driven primarily by Cmax**
  - **APOE4 genotype is a significant covariate in the model**
- PK/PD model confirmed that incidence of ARIA-E is
  - higher and distinct in *APOE4* homozygous subjects
  - similar in *APOE4* heterozygous and *APOE4* noncarriers
- Model-predicted ARIA-E by Cmax in Core confirmed the observed ARIA-E in OLE

Model Predicted ARIA-E by Cmax in Core

Category	10 mg/kg Monthly (Cmax=239 ug/mL)	10 mg/kg Biweekly (Cmax=280 ug/mL)
APOE4+		
Homo	**17.7%**	**22.5%**
Hetero	**5.1%**	**6.8%**
APOE4-	**4.0%**	**5.4%**

Observed ARIA-E Incidence in OLE

Category	Newly Treated Core placebo* (N=45)
APOE4+	
Homo	1/4 (**25.0%**)
Hetero	3/27 (**11.1%**)
APOE4-	0/14 (**0%**)

APOE4, apolipoprotein E4; ARIA-E, amyloid related imaging abnormalities – edema; C_{max}, maximum serum concentration; OLE, open label extension.

* 10mg/kg bi-weekly

Lecanemab ARIA-H Events:

Overall and by APOE Genotype

	CORE						OLE	
		Lecanemab					Lecanemab	
	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 (%)	Newly Treated Core Placebo (N=45) n (%)	Overall (N=180) n (%)
ARIA-H	12 (4.9)	2 (3.8)	7 (13.7)	13 (14.1)	24 (9.5)	10 (6.2)	6 (13.3)	20 (11.1)
APOE4+	9/174 (5.2)	2/38 (5.3)	6/40 (15.0)	13/84 (15.5)	22/225 (9.8)	6/49 (12.2)	5/31 (16.1)	17/125 (13.6)
Homo	1/40 (2.5)	0/5 (0)	3/12 (25.0)	1/14 (7.1)	9/60 (15.0)	3/10 (30.0)	2/4 (50.0)	9/28 (32.1)
Hetero	8/134 (6.0)	2/33 (6.1)	3/28 (10.7)	12/70 (17.1)	13/165 (7.9)	3/39 (7.7)	3/27 (11.1)	8/97 (8.2)
APOE4-	3/71 (4.2)	0/14 (0)	1/11 (9.1)	0/8 (0)	2/28 (7.1)	4/112 (3.6)	1/14 (7.1)	3/55 (5.5)
ARIA-E & ARIA-H	1 (0.4)	0 (0)	1 (2.0)	0 (0)	11 (4.3)	6 (3.7)	1 (2.2)	6 (3.3)
APOE4+	1/174 (0.6)	0/38 (0)	1/40 (2.5)	0/84 (0)	10/225 (4.4)	4/49 (8.2)	1/31 (3.2)	5/125 (4.0)
Homo	0/40 (0)	0/5 (0)	1/12 (8.3)	0/14 (0)	5/60 (8.3)	3/10 (30.0)	1/4 (25.0)	3/28 (10.7)
Hetero	1/134 (0.7)	0/33 (0)	0/28 (0)	0/70 (0)	5/165 (3.0)	1/39 (2.6)	0/27 (0)	2/97 (2.1)
APOE4-	0/71 (0)	0/14 (0)	0/11 (0)	0/8 (0)	1/28 (3.6)	2/112 (1.8)	0/14 (0)	1/55 (1.8)

APOE4, apolipoprotein E4; ARIA-E, amyloid related imaging abnormalities – edema; ARIA-H, amyloid related imaging abnormalities - hemorrhage ; OLE, open label extension.

Lecanemab ARIA-E & ARIA-H Events:

Study Drug Action Taken in Study 201 OLE

	Overall	APOE4 homozygous	APOE4 heterozygous	APOE4 noncarriers
With ARIA-E and ARIA-H	6	3	2	1
Dosed through (ie, no study drug interruption)	2	1 (5MO)	1 (10MO)	0
With study drug interruption	4	2 (PBO, 5MO)	1 (5MO)	1 (10MO)

- In OLE, there are 6 subjects with treatment-emergent ARIA-E and ARIA-H
  - Two subjects with ARIA-E and ARIA-H with no study drug interruption (1 APOE4 homozygous, 1 APOE4 heterozygous)
  - Four subjects had ARIA-E and ARIA-H and study drug interruption (2 APOE4 homozygous, 1 APOE4 heterozygous, 1 APOE4 noncarrier

APOE4, apolipoprotein E4; ARIA-E, amyloid related imaging abnormalities – edema; ARIA-H, amyloid related imaging abnormalities - hemorrhage ; OLE, open label extension; PBO, placebo.

Overall Summary and Conclusions

The 18-month, proof-of-concept study explored the dose response of lecanemab with the objective to establish the most effective (ED90) dose of lecanemab based on ADCOMS

- A 12-month Bayesian primary endpoint was utilized to allow for the opportunity to accelerate the development program through the use of a Bayesian adaptive design
- Study was to complete the blinded 18-month treatment period regardless of the 12-month outcome.
- The Bayesian design identified 10 mg/kg biweekly as the ED90 dose.

Rapid and Thorough Amyloid Reduction Correlates with Clinical Benefit

- Lecanemab treatment can be initiated without titration
- Amyloid reduction achieved within 3 months of treatment and clinical efficacy within 6 months of treatment
- >40% amyloid negative (by visual read) as early as 3 months in OLE

Low Incidence of ARIA-E (<10%) and Symptomatic ARIA Rate (<2%) in Core and OLE

- Most ARIA-E occurred ≤3 months and most were mild/moderate; MRI findings resolved within 4-16 weeks
- Exposure response modelling showed observed ARIA-E is correlated by Cmax quartiles across all doses

These data are hypothesis generating and will be further evaluated in Clarity AD

ADCOMS, Alzheimer's Disease Composite Score; APOE4, apolipoprotein E4; ARIA-E, amyloid related imaging abnormalities – edema; C_{max}, maximum serum concentration; OLE, open label extension.

Acknowledgments

We thank the participants, their families and study partners, and the sites and staff participating in this study for their significant contributions

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