Update on Lecanemab Clinical Development Including New Subcutaneous (SC) Formulation

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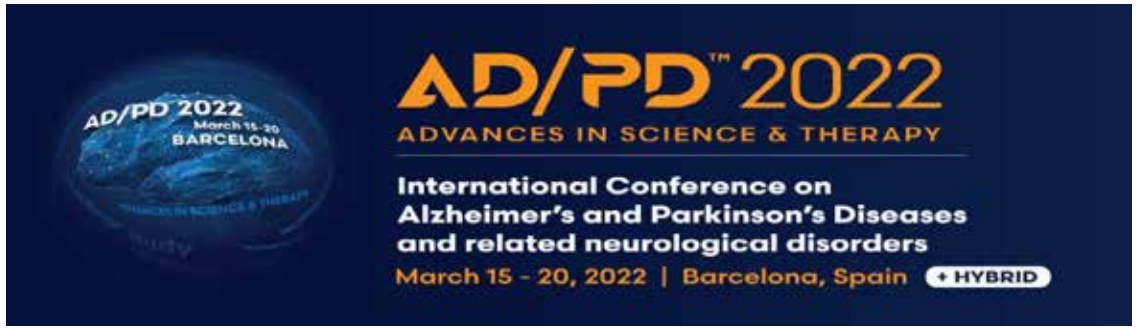
Presenter Disclosures



	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)
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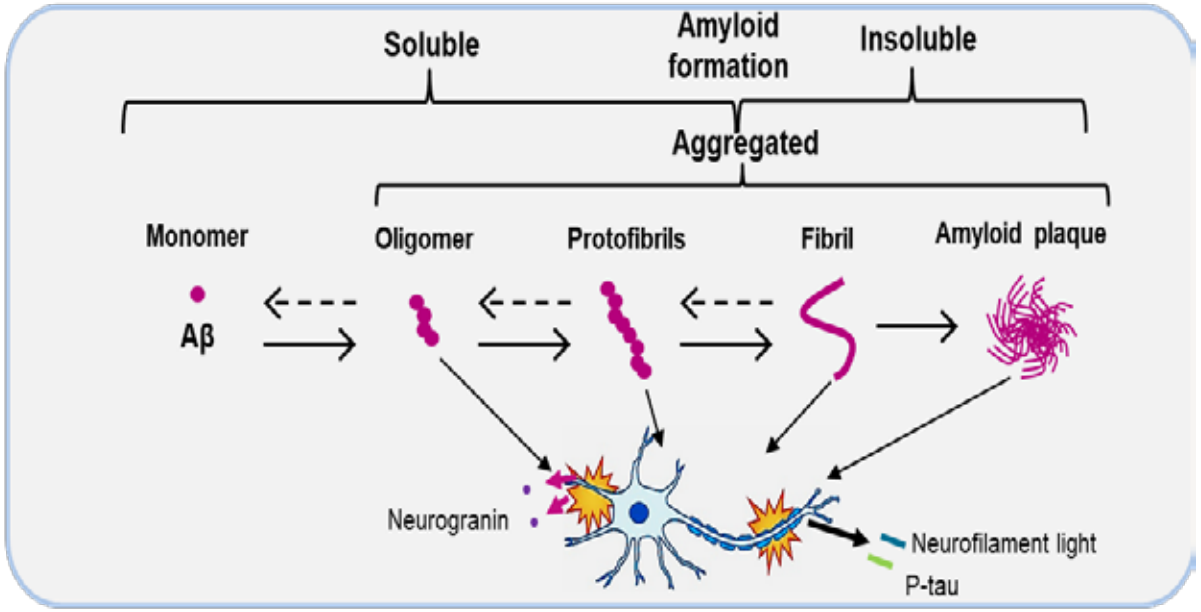
Objectives

- **Update on the clinical development of lecanemab**
  - **Phase 2b OLE study of lecanemab in early AD – dosing substudy**
  - **Phase 3 study of lecanemab in early AD (Clarity AD)**
  - **Phase 3 study of lecanemab in preclinical AD (AHEAD 3-45)**
  - **Lecanemab as backbone anti-amyloid therapy for anti-tau combination in DIAN-TU**
- **Rationale and clinical development for SC lecanemab**

AD, Alzheimer's disease; OLE, open-label extension; SC, subcutaneous.

Lecanemab Preferentially Binds Large Soluble Aβ Aggregates

- 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]
- Placebo-controlled, randomized phase 2 study (N=856)[6]
  - Reduction in brain amyloid accompanied by a consistent reduction of clinical decline across several clinical and biomarker endpoints was demonstrated
  - Well-tolerated with 9.9% ARIA-E at 10 mg/kg IV biweekly



Aβ, amyloid-beta; ARIA-E, amyloid related imaging abnormalities - edema; IV, intravenous; p-tau, phosphorylated tau.

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. 6. Swanson et al. Alzheimers Res Ther. 2021;13(1):80.

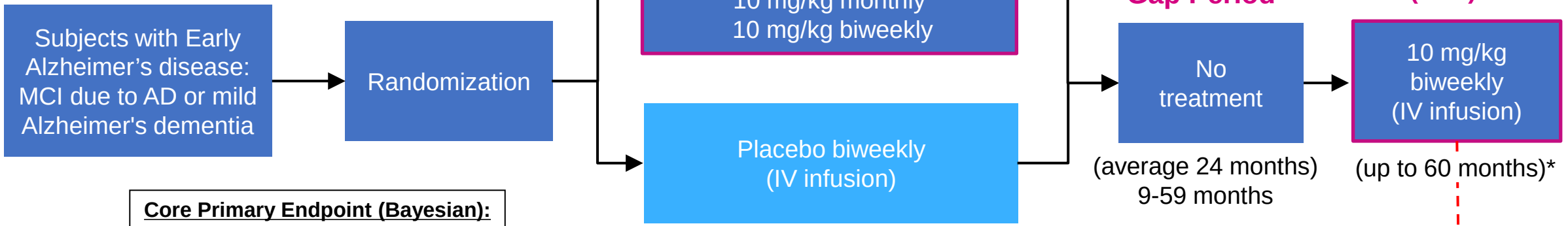
Lecanemab Phase 2b

Dosing Substudy in OLE

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

OLE Primary Endpoint:
Long-term Safety & Tolerability

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

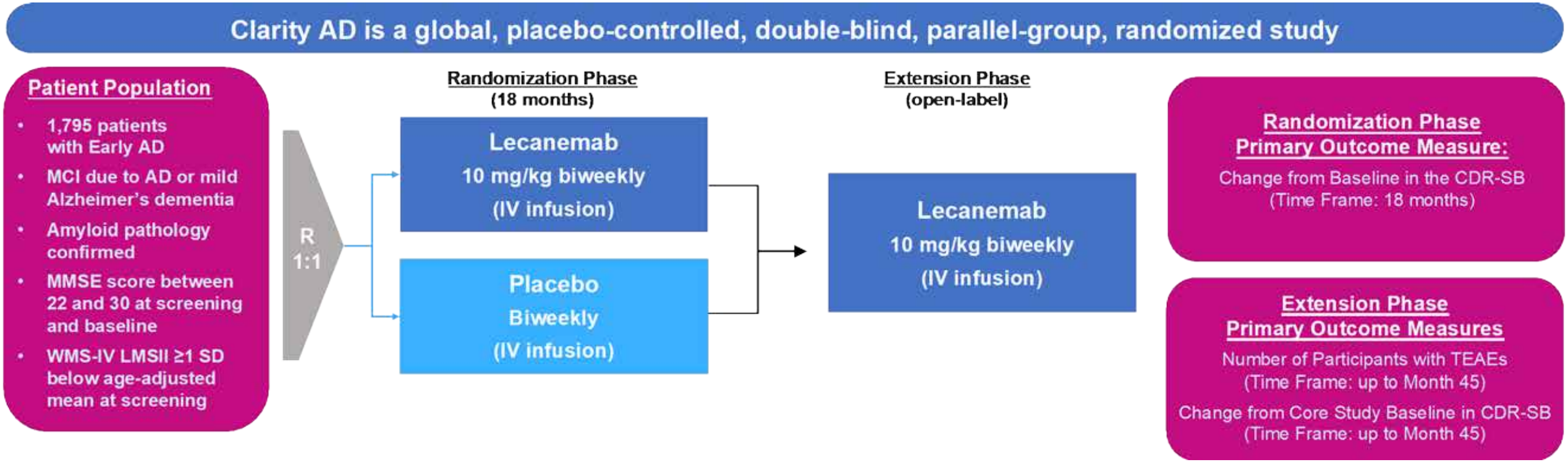
OLE Dosing Substudy:
Plasma Ab42/40
Plasma p-tau181
Amyloid PET

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; p-tau, phosphorylated tau; q2wk, every 2 weeks; q4wk, every 4 weeks.

*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. All subjects not continuing into the Extension Phase had a Follow-Up Visit 3 months after the last dose of study drug in the Randomization Phase.

Eisai Inc. Data on file. 2019. [†]Randomization assignment was determined by Bayesian Adaptive Design methodology.

Clarity AD Study Design



Randomization will be stratified according to

- Clinical subgroup (MCI due to AD or mild AD dementia)
- Presence or absence of ongoing approved AD treatment (eg, acetylcholinesterase inhibitors, memantine, or both)
- ApoE4 status (ie, carriers or non-carriers)
- Geographical region

3 optional longitudinal sub-studies

- Amyloid burden (amyloid PET)
- Brain tau pathology (tau PET)
- CSF biomarkers of neurodegeneration

AD, Alzheimer's disease; ApoE4, apolipoprotein E4; CDR-SB, Clinical Dementia Rating-sum of boxes; CSF, cerebrospinal fluid; IV, intravenous; MCI, mild cognitive impairment; MMSE, Mini-Mental State Exam; PET, positron emission tomography; SD, standard deviation; TEAEs, treatment emergent adverse events; WMS-IV LMSII, Wechsler Memory Scale IV-Logical Memory (subscale) II.

Phase 3 Study Optimally Designed to Confirm Phase 2b Results

	Study 201 (Phase 2b)	Clarity AD (Phase 3)
Study Design	**Placebo-Controlled, Double-Blind, Bayesian Adaptive Randomization Design and Dose Regimen-finding Study with OLE**	**Global, Placebo-Controlled, Double-blind, Randomized Trial with OLE**
Study Population	**MCI due to AD or mild AD dementia (NIA-AA criteria, CDR 0.5-1)** • Confirmed amyloid pathology (amyloid PET or CSF) • Memory impairment (WMS-IV LMSII ≥1 SD below age-adjusted mean) • MMSE 22-30 **SELECTED EXCLUSIONS** • Neurological condition that may be contributing to cognitive impairment beyond that caused by AD • Medical conditions which are not adequately controlled, could affect safety or the study assessments	
Treatment	**DOUBLE BLIND PHASE (18-month treatment)** • Lecanemab 2.5, 5, or 10 mg/kg IV q2wk • Lecanemab 5 or 10 mg/kg IV q4wk • Placebo	**DOUBLE BLIND PHASE (18-month treatment)** • Lecanemab 10 mg/kg IV q2wk • Placebo
	OPEN LABEL EXTENSION • Lecanemab 10 mg/kg IV q2wk • Planning to incorporate: (1) Biomarker-guided transition to less frequent maintenance dosing	**OPEN LABEL EXTENSION** • Lecanemab 10 mg/kg IV q2wk • Planning to incorporate: (1) SC dosing; and (2) Biomarker-guided maintenance dosing

AD, Alzheimer's disease; CDR, clinical dementia rating; CSF, cerebrospinal fluid; IV, intravenous; MCI, mild cognitive impairment; MMSE, Mini-Mental State Exam; NIA-AA, National Institute on Aging and Alzheimer's Association; OLE, open label extension; PET, positron emission tomography; q2wk, every 2 weeks; q4wk, every 4 weeks; SC, subcutaneous; SD, standard deviation; WMS-IV LMSII, Wechsler Memory Scale IV-Logical Memory (subscale) II.

Phase 3 Study Optimally Designed to Confirm Phase 2b Results

	Study 201 (Phase 2b)	Clarity AD (Phase 3)
Primary Outcome	**ADCOMS at 12 months for LEC10BW versus placebo:** • 64% & 98% probability of super-superiority & superior • 30% less decline(frequentist: p=0.027) • Effects sustained in GAP period off-drug prior to OLE	**CDR-SB at 18 months** (Global scale for cognitive and function)
Secondary Outcomes	• ADCOMS at 18 months: 30% less decline, p=0.034 • ADAS-cog14 at 18 months: 47% less decline, p=0.017 • CDR-SB at 18 months: 26% less decline, p=0.125	• Cognitive: ADAS-cog14 • Functional: ADCS-ADL-MCI • Global: ADCOMS, modified iADRS
Biomarker Outcomes	• Amyloid PET: Dose & time dependent reduction of amyloid as early as 3 months. • >80% amyloid negative at 18 months. • Reduction of CSF p-tau • Dose & time dependent changes in Ab42/40 ratio & p-tau • Effects sustained in GAP period off-drug prior to OLE	• Imaging: amyloid PET, tau PET, volumetric MRI • Blood and CSF, including: Aβ[1-42], neurogranin, NFL, total-tau, and p-tau
Safety	• TEAE & SAE: Similar incidence to placebo • ARIA-E: 9.9% for LEC10BW; 14.3% in APOE4+ • Infusion reactions: 19.9% LEC10BW, most mild-mod	• AE, SAE, labs, EKG, VS, C-SSRS, safety MRI • AEs of special interest – ARIA-E, ARIA-H, infusion related reactions
Sample Sizes	• 854 randomized • In U.S., 3.1% Black, 5.4% Hispanic	• >90% power to detect >0.37 treatment difference in CDR-SB at 18 months • 1,795 randomized; In U.S., 4.5% Black, 22.5% Hispanic

Ab, amyloid beta; ADAS-cog14, 14-item Alzheimer's Disease Assessment Scale-cognitive subscale; ADCOMS, Alzheimer's Disease Composite Score; ADCS-ADL-MCI, Alzheimer's Disease Cooperative Study – Activities of Daily Living Scale – mild cognitive impairment; AE, adverse event; APOE4+, apolipoprotein E4 positive; ARIA-E, amyloid related imaging abnormalities – edema; ARIA-H, amyloid related imaging abnormalities – hemosiderin; CDR-SB, Clinical Dementia Rating Scale sum of boxes; CSF, cerebrospinal fluid; C-SSRS, Columbia-Suicide Severity Rating Scale; EKG, electrocardiogram; iADRS, Integrated Alzheimer's Disease (AD) Rating Scale; LEC10BW, lecanemab 10mg/kg biweekly; MRI, magnetic resonance imaging; OLE, open label extension; PET, positron emission tomography; p-tau, phosphorylated tau; q2wk, every 2 weeks; q4wk, every 4 weeks; SAE, serious adverse event; TEAE, treatment emergent adverse event; U.S., United States.

Clarity AD Baseline Characteristics

Characteristic	Combined Total N=1795	United States N=948
Age, median (range), years	72 (50, 90)	73(50,90)
Age Group, n (%)		
<65 years	353 (19.7)	158 (16.7)
≥65 to <80	1203 (67.0)	637 (67.2)
≥80	239 (13.3)	153 (16.1)
Female , n (%)	938 (52.3)	487 (51.4)
Race, n (%)		
Asian	303 (16.9)	7 (<1)
Black	47 (2.6)	43 (4.5)
Caucasian	1381 (76.9)	896 (94.5)
Native American	2 (<1)	1 (<1)
Native Hawaiian or Other Pacific Islander	1 (<1)	1 (<1)
Other	33 (1.8)	0
Missing	28 (1.6)	0
Ethnicity, n (%)		
Hispanic or Latino	232 (12.9)	213 (22.5)
Not Hispanic or Latino	1527 (85.1)	734 (77.4)
Missing	36 (2.0)	1 (<1)
Region, n (%)		
North America	1072 (59.7)	948 (100)
Europe	429 (23.9)	0
Asia-Pacific	294 (16.4)	0

data cutoff of May 3, 2021

Comparison of Clarity AD and Phase 2 Populations

	Clarity AD Total N=1795	Lecanemab Phase 2 Study Total N=854
Patient Characteristic		
Age, median (range), years	72 (50, 90)	72 (50, 90)
Age ≥65, %	80	80
Female, %	52	50
Caucasian, %	77	90
MCI due to AD, %	62	64
ApoE4 carriers,* %	69	71
Clinical Endpoints		
CDR-SB, mean (SD)	3.2 (1.3)	3.0 (1.4)
ADCOMS, mean (SD)	0.4 (0.1)	0.4 (0.2)
ADAS-Cog, mean (SD)	25.3 (7.3)	22.2 (7.4)
MMSE, mean (SD)	25.6 (2.2)	25.6 (2.4)
Global CDR, mean (SD)	0.6 (0.2)	0.6 (0.2)

*by laboratory.
data cutoff of May 3, 2021

AD, Alzheimer's disease; ADAS-cog: Alzheimer's Disease Assessment Scale–cognitive subscale; ADCOMS: Alzheimer's Disease Composite Score; ApoE4, apolioprotein E4; CDR, clinical dementia rating; CDR-SB, Clinical Dementia Rating-sum of boxes; MCI, mild cognitive impairment; MMSE, Mini-Mental State Exam; SD, standard deviation.

AHEAD 3-45 Study Design:

Dosing Regimens Tailored to Baseline Amyloid PET Levels and Normal Cognition

A45 – Elevated amyloid (>40 centiloids) aimed at preventing cognitive decline

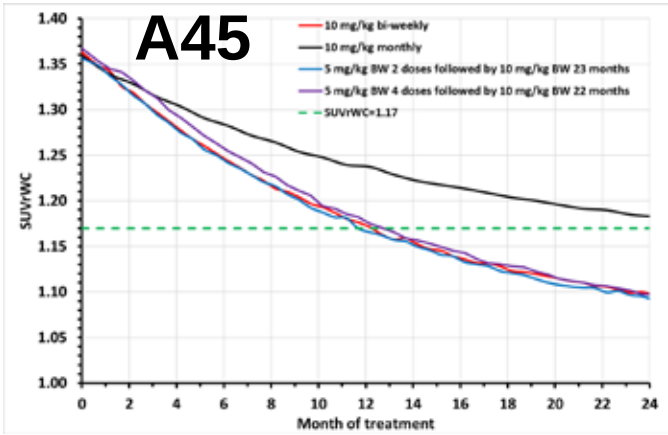
- 4-year phase 3 trial (n=500/arm)
- 5 mg/kg Q2W titration, 10 mg/kg Q2W induction, then 10 mg/kg Q4W maintenance
- Cognitive primary outcome (PACC-5)
- Amyloid and Tau PET key secondary
- Additional cognitive, participant reported, plasma and CSF biomarker outcomes

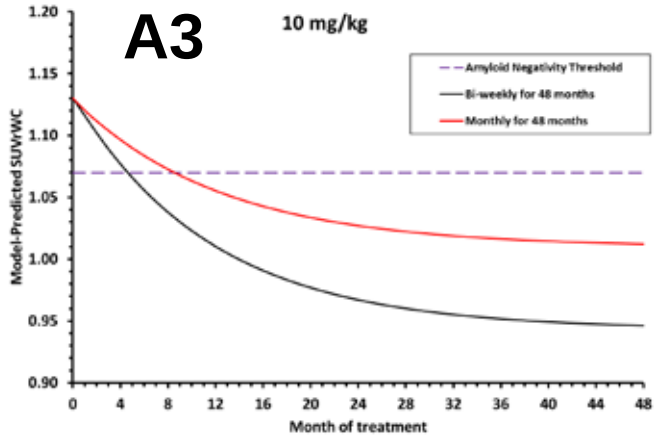
A3 – Intermediate amyloid (20-40 centiloids) aimed at slowing Aβ accumulation

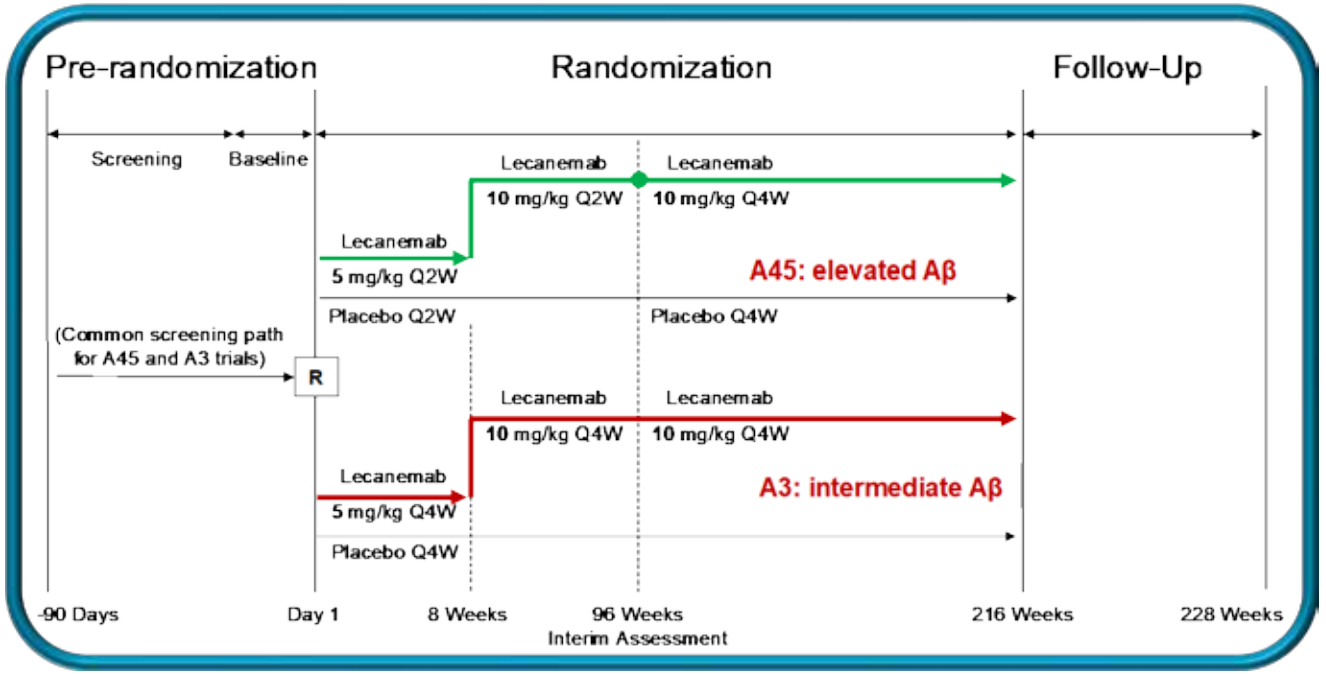
- 4-year phase 2 trial (n=200/arm)
- 5 mg/kg Q4W titration, 10 mg/kg Q4W treatment
- Amyloid PET primary outcome
- Tau PET key secondary
- Cognition exploratory (PACC-5 and C3)
- Additional cognitive, participant reported, plasma and CSF biomarker outcomes

Study Conduct

- Plasma pre-screening to enrich for subjects with intermediate and elevated amyloid
- About 100 sites world-wide planned, 99 activated in US, Japan, UK and Australia
- First participant randomized on September 17, 2020, in US
- >2500 screened. 261 enrolled (A45: 176. A3: 85)







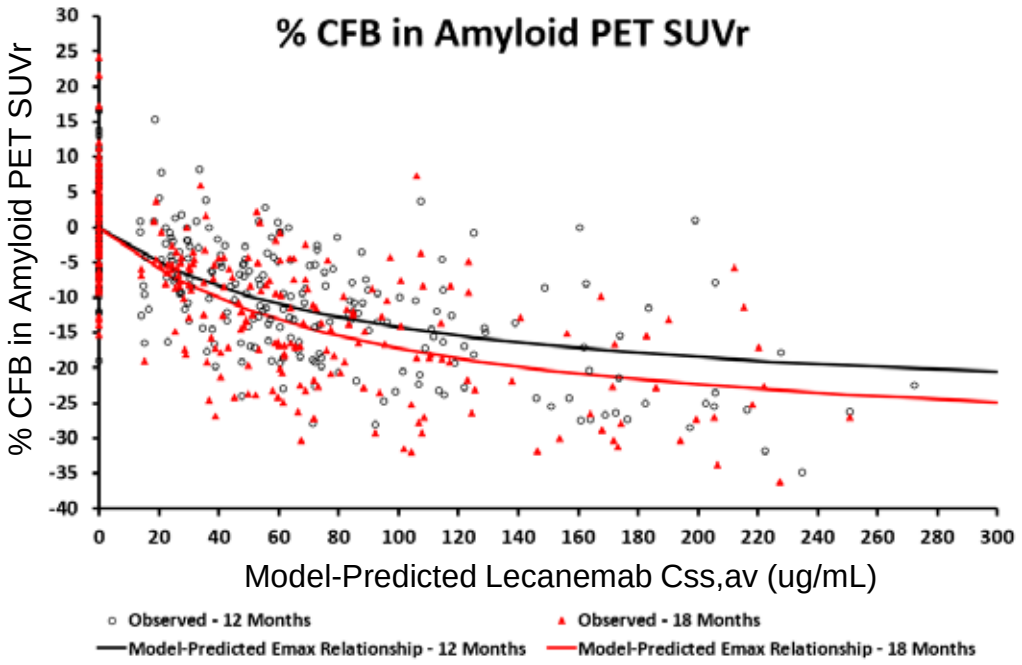
Ab, amyloid beta; BW, biweekly; C3, Computerized Cognitive Composite; CSF, cerebrospinal fluid; PACC-5, preclinical Alzheimer's cognitive composite 5; PET, positron emission tomography; Q2W, every 2 weeks; Q4W, every 4 weeks; SUVrWC, standardized uptake value ratio whole cerebellum; UK, United Kingdom; US, United States.

Lecanemab SC Formulation: PK/PD Modeling

Exposure (C_{ave}) predicts amyloid reduction and clinical effect while C_{max} predicts ARIA-E

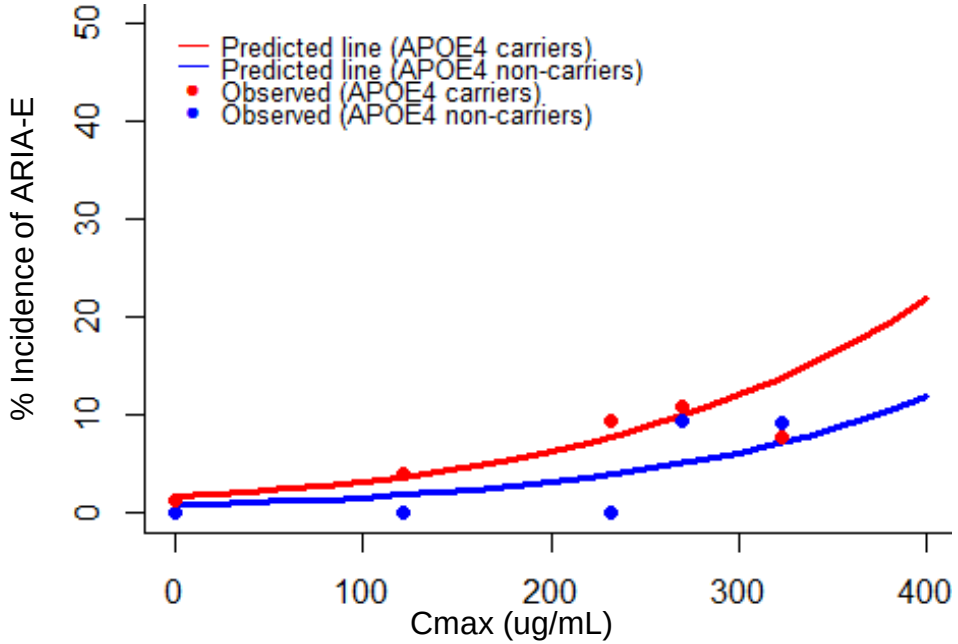
Exposure-Response Modeling of Phase 2 Lecanemab Data

C_{ave} is correlated with PET SUVr



Higher C_{ave} is correlated with greater amyloid reduction (example shown) and clinical effect

C_{max} is correlated with incidence of ARIA-E



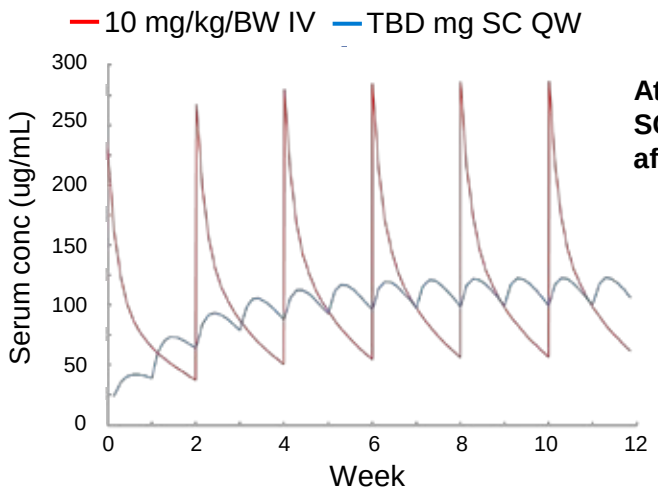
Lower C_{max} is correlated with lower incidence of ARIA-E

ApoE4, apolioprotein E4; ARIA-E, amyloid related imaging abnormality-edema; C_{ave}, average concentration; CFB, change from baseline; C_{max}, maximum serum concentration; Css, steady state concentration; PET, positron emission tomography; PD, pharmacodynamic; PK, pharmacokinetic; SC, subcutaneous; SUVr, standardized uptake value ratio.

Lecanemab SC Formulation: Dose Selection

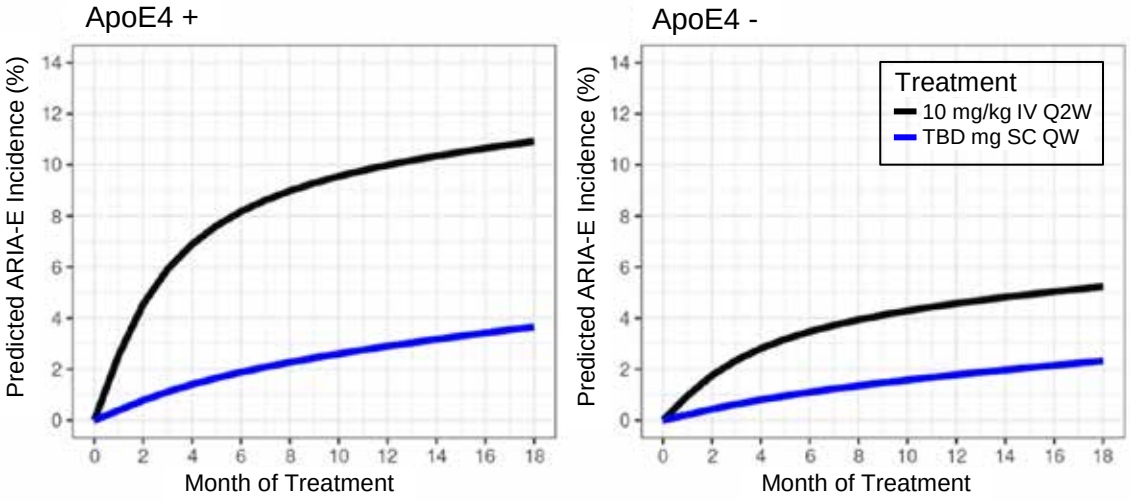
SC vs. IV: Similar C_{ave} (comparable efficacy and PD effect) with lower C_{max} (lower ARIA-E) for SC

Predicted PK



At similar exposure (C_{ave}), SC has lower C_{max} than IV after each administration.

Predicted Incidence of ARIA-E



Exposure comparability is based on C_{ave}

SC results in lower C_{max} at comparable C_{ave}

Dose	C_{ave} (ug/mL)	C_{max} (ug/mL)	C_{min} (ug/mL)
10 mg/kg IV biweekly	115	286	57
TBD mg SC weekly	114	123	100

ARIA-E Incidence	ApoE+	ApoE-
10 mg/kg IV Q2W	10.9	5.2
TBD mg SC QW	3.7	2.3

Goal: Target SC C_{ave} to be equivalent to 10 mg/kg biweekly IV

Outcome: Comparable SC efficacy with lower predicted incidence of ARIA-E due to lower C_{max} with SC

Lower C_{max} is expected to have lower ARIA-E rate

ApoE4, apolioprotein E4; ARIA-E, amyloid related imaging abnormality-edema; BW, biweekly; C_{ave}, average concentration; C_{max}, maximum concentration; IV, intravenous; PD, pharmacodynamic; PK, pharmacokinetic; QW, weekly; SC, subcutaneous.

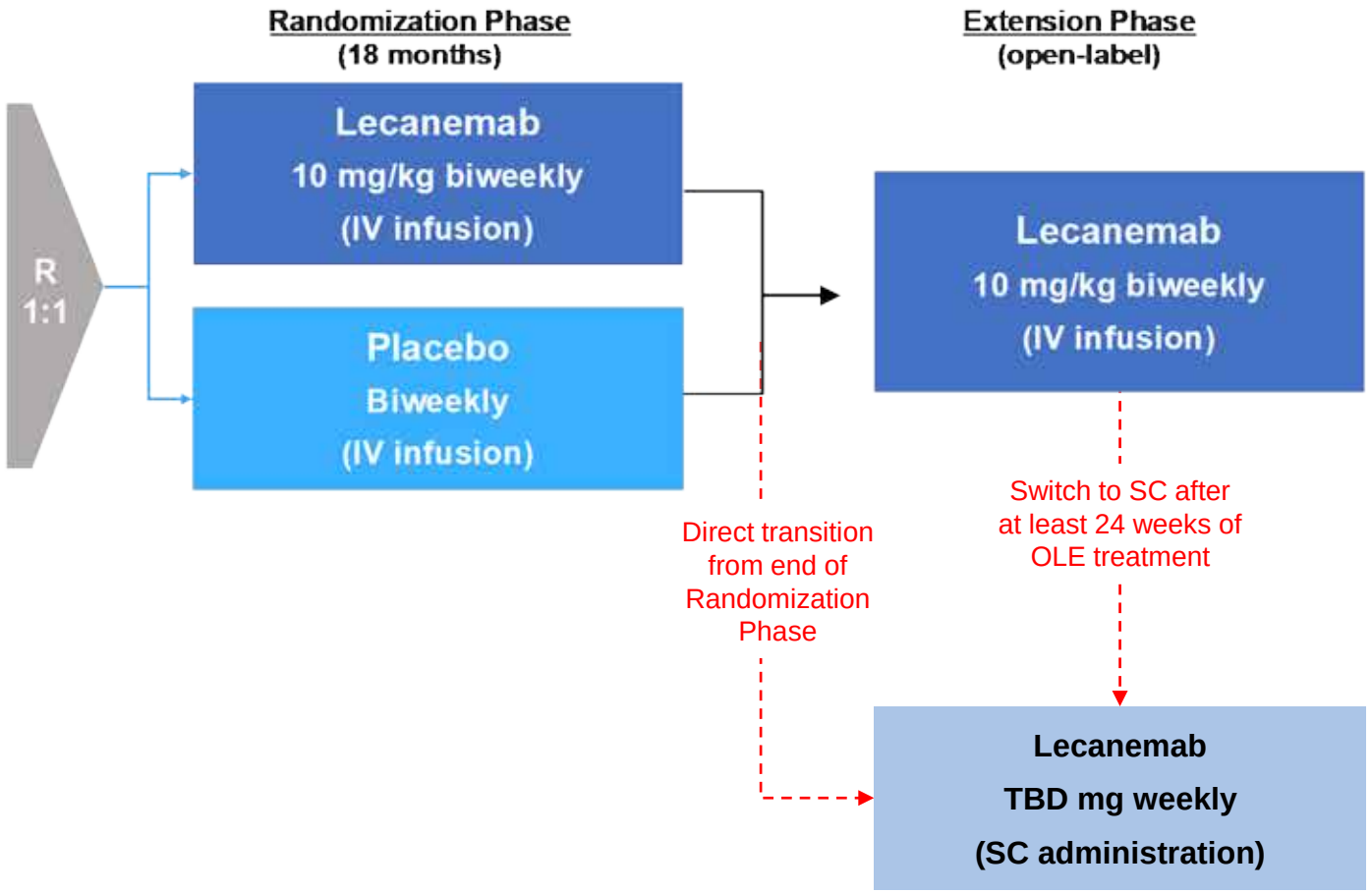
Clarity AD Study Design

SC Substudy

Clarity AD is a global, placebo-controlled, double-blind, parallel-group, randomized study

Patient Population

- 1,795 patients with Early AD
- MCI due to AD or mild Alzheimer's dementia
- Amyloid pathology confirmed
- MMSE score between 22 and 30 at screening and baseline
- WMS-IV LMSII ≥1 SD below age-adjusted mean at screening



Randomization Phase Primary Outcome Measure:

Change from Baseline in the CDR-SB (Time Frame: 18 months)

Extension Phase Primary Outcome Measures

Number of Participants with TEAEs (Time Frame: up to Month 45)

Change from Core Study Baseline in CDR-SB (Time Frame: up to Month 45)

SC Substudy Primary Outcome Measures

Safety

Pharmacokinetics

AD, Alzheimer's disease; CDR-SB, Clinical Dementia Rating-sum of boxes; CSF, cerebrospinal fluid; IV, intravenous; MCI, mild cognitive impairment; MMSE, Mini-Mental State Exam; OLE, open-label extension; SC, subcutaneous; SD, standard deviation; TEAEs, treatment emergent adverse events; WMS-IV LMSII, Wechsler Memory Scale IV-Logical Memory (subscale) II.

Summary: Clinical Development

- **The lecanemab phase 2b proof-of-concept study provided a robust framework to optimally design the confirmatory phase 3 Study Clarity AD and support dosing for lecanemab in AHEAD 3-45 Study and DIAN-TU-001 Study**
- **Clarity AD is intended to verify the hypotheses generated from the phase 2b Core study and OLE**
  - Lecanemab 10 mg/kg IV biweekly, without titration, is the optimal dose for amyloid clearance, downstream biomarker effects, and clinical efficacy
  - Amyloid clearance correlates with clinical benefit
  - Potential for disease modification (determined by biomarkers and delayed-start design in OLE)
  - Potential of plasma biomarkers to monitor for lecanemab treatment effects
  - Low incidence of ARIA-E (<10%) and Symptomatic ARIA Rate (<2%) in the phase 2b Core and OLE

AD, Alzheimer's disease; ARIA-E, amyloid-related imaging abnormality-edema; IV, intravenous; OLE, open-label extension.

Summary: Subcutaneous Formulation

- **Lecanemab SC formulation is intended to be patient friendly and provide greater access to treatment**
  - Replace biweekly IV infusion with weekly SC administration with comparable efficacy
  - Administered at home by patient or caregiver via an auto-injector
  - More rapid administration than IV (<15 second SC injection versus ~1h infusion)
  - No requirement for IV access, infusion center, or healthcare professional to administer doses
  - Potential for reduced incidence of ARIA-E relative to IV

ARIA-E, amyloid-related imaging abnormality-edema; IV, intravenous; OLE, open-label extension; SC, subcutaneous.

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