A Biogen Perspective on Drug Development for Neurological Diseases: The Example of Alzheimer's Disease

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EVP, Research and Development

Biogen, Inc.

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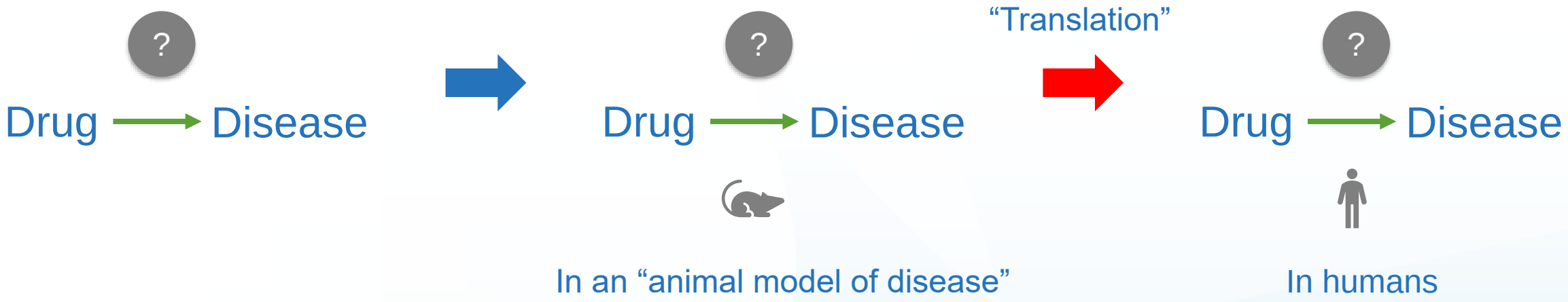
Legal disclaimer

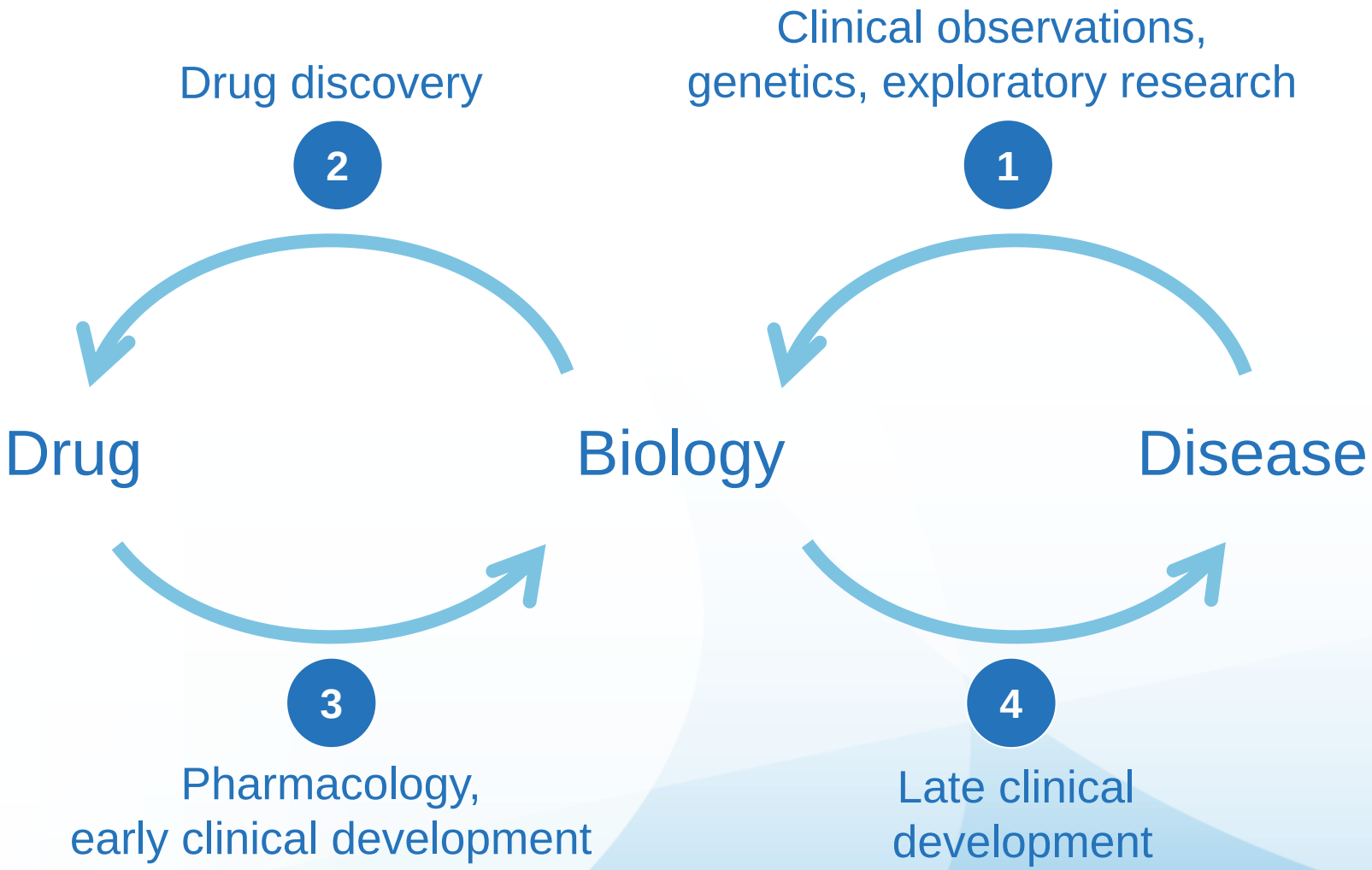
- Aducanumab is an investigational compound and is not yet approved in any country
- Biogen licensed the worldwide rights to aducanumab from Neurimmune Holding AG in 2007 and is responsible for its development and commercialization
- As of October 22, 2017, Biogen and Eisai are collaborating on the development and commercialization of aducanumab globally

There may have been over-reliance on the predictability of animal models in the drug development process

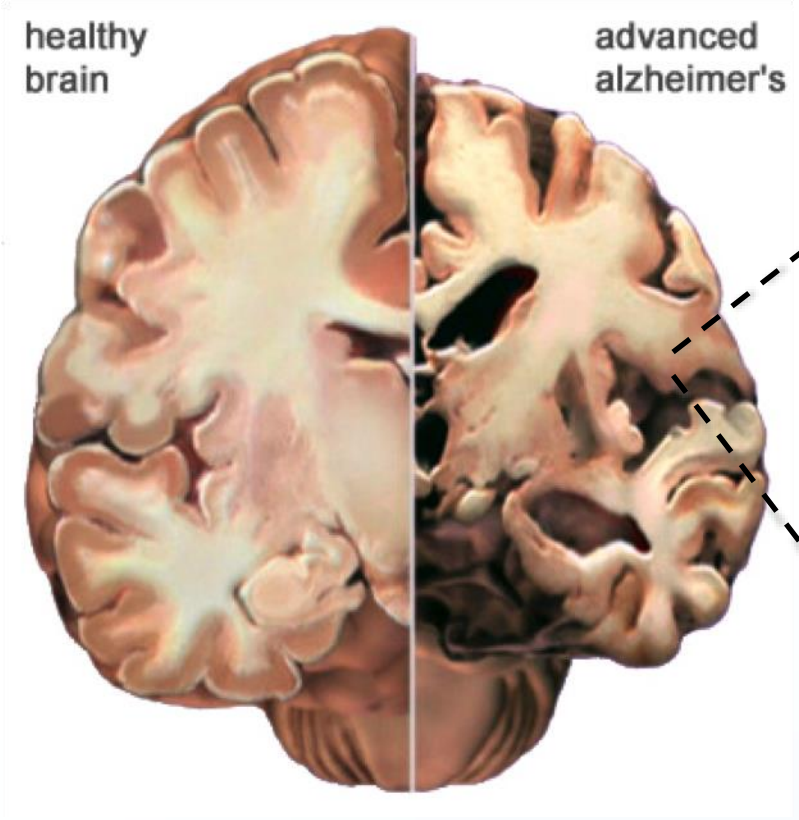


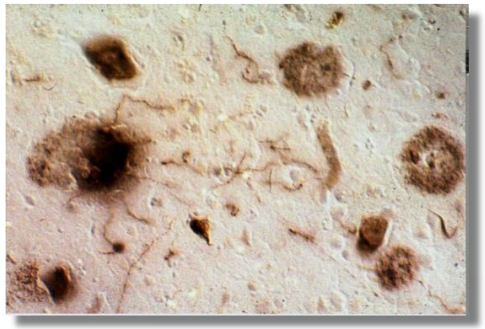
This may be a better approach for "symptomatic therapies" than for drugs that alter the natural history of disease, i.e., "disease-modifying therapies"

A “human biology” approach to developing drugs for neurological disease



AD Pathology





Amyloid Plaques (Aβ)

Neuro-fibrillary Tangles (p-tau)

The Human Genetic Basis of the Amyloid Hypothesis

Familial Alzheimer's disease

- Trisomy 21 (Down's syndrome)—increases Aβ42[1] •
- APP missense mutation—increases Aβ deposition[2,3] •
- PSEN1, PSEN2 (catalytic subunit of Ɣ-secretase)—increases Aβ42/Aβ40 ratio[4-6] •

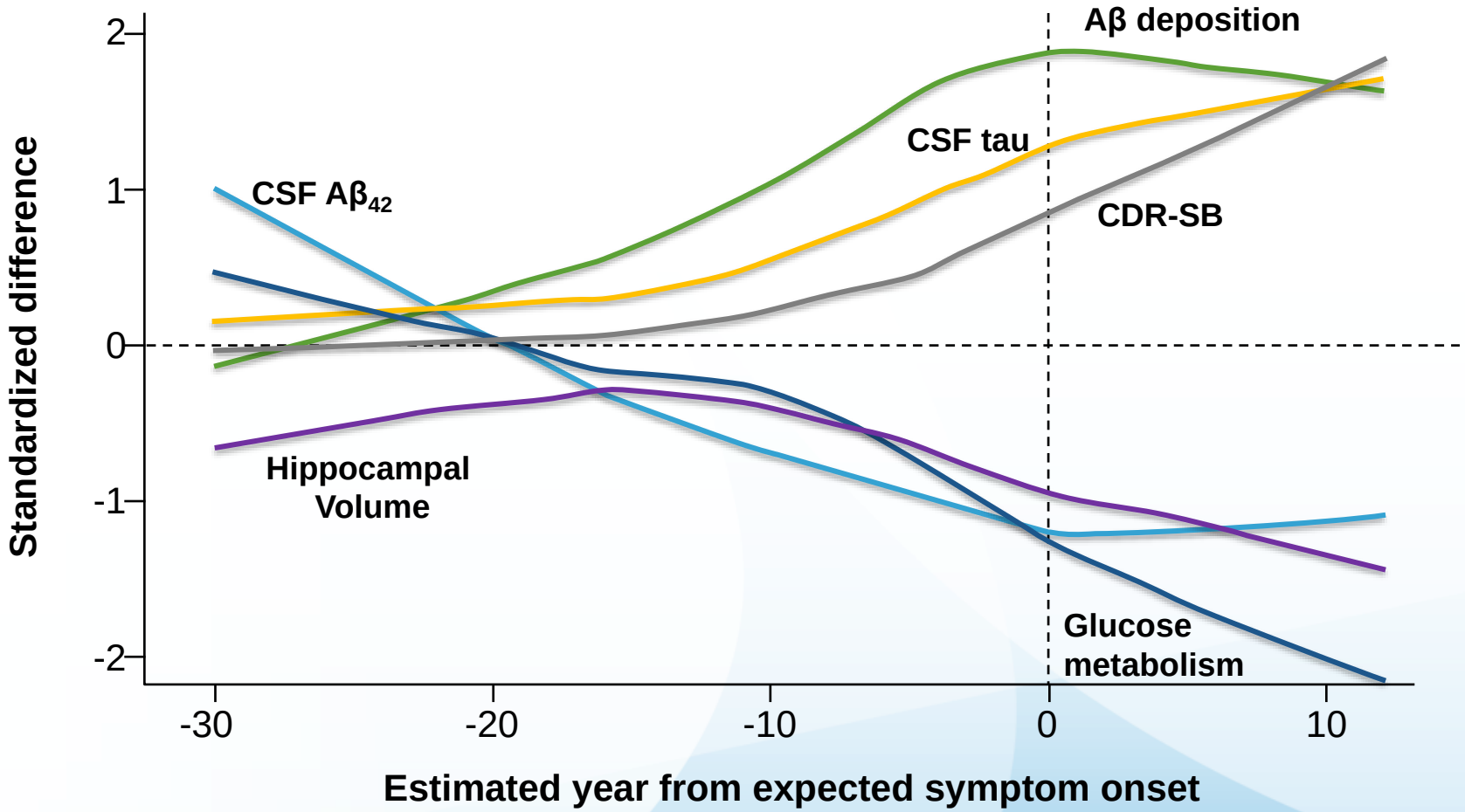
Sporadic Alzheimer's disease

- ApoE4—decreases Aβ clearance[7,8] •
- A673T mutation in APP—reduces cleavage of APP into Aβ42 by β-secretase[9] •

• Increases risk of AD • Decreases risk of AD

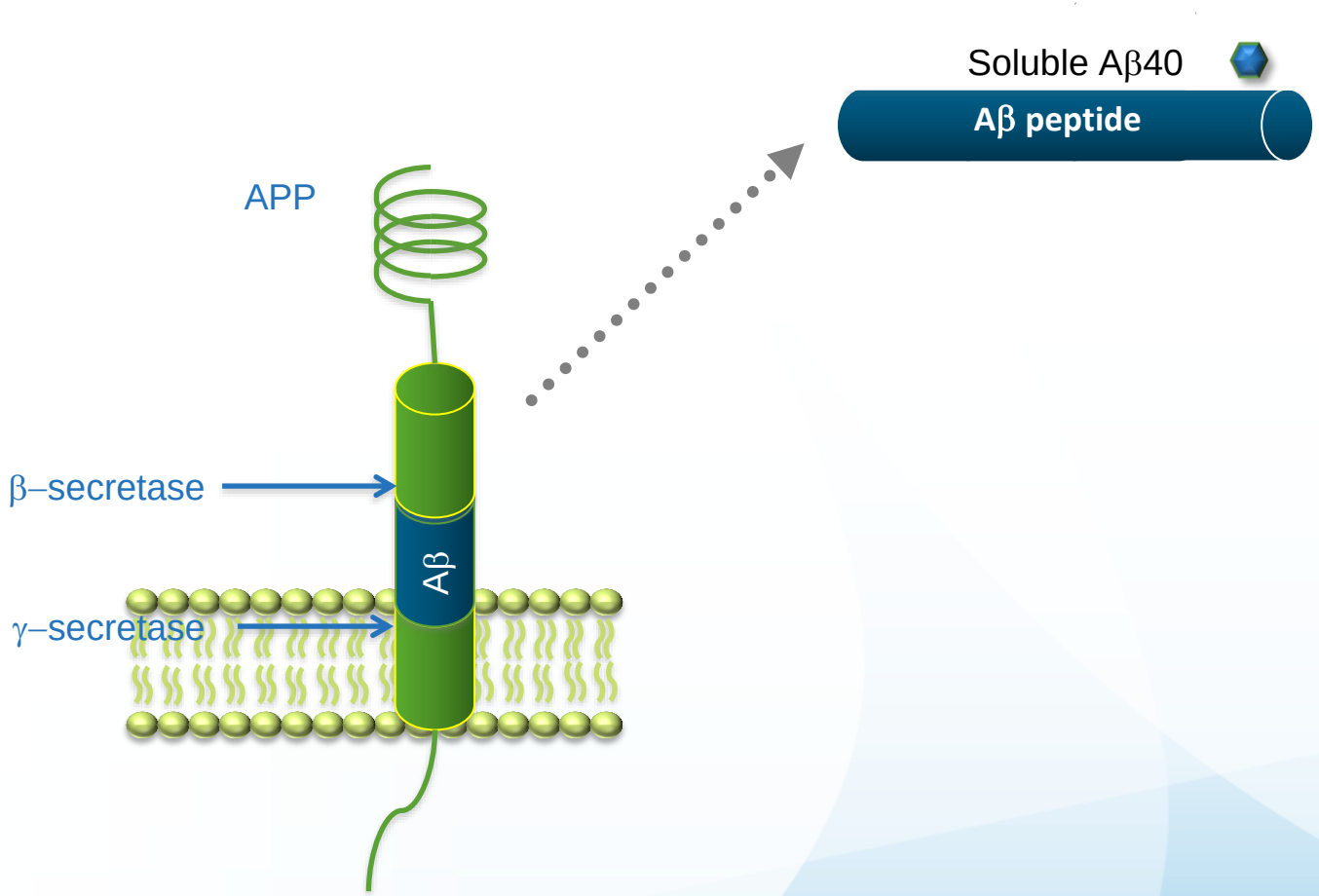
1. Tokuda T, et al. *Ann Neurol*. 1997;41:271-273; 2. Games D, et al. *Nature*. 1995;373:523-527; 3. Sturchler-Pierrat C, et al. *Proc Natl Acad Sci*. 1997;94:13287-13292; 4. Sherrington R, et al. *Nature*. 1995;375:754-760; 5. Rogaev E, et al. *Nature*. 1995; 376;775-778; 6. Scheuner D, et al. *Nat Med*. 1996;2:864-70; 7. Deane R, et al. *J Clin Invest*. 2008;118:4002-4013; 8. Castellano JM, et al. *Sci Transl Med*. 2011;3:89ra57; 9. Jonsson T, et al. Nature. 2012;488:96-99.

Clinical and biomarker changes in dominantly inherited Alzheimer's disease

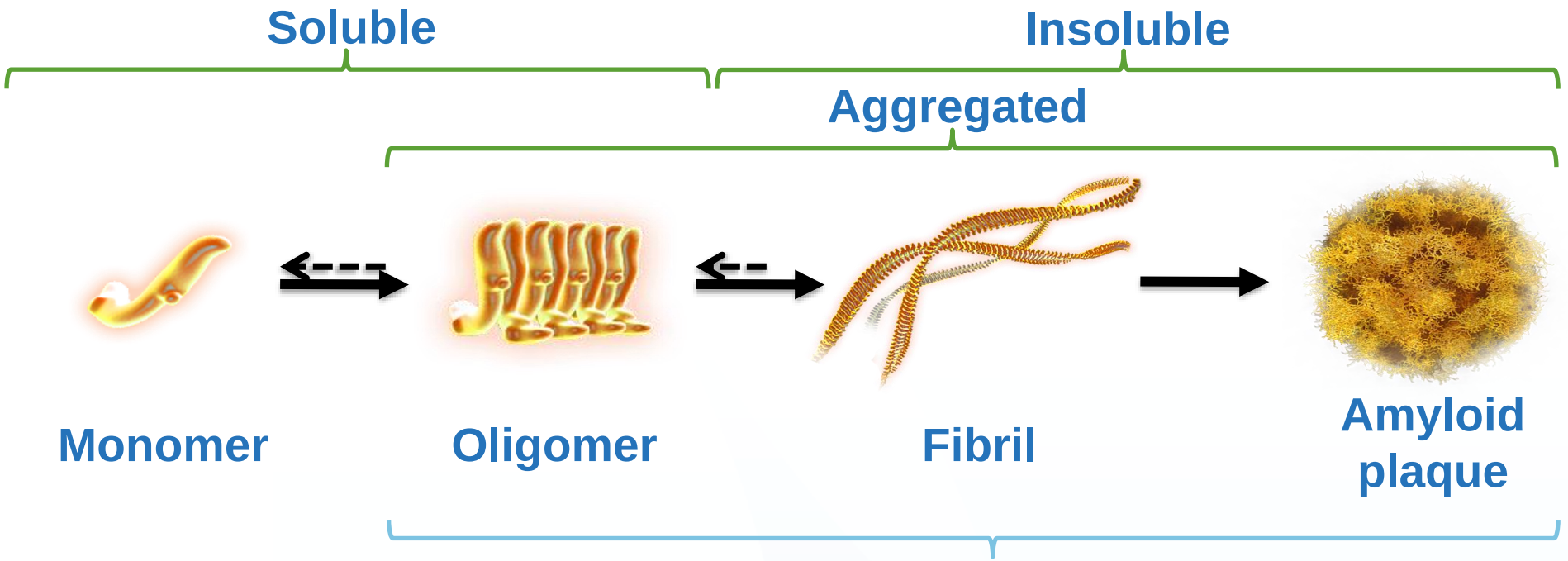


Bateman et al. *N Engl J Med.* 2012;367:795-804.
Aβ, amyloid beta; CDR-SB, Clinical Dementia Rating Scale – Sum of Boxes; CSF, cerebrospinal fluid.

Aβ40 and 42 are peptides cleaved from Amyloid Precursor Protein on the cell surface



Aβ40 and 42 are prone to aggregation



Altered neuronal and synaptic morphology[2,3]

Structural and functional disruption of neuronal networks[3-6]

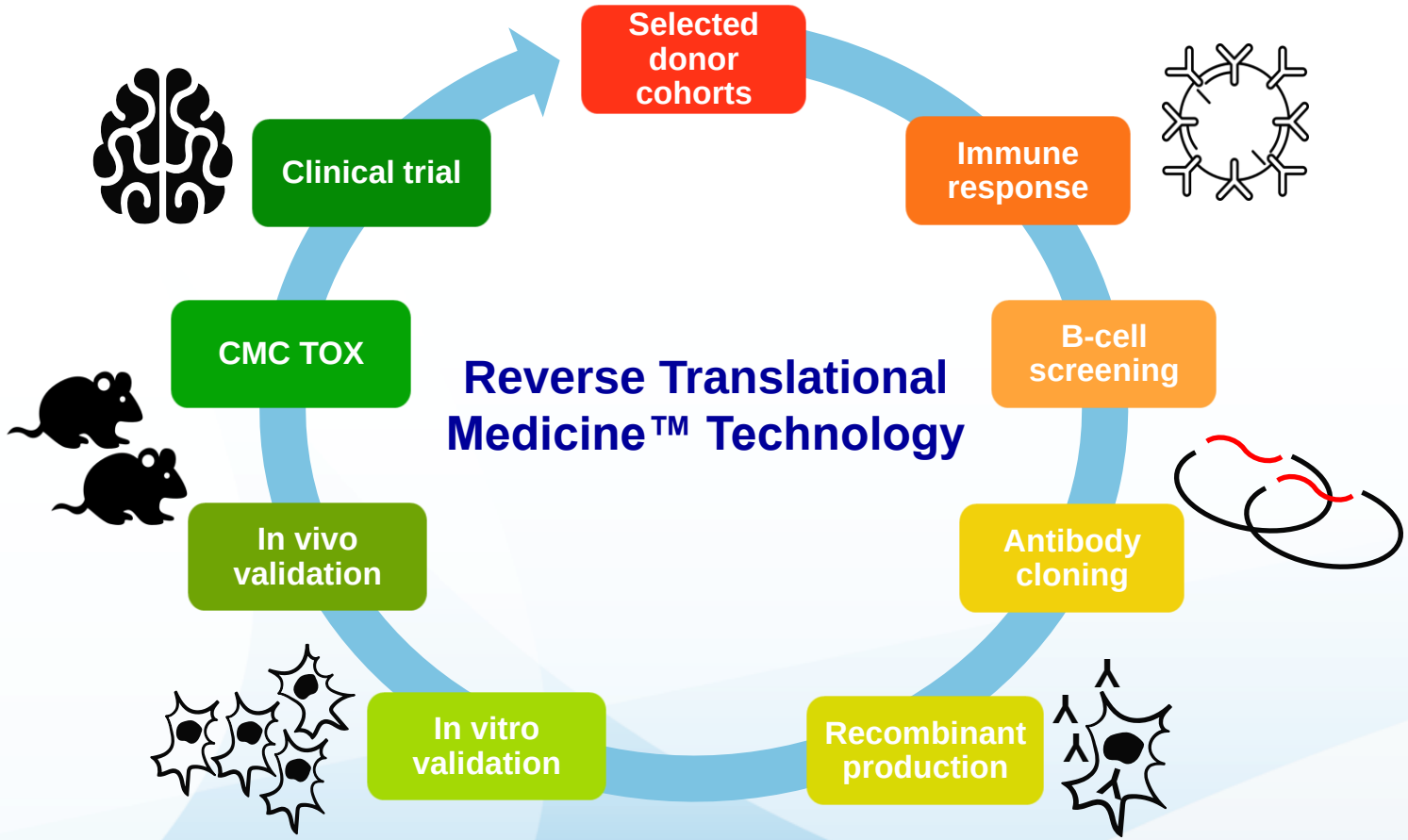
Postulated as causative of Alzheimer's disease[6,7]

Image adapted from Huang L, et al. *Int J Mol Sci*. 2013;14:19109–19127.

1. Koffie RM, et al. *PNAS*. 2009;106:4012–4017; 2. Spires-Jones TL, et al. *Neurobiol Dis*. 2009;33:213–220; 3. Kuchibhotla KV, et al. *Neuron*. 2008 July 31; 59(2): 214–225; 4. Meyer-Luehmann M, et al. *Nature*. 2008;451:720–724; 5. Haass C & Selkoe DJ. *Nat Rev Mol Cell Biol*. 2007;8:101–112; 6. Selkoe DJ & Hardy J. *EMBO Mol Med*. 2016;8:595–608; 7. Wang ZX, et al. *Mol Neurobiol*. 2016;53:1905–24.

Aducanumab is a human IgG1 anti-Aβ monoclonal antibody developed by Biogen and Neurimmune

- **Human donor cohorts**
  - Healthy “agers”
  - Individuals with Alzheimer’s disease and unusually slow disease progression
- De-identified human memory B-cell libraries were screened for **antibodies that stained β-amyloid plaques** on brain tissue sections from patients with Alzheimer’s disease and aged plaque-bearing APP transgenic mice
- Selection for antibodies that **recognize aggregated,** but not monomeric, forms of Aβ
- Molecular cloning and recombinant expression within a **human IgG1/kappa antibody frame** were used to produce aducanumab



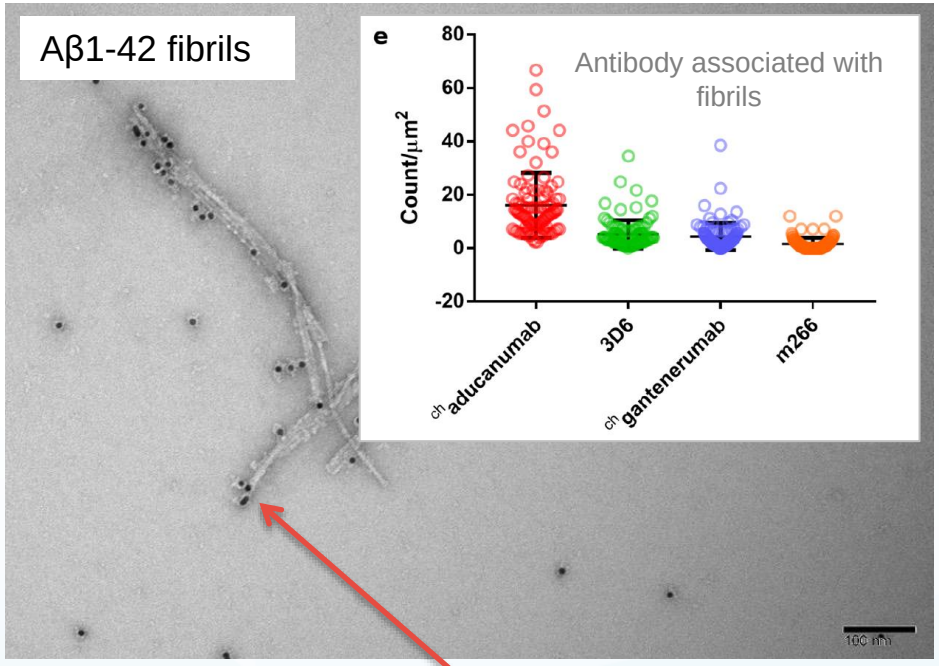
Dunstan R et al. *Alzheimer's and Dementia* 2011;7:S457. Data presented at AAIC 2011; Neurimmune. Reverse Translational Medicine™ Technology Platform, 2016. http://www.neurimmune.com/-technology/rtm-technology-platform-.html. Accessed August 12, 2020; Sevigny J et al. *Nature*. 2016;537:50–56.
Aβ, amyloid beta; APP, amyloid precursor protein; CMC, chemistry and manufacturing controls; IgG, immunoglobulin G; Tox, toxicology.

Aducanumab is highly selective for Aβ aggregates

- **Direct comparative studies** with murine analogs of gantenerumab, bapineuzumab and solanezumab **demonstrate that aducanumab shows the highest selectivity for Aβ aggregates** among all antibodies tested

- This selectivity is **driven by weak monovalent affinity, fast binding kinetics, and strong avidity** for epitope-rich Aβ oligomers and fibrillary aggregates

Negative stain electron microscopy



Binding of immunogold-labeled aducanumab

Antibody constructs were engineered with chimeric mIgG2 constant regions for all antibodies and with parental murine variable regions for bapineuzumab (3D6) and solanezumab (m266).

1. Arndt J, et al. *Sci Rep*. 2018;8:6412.

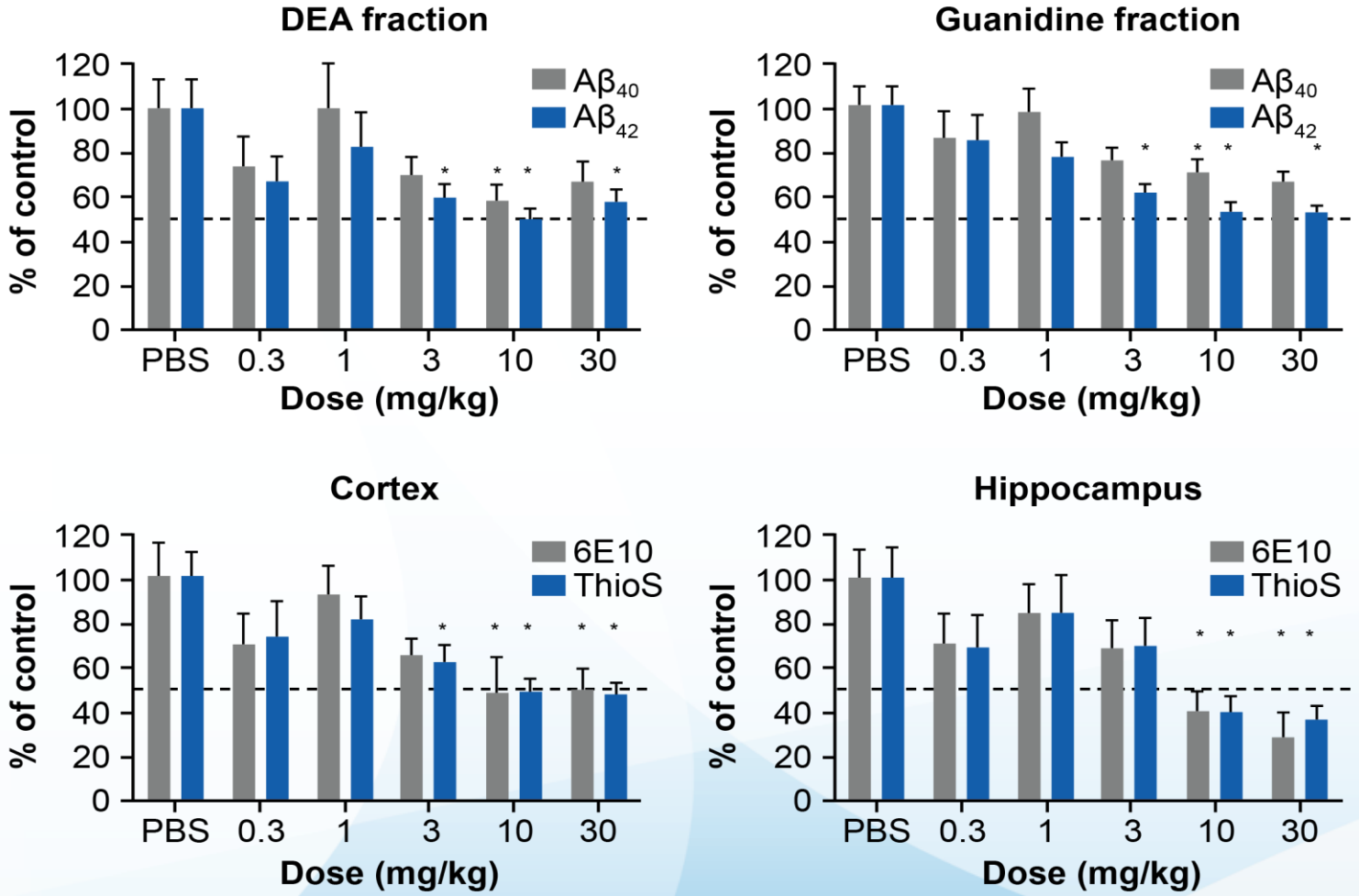
Aβ, amyloid beta.

Aducanumab reduces amyloid plaque in a dose-dependent manner in transgenic mice

DEA and Guanidine are biochemical measures of Aβ

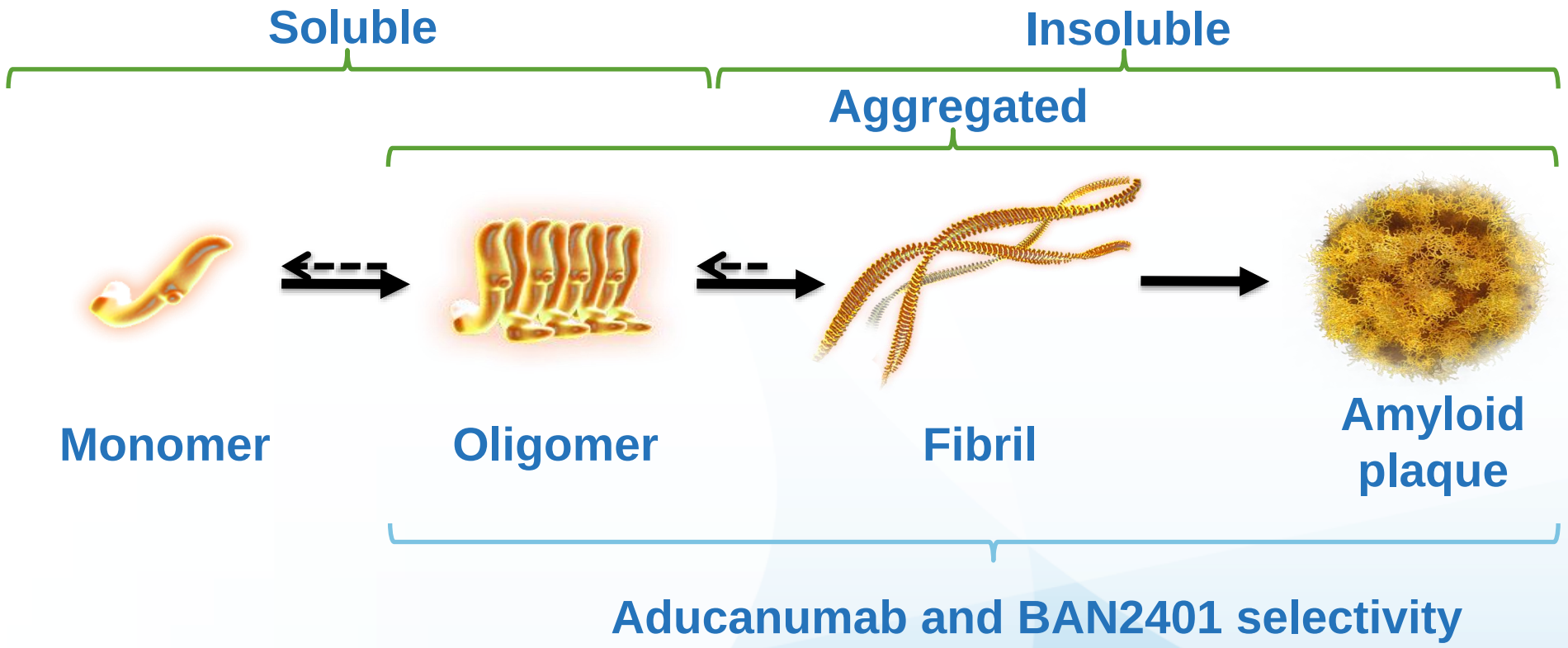
Tg2576 mice were dosed for 6 months with murine chimeric aducanumab analog

6E10 and ThioS are histochemical measures of Aβ



*P<0.05 versus control. Sevigny J et al. *Nature*. 2016;537:50-56.
DEA, diethylamine; ThioS, thioflavin S.

Aducanumab and BAN2401 are highly selective for aggregated Aβ

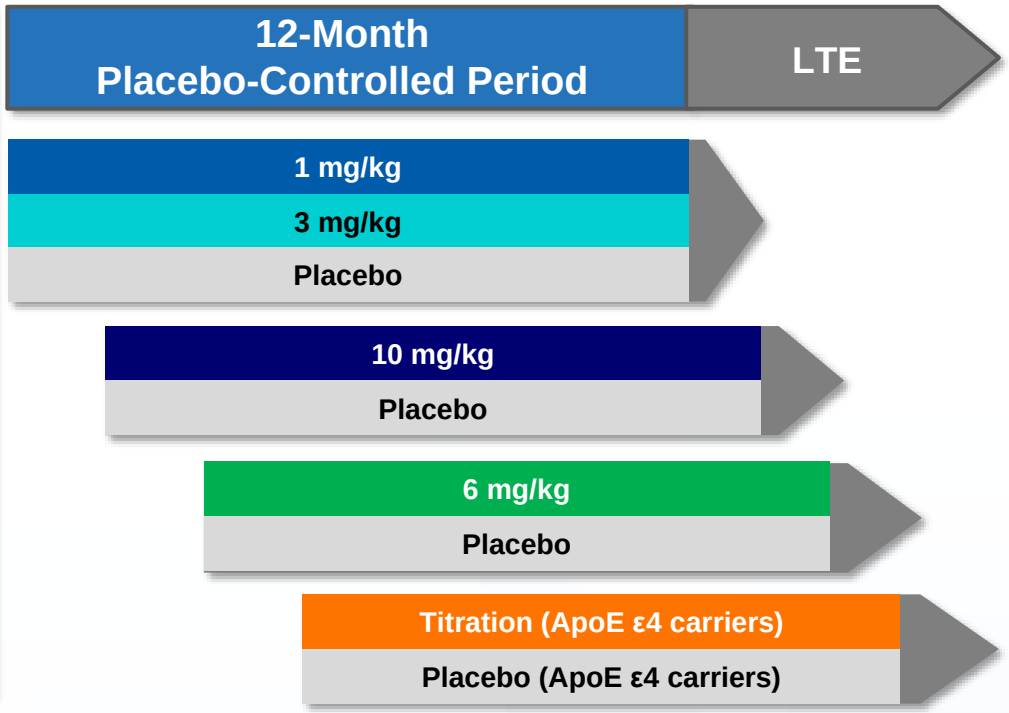


PRIME: study design

Staggered Parallel-Group Design

Population

- Prodromal Alzheimer's disease or mild Alzheimer's disease dementia
- MMSE ≥20
- Stable concomitant medications
- Positive amyloid PET scan



Endpoints

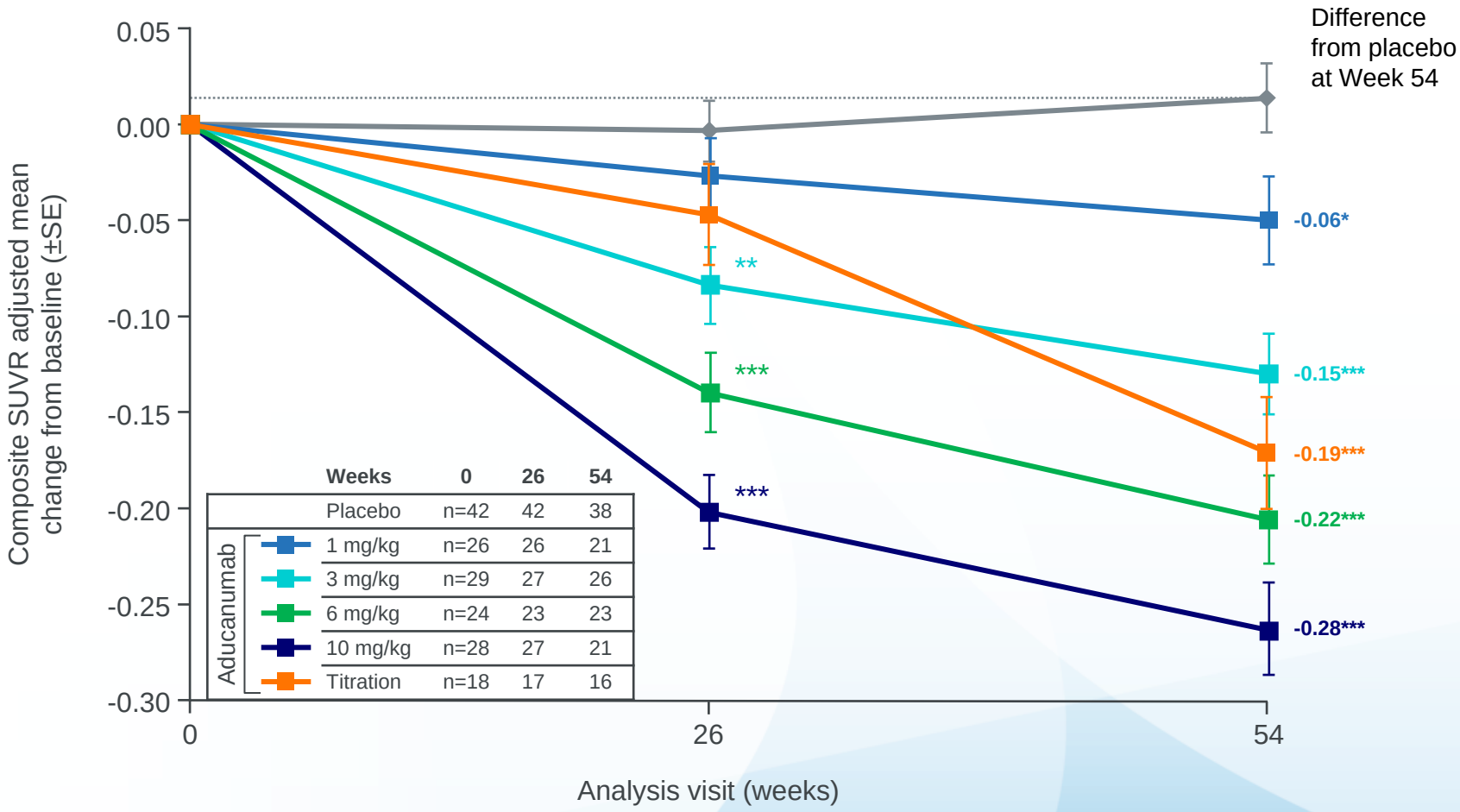
- **Primary endpoint**: safety and tolerability
- **Secondary endpoints**: serum PK, immunogenicity, change in amyloid PET (Week 26)
- **Exploratory endpoints** included CDR–SB, MMSE, change in amyloid PET (Week 54)

- **Randomization**: 3:1 active: placebo within cohorts, fixed-dose cohorts stratified by ApoE ε4 status
- **Planned sample size**: 188 patients
- **Titration cohort** of ApoE ε4 carriers added after enrollment into fixed-dose arms was complete (planned sample size: 21 aducanumab: 7 placebo)

Viglietta V, et al. *Neurology*. 2017;88:S7.003.

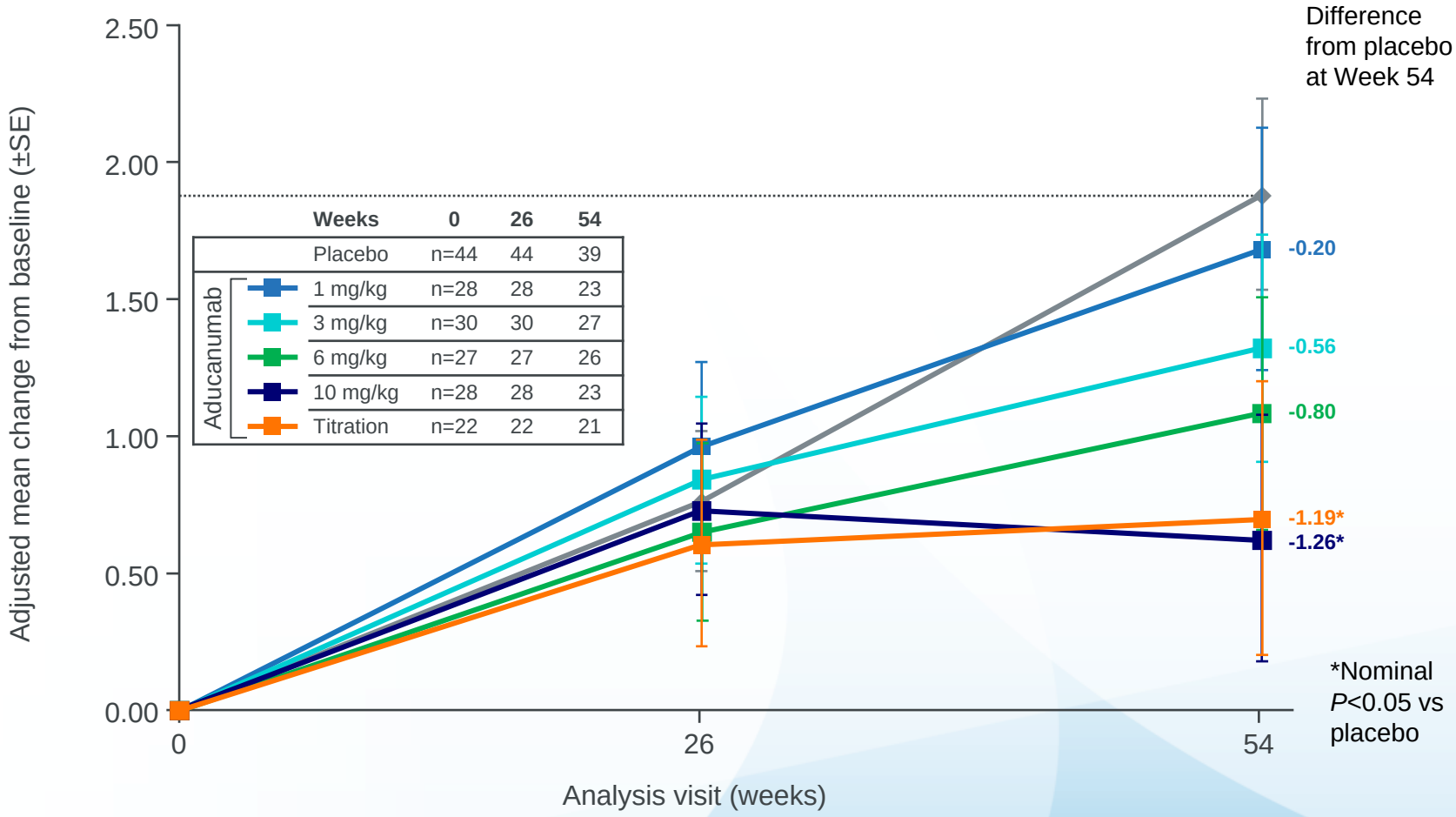
ApoE, apolipoprotein; CDR-SB, Clinical Dementia Rating Scale – Sum of Boxes; MMSE, Mini Mental State Examination; PK, pharmacodynamics; PET, positron emission tomography.

PRIME 12-month analysis: Longitudinal change from baseline in amyloid PET SUVR



Nominal p values: * P<0.05; **P<0.01; ***P<0.001 vs placebo. Analyses based on observed data. ANCOVA for change from baseline with factors of treatment, laboratory ApoE ε4 status (carrier and non-carrier), and baseline composite SUVR. PD analysis population is defined as all randomized patients who received at least 1 dose of study medication and had at least 1 post-baseline assessment of the parameter.
Viglietta V, et al. *J Prev Alz Dis* 2016;3:278. Data presented at CTAD 2016. ANCOVA, analysis of covariance; PET, positron emission tomography; SUVR, standardize uptake value ratio.

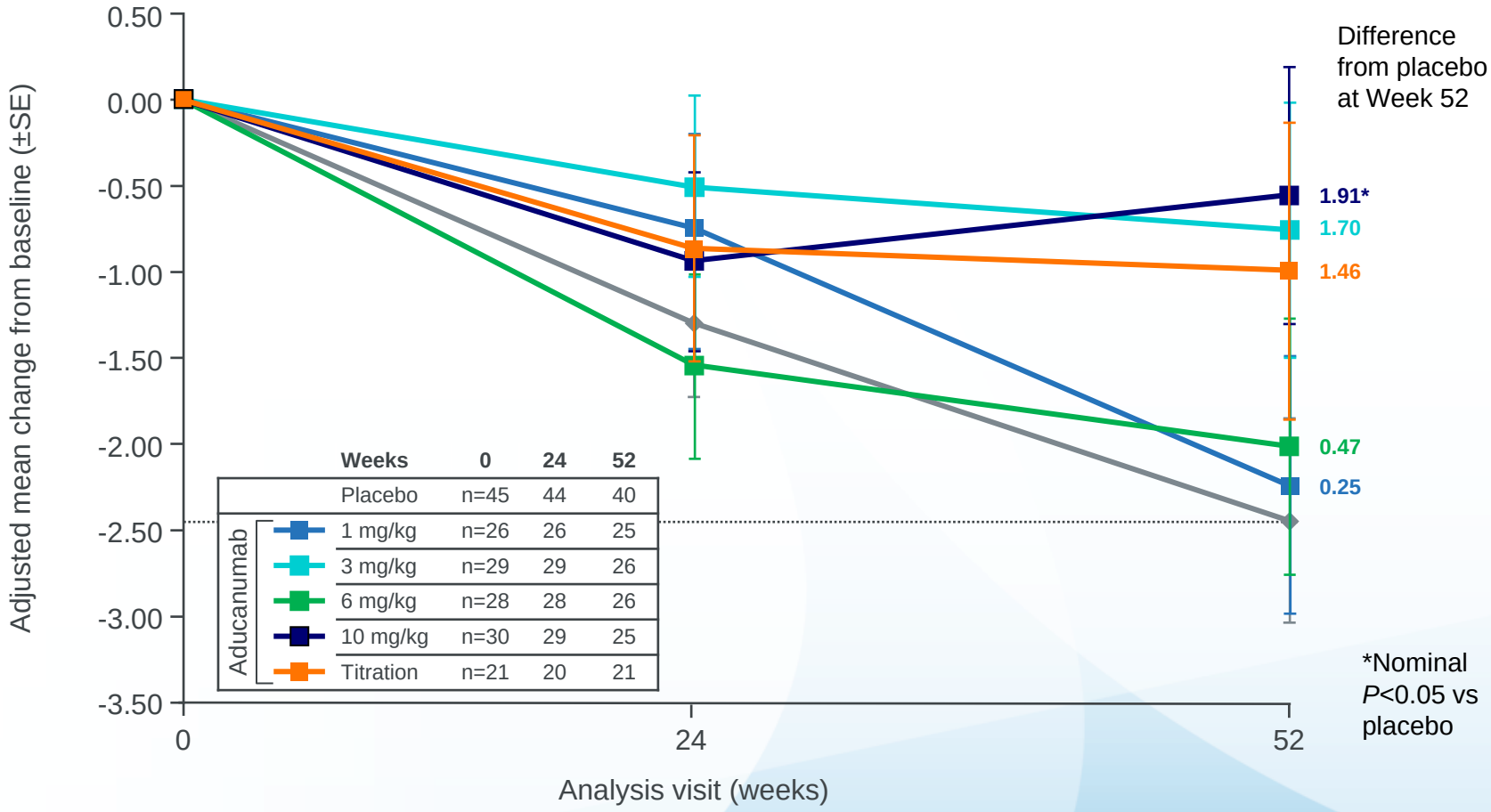
PRIME 12-month analysis: Longitudinal change from baseline in CDR-SB (exploratory endpoint)



CDR-SB is an exploratory endpoint. Analyses based on observed data. ANCOVA for change from baseline with factors of treatment, laboratory ApoE ε4 status (carrier and non-carrier), and baseline CDR-SB. Efficacy analysis population is defined as all randomized patients who received at least 1 dose of study medication and had at least 1 post-baseline questionnaire assessment.

Viglietta V, et al. *J Prev Alz Dis* 2016;3:278. Data presented at CTAD 2016. CDR-SB, Clinical Dementia Rating Scale – Sum of Boxes.

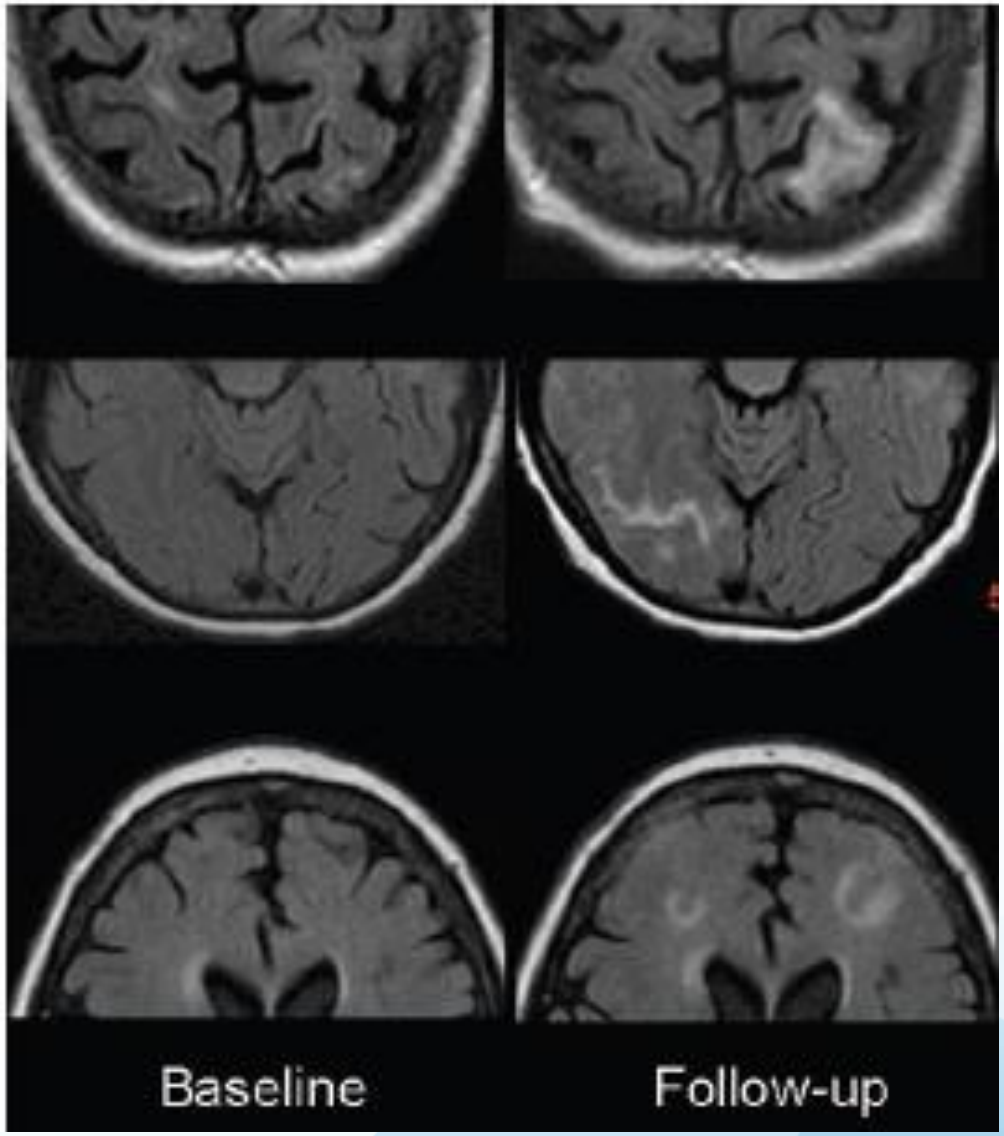
PRIME 12-month analysis: Longitudinal change from baseline in MMSE (exploratory endpoint)



MMSE is an exploratory endpoint. Analyses based on observed data. ANCOVA for change from baseline with factors of treatment, laboratory ApoE ε4 status (carrier and non-carrier), and baseline MMSE. Efficacy analysis population is defined as all randomized patients who received at least 1 dose of study medication and had at least 1 post-baseline questionnaire assessment.

Viglietta V, et al. *J Prev Alz Dis* 2016;3:278. Data presented at CTAD 2016. MMSE, Mini Mental State Examination.

Amyloid Related Imaging Abnormalities [ARIA-E]



Barkhof F, et al. *Brain*. 2013;1550-1555.

PRIME 12-month analysis: Dose titration attenuated incidence of ARIA-E versus higher fixed doses

		Aducanumab				
	Placebo	1 mg/kg	3 mg/kg	6 mg/kg	10 mg/kg	Titration
Patients with at least 1 post-baseline MRI	46	31	32	30	32	23
ARIA-E[a], n/total (%)	0/46	1/31 (3)	2/32 (6)	11/30 (37)	13/32 (41)	8/23 (35)
ApoE ε4 carriers	0/32	1/19 (5)	1/21 (5)	9/21 (43)	11/20 (55)	8/23 (35)
ApoE ε4 non-carriers	0/14	0/12	1/11 (9)	2/9 (22)	2/12 (17)	-
Isolated ARIA-H, n (%)	3/46 (7)	2/31 (5)	3/32 (9)	0/30	2/32 (6)	0/23

[a]ARIA-E with or without ARIA-H. Incidence of ARIA based on MRI.
Viglietta V, et al. *J Prev Alz Dis* 2016;3:278. Data presented at CTAD 2016.
ARIA-E, ARIA due to vasogenic edema; ARIA-H, amyloid-related imaging abnormalities due to micro-hemorrhages, macro-hemorrhages.

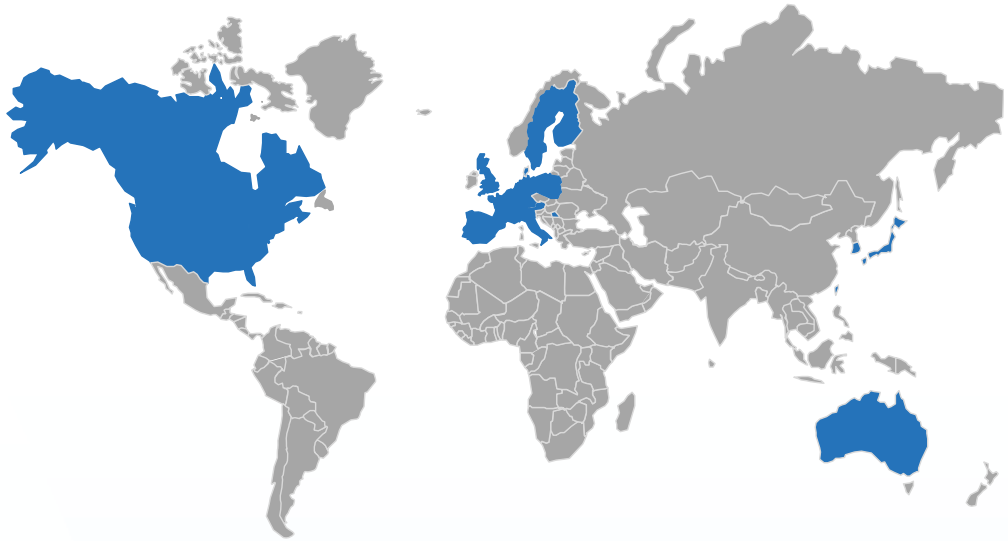
Summary of PRIME 12-month results*

- Aducanumab treatment significantly reduced amyloid plaque burden in a dose- and time-dependent manner
- Aducanumab treatment also reduced clinical decline as measure by the CDR-SB and MMSE in a dose- and time-dependent manner
- ARIA was the main adverse event associated with Aducanumanb
    - Titration up to 10 mg/kg may reduce incidence of ARIA-E compared with higher fixed dosing based on the ApoE ε4 cohort studied
- PRIME results supported the study design of the EMERGE and ENGAGE Phase 3 trials, which investigated the clinical efficacy and safety of aducanumab in patients with early stages of Alzheimer's disease

*PRIME is a small study and the efficacy endpoints were exploratory. In PRIME, safety and tolerability was the primary endpoint.
Viglietta V, et al. *J Prev Alz Dis* 2016;3:278. Data presented at CTAD 2016.
ARIA-E, ARIA due to vasogenic edema; CDR-SB, Clinical Dementia Rating–Sum of Boxes; MMSE, Mini-Mental State Examination.

Aducanumab Phase 3 studies EMERGE and ENGAGE

Studies	Two 18-month, randomized, double-blind, placebo-controlled, Phase 3 studies
Geography/ sample size	3285 patients at 348 sites in 20 countries
Population	▪ Early Alzheimer's disease (MCI due to Alzheimer's disease + mild Alzheimer's disease dementia) • MMSE 24-30, CDR-G 0.5, RBANS ≤ 85, with confirmed amyloid pathology
Doses	▪ Two dosing regimens (low and high) and placebo; randomized 1:1:1
Primary endpoint	▪ CDR-SB at 18 months
Other endpoints	▪ Secondary: MMSE, ADAS-Cog 13, ADCS-ADL-MCI ▪ Sub-studies: amyloid PET, tau PET, CSF disease-related biomarkers



Countries with active sites included:
Australia, Austria, Belgium, Canada, Denmark, Finland, France, Germany, Italy, Japan, the Netherlands, Poland, Portugal, South Korea, Spain, Sweden, Switzerland, Taiwan, United Kingdom, United States

1. ClinicalTrials.gov: https://clinicaltrials.gov/ct2/show/NCT02477800. Accessed August 12, 2020; ClinicalTrials.gov: https://clinicaltrials.gov/ct2/show/NCT02484547. Accessed August 12, 2020; Data on file.
ADAS-Cog 13, Alzheimer's Disease Assessment Scale–Cognitive Subscale (13-item); ADCS-ADL-MCI, Alzheimer's Disease Cooperative Study–Activities of Daily Living Inventory (mild cognitive impairment version); CDR-SB, Clinical Dementia Rating–Sum of Boxes; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; PET, positron-emission tomography; RBANS, Repeatable Battery for Assessment of Neuropsychological Status.

Summary of aducanumab Phase 3 topline results (1 of 2)

- **In the aducanumab Phase 3 trial program, modification of biomarkers of underlying disease pathology was associated with statistically significant slowing of clinical decline**
- In the amyloid PET sub-study, there was a dose- and time-dependent reduction in amyloid PET SUVR at Week 78 in both EMERGE and ENGAGE
  - The reduction in amyloid PET SUVR in ENGAGE was smaller than the reduction observed in EMERGE
- Data from EMERGE showed a statistically significant advantage of high-dose aducanumab over placebo on the pre-specified primary endpoint, CDR-SB, at Week 78
  - A statistically significant slowing of clinical decline was also detected across three secondary endpoints – MMSE, ADAS-Cog13, and ADCS-ADL-MCI
- In ENGAGE, aducanumab did not reduce clinical decline
  - In a post hoc analysis, data from a subset of patients from ENGAGE with the opportunity to receive 10 mg/kg aducanumab support the positive findings of EMERGE

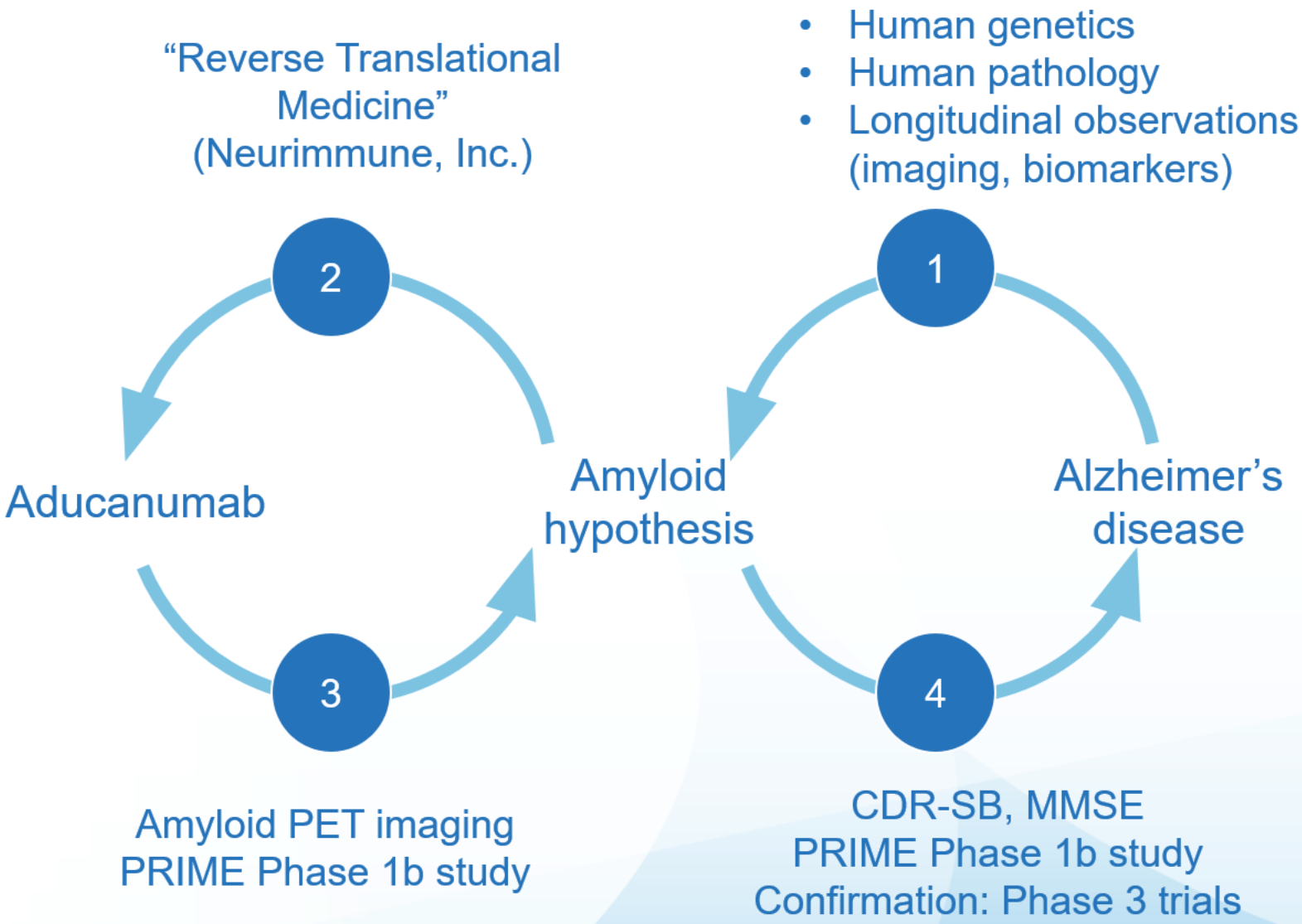
ADAS-Cog 13, Alzheimer's Disease Assessment Scale–Cognitive Subscale (13-item); ADCS-ADL-MCI, Alzheimer's Disease Cooperative Study–Activities of Daily Living Inventory (mild cognitive impairment version); CDR-SB, Clinical Dementia Rating–Sum of Boxes; CSF, cerebrospinal fluid; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; PET, positron emission tomography; SUVR, standardized uptake value ratio.

Summary of aducanumab Phase 3 topline results (2 of 2)

- Results from biomarker sub-studies of downstream biomarkers specific to Alzheimer's disease (tau PET and CSF p-tau) and neurodegeneration (CSF t-tau) further support the clinical findings
  - In EMERGE and ENGAGE, there was a statistically significant reduction in CSF p-tau
  - In EMERGE, there was a numerical reduction in CSF t-tau in both dose groups and in ENGAGE there was a numerical reduction in t-tau in the low dose group
  - In the tau PET sub-study (patients pooled across both studies) there was a statistically significant and dose-dependent reduction in tau PET SUVR in the medial temporal, temporal and frontal regions in patients treated with aducanumab versus placebo
- The most common AEs in EMERGE and ENGAGE were ARIA-E and headache
- A re-dosing study, EMBARK, is currently offering aducanumab to eligible patients who were actively enrolled in the aducanumab clinical studies
- The FDA has accepted regulatory submission for aducanumab under priority review
- Biogen is planning to submit a new drug application for aducanumab in Japan

AE, adverse event; ARIA, amyloid-related imaging abnormalities; ARIA-E, amyloid-related imaging abnormalities due to vasogenic edema; CSF, cerebrospinal fluid; FDA, U.S. Food and Drug Administration; PET, positron emission tomography; SUVR, standardized uptake value ratio.

The example of Aducanumab



CDR-SB, Clinical Dementia Rating Scale – Sum of Boxes; MMSE, Mini Mental State Examination; PET, positron emission tomography.
Sevigny J et al. *Nature*. 2016;537:50–56.

Conclusions

We are in an era of redefining neurologic diseases in actionable terms

- Genetics, targets within causal biological pathways

We have advanced the measurement of disease progression

- To obtain early POC
- To obtain registration

We have tools that decrease the risk of drug development in neurology

- Identify patient early in their disease
- Identify subpopulations of patients
- With biomarkers, measure target engagement or desired biological response

We have new therapeutic approaches that enable rapid R&D from gene to drug

- Antisense oligonucleotides
- Monoclonal antibodies

Acknowledgements

My colleagues at Biogen, Eisai, and Neurimmune

All the advisors, investigators, patients, and family members who participated in the aducanumab studies