What have we learned from aducanumab?

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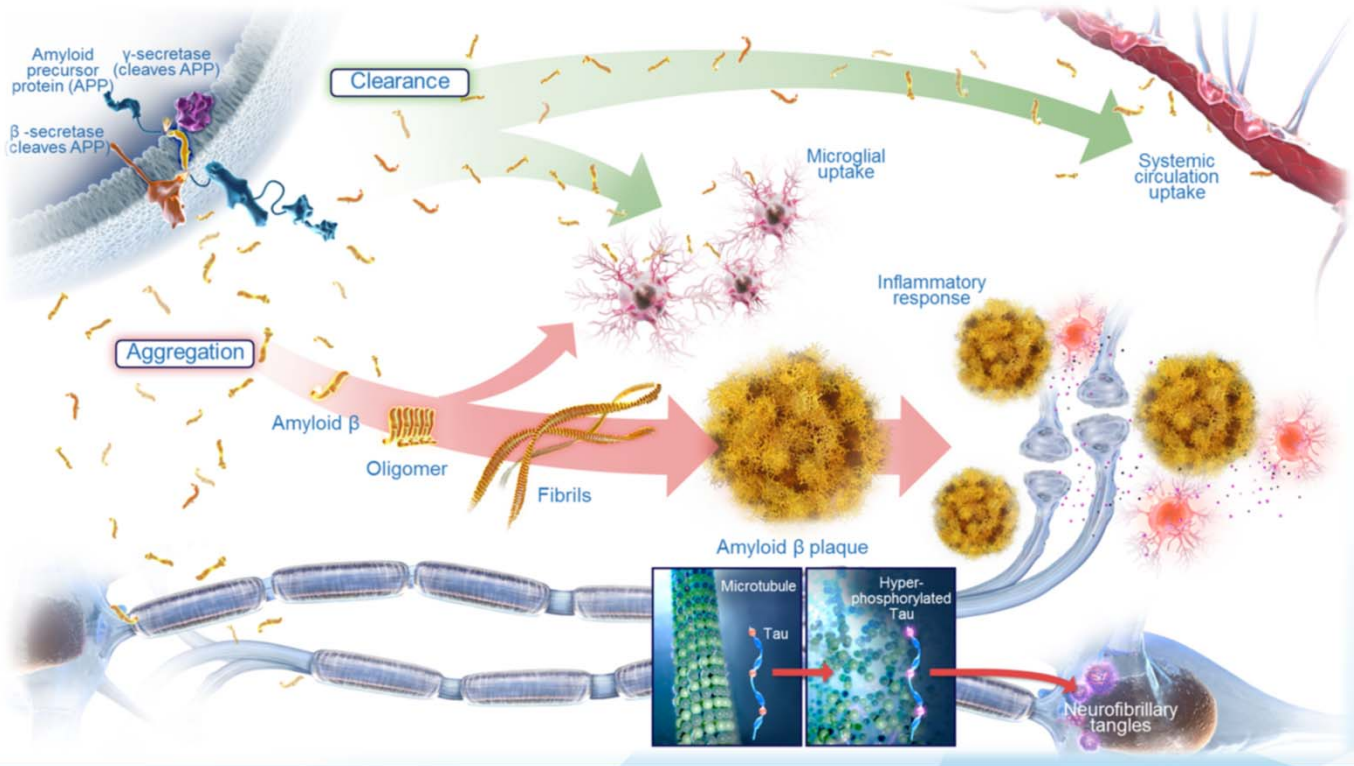
October 25, 2018

Disclaimer

- Aducanumab, is an investigational medicine and the benefit/risk profile has not been fully established. It has not received any marketing authorization and there is no guarantee that it will obtain such authorization in the future
- The information and any data presented is early interim data from ongoing clinical trials and it is made available for scientific discussion only, in consideration of the general interest of the scientific community with respect to any progress in the research and development of possible treatments for Alzheimer disease
- The information and any data presented are developed from scientific research and are not intended to predict the availability of any particular drug or therapy

Biogen licensed the worldwide rights to aducanumab from Neurimmune Holding AG in 2007 and is responsible for its development and the commercialization. As of October 22, 2017, Biogen and Eisai are collaborating on the development and commercialization of aducanumab globally.

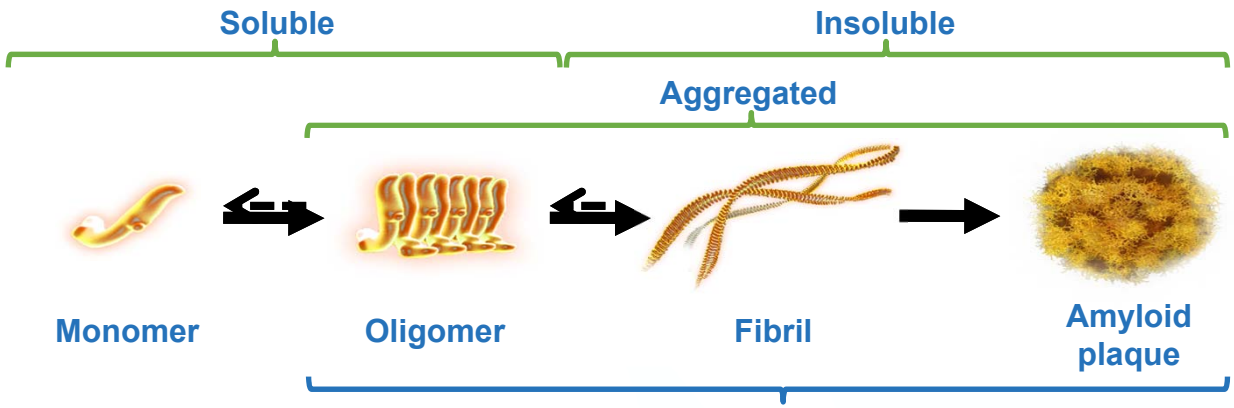
Accumulation of Aβ is a core pathology in Alzheimer's disease (AD)



Aβ, amyloid beta; APP, amyloid precursor protein.

2017 Alzheimer's Disease Facts and Figures. http://www.alz.org/documents_custom/2017-facts-and-figures.pdf. Accessed June 4, 2018; Dubois B, et al. Alzheimer's & Dementia. 2016;12:292–323; Jack CR, et al. Brain. 2009;132:1355-1364.

Our understanding of the amyloid pathway today



- The relevant pathological form of Aβ remains elusive
- Soluble oligomers &/or insoluble fibrils may play important roles in disease

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.

Profiles of amyloid-targeted immunotherapies

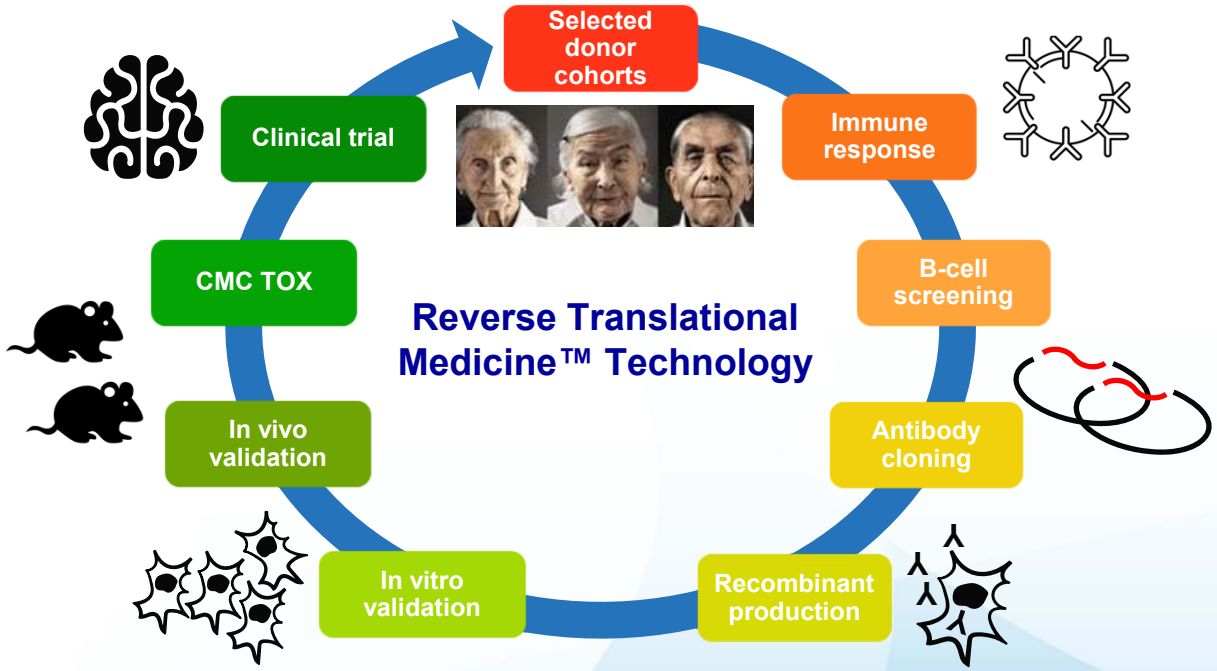
	Aducanumab[1,2]	BAN2401[3]	Gantenerumab[4]	Crenezumab[5,6]	MEDI-1814[7]	LY3002813[8]	Bapineuzumab[9]	Solanezumab[10]
Current Status	Phase 3	Phase 2	Phase 3	Phase 3	Phase 1	Phase 2 (Combo with BACEi)	Discontinued	Partially halted
Origin	Human (RTM)	Humanized	Human (Phage display library + affinity maturation)	Humanized	Human (Phage display library + affinity maturation)	Humanized	Humanized	Humanized
Target	Fibrillar and Oligomeric Aβ	Fibrillar and Oligomeric Aβ	Fibrillar and Oligomeric Aβ	All forms of Aβ: **Oligomeric>** Fibrillar, Monomeric	Soluble monomeric Aβ(1-42)	N3pG	All forms of Aβ: Fibrillar, Oligomeric, Monomeric	Soluble monomeric Aβ
Epitope	N-terminus (3-7)	N-terminus (1-16)	Nt (3-11) + mid (18-27)	Mid-domain (13-24)	C-terminus (X-42)	Aβp3-x	N-terminus (1-5)	Mid-domain (16-26)
Effector Function	Yes	Yes	Yes	Reduced	Reduced	Yes	Yes	Yes
Plaque/CAA binding	Yes	Yes	Yes	Low	?	Yes	Yes	No
ARIA	Yes	Yes	Yes	No	No	Yes	Yes	No

RTM, reverse translational medicine; BACEi, β-site APP-cleaving enzyme inhibitor; N3pG, pyroglutamate amyloid beta.

1. Sevigny et al, Nature. 2016;537:50-56; 2. Arndt J, et al. Sci Rep. 2018;8:6412; 3. Lord et al. Neurobiol Dis. 2009;36:425-34; 4. Bohrmann et al. J Alzheimers Dis. 2012;28:49-69; 5. Adolfsson et al. J Neurosci. 2012;32:9677-9689; 6. Atwal et al, Neurodegener Dis. 2017;17:591-1890. P828. 7. Bogstedt et al., J Alzheimers Dis. 2015;46:1091-1101; 8. DeMattos et al. Neuron. 2012 Dec 6;76:908-20; 9. Bard et al. Nat Med. 2000;6:916-919; 10. DeMattos et al. Proc Natl Acad Sci U S A. 2001;98:8850-8855.

What we have learned about the molecular characteristics of aducanumab

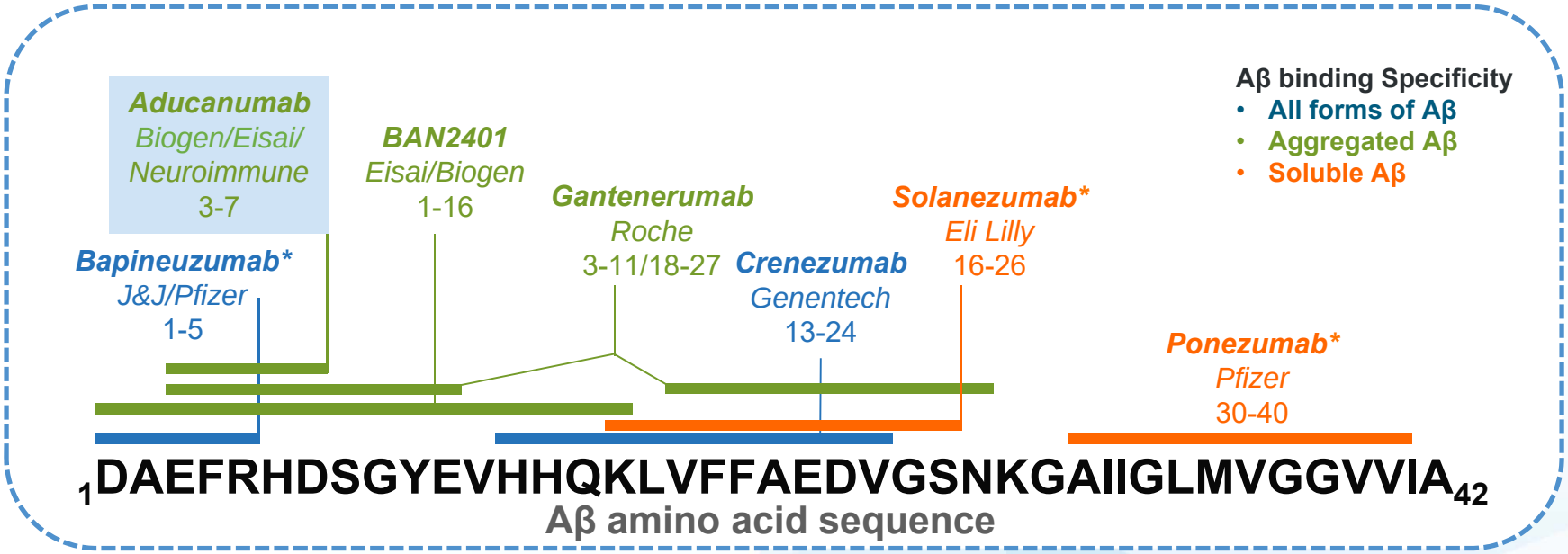
Aducanumab is a human IgG1 anti-Aβ monoclonal antibody developed in partnership with Neurimmune



CMC, chemistry and manufacturing controls; IgG, immunoglobulin G; Tox, toxicology.

Neurimmune. Reverse Translational Medicine™ Technology Platform, 2016. http://www.neurimmune.com/-technology/rtm-technology-platform-.html. Accessed June 4, 2018; Sevigny J et al. Nature. 2016;537:50–56.

Aducanumab targets the N-terminus of Aβ

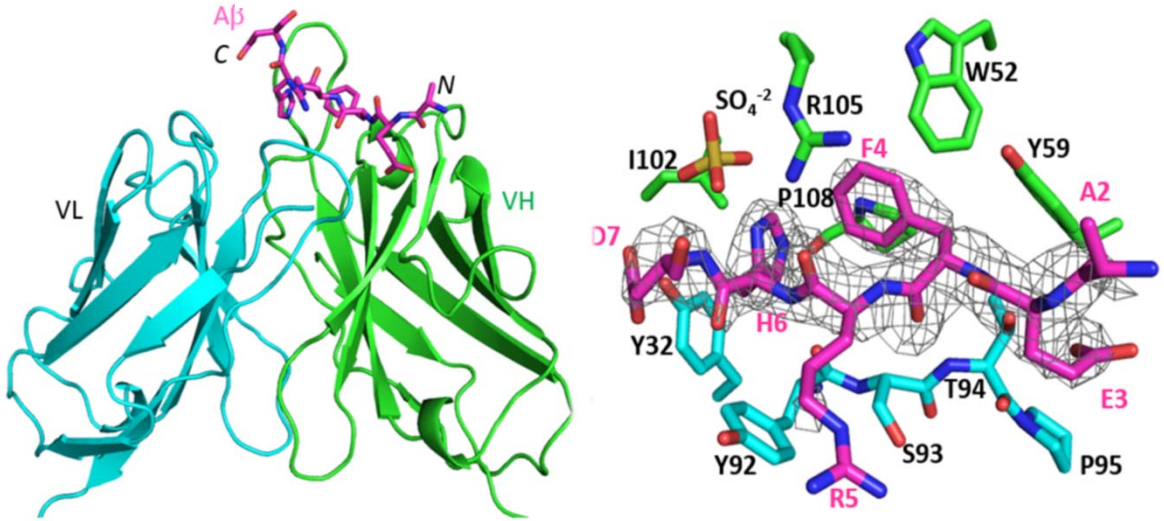


*Denotes development that has been discontinued or partially halted.

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

Structure of aducanumab Fab with Aβ1-11 shows minimal conformational change in Fab upon peptide binding

(2.1 Å) of aducanumab Fab with Aβ1-11



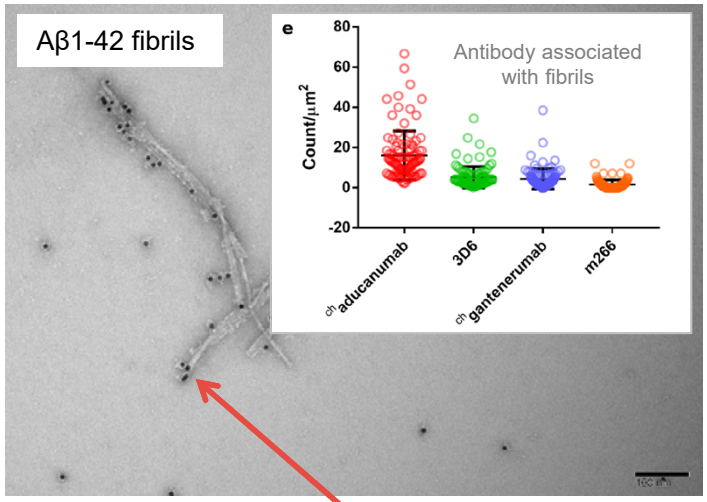
- Residues 2-7 adopt an extended conformation
- Key interactions with CDRs H2, H3, L3

CDRs, complementary-determining regions.

Arndt J, et al. Sci Rep. 2018;8:6412; Sevigny, J. et al. Nature. 2016;537:50–56.

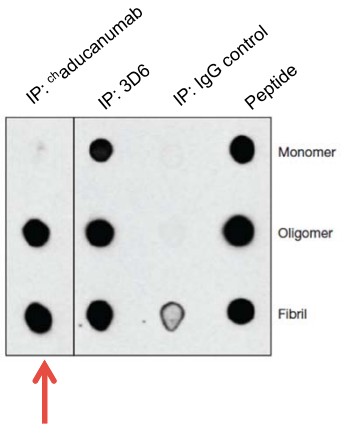
Aducanumab is highly selective for Aβ aggregates

Negative Stain Electron Microscopy[1]



Binding of immunogold-labeled aducanumab

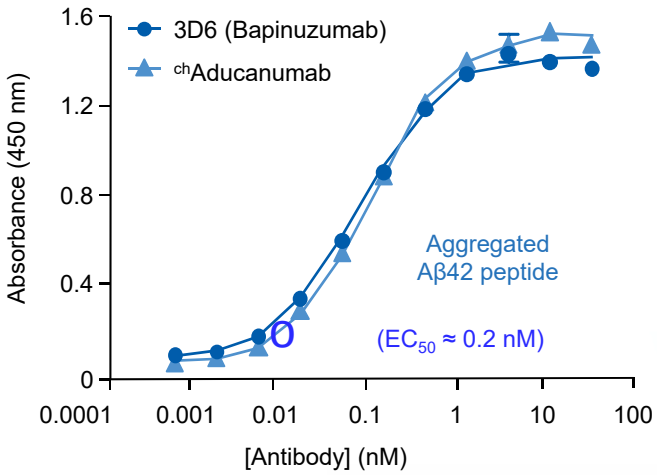
Dot Blot[2]

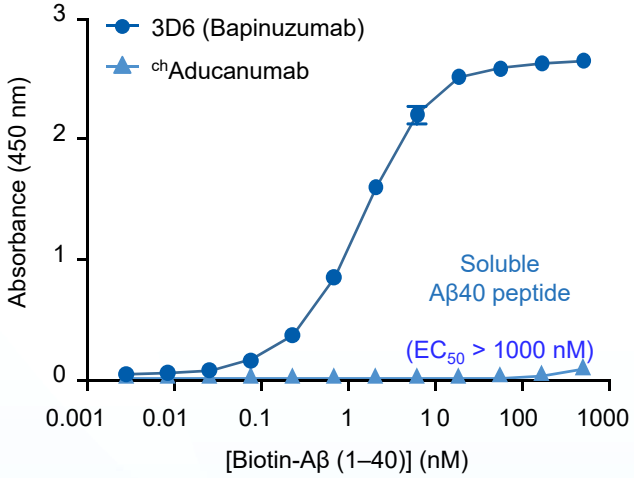


Binding to insoluble fibrillar and soluble oligomeric Aβ1-40

Right image reprinted with permission from Macmillan Publishers Ltd.
1. Arndt J, et al. Sci Rep. 2018;8:6412; 2. Sevigny J, et al. Nature. 2016;537(7618):50–56, copyright 2016.

Aducanumab does not bind to soluble monomeric Aβ

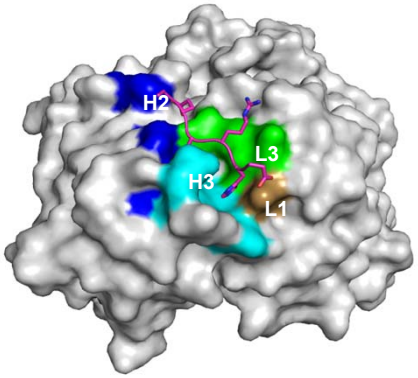




- **Biochemical assays demonstrate:**
  - High affinity binding of BIIB037 for aggregated Aβ (EC_{50} ≈ 0.2nM)
  - No binding of BIIB037 to soluble monomeric Aβ (EC_{50} > 1000nM)

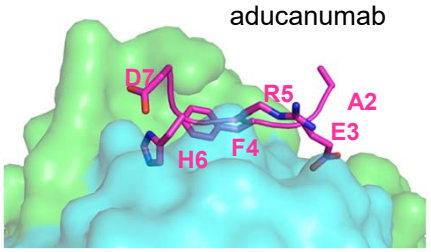
EC_{50}, half maximal effective concentration.

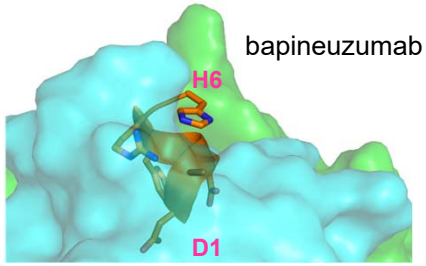
Aducanumab binding epitope may determine selective binding to Aβ aggregates



Aducanumab Fab complexed with Aβ(1-11) peptide (2.1Å)

Adu binds to Aβ 3-7



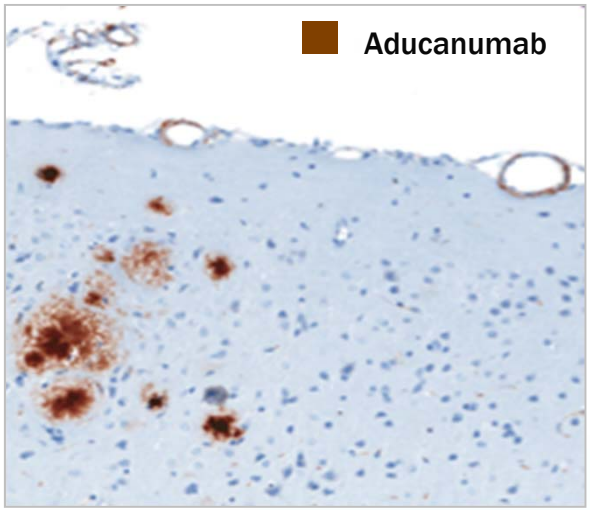


	Buried Surface Area (Å^2)	Contacts
aducanumab	506	12
BAN2401	610	18
PFA1	670	20
bapineuzumab	565	23
gantenerumab	903	24

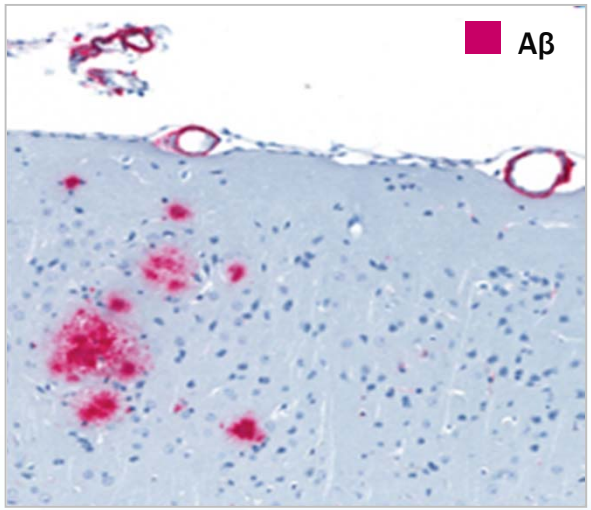
- A shallow and compact epitope may contribute to the selectivity for high molecular weight Aβ forms, without targeting Aβ monomers

BSA, buried surface area; CDRs, complementary-determining regions.
Arndt J, et al. Sci Rep. 2018;8:6412.
Protein data bank (PDB): http://www.rcsb.org/pdb/home/home.do. Accessed October 24, 2018. Bapineuzumab structure: PDB ID 4HIX; Gantenerumab structure: PDB ID 5CSZ; PFA1 structure: PDB ID 2IPU.

Aducanumab achieves sufficient brain exposure to bind amyloid deposits in APP transgenic mice (Tg2576)



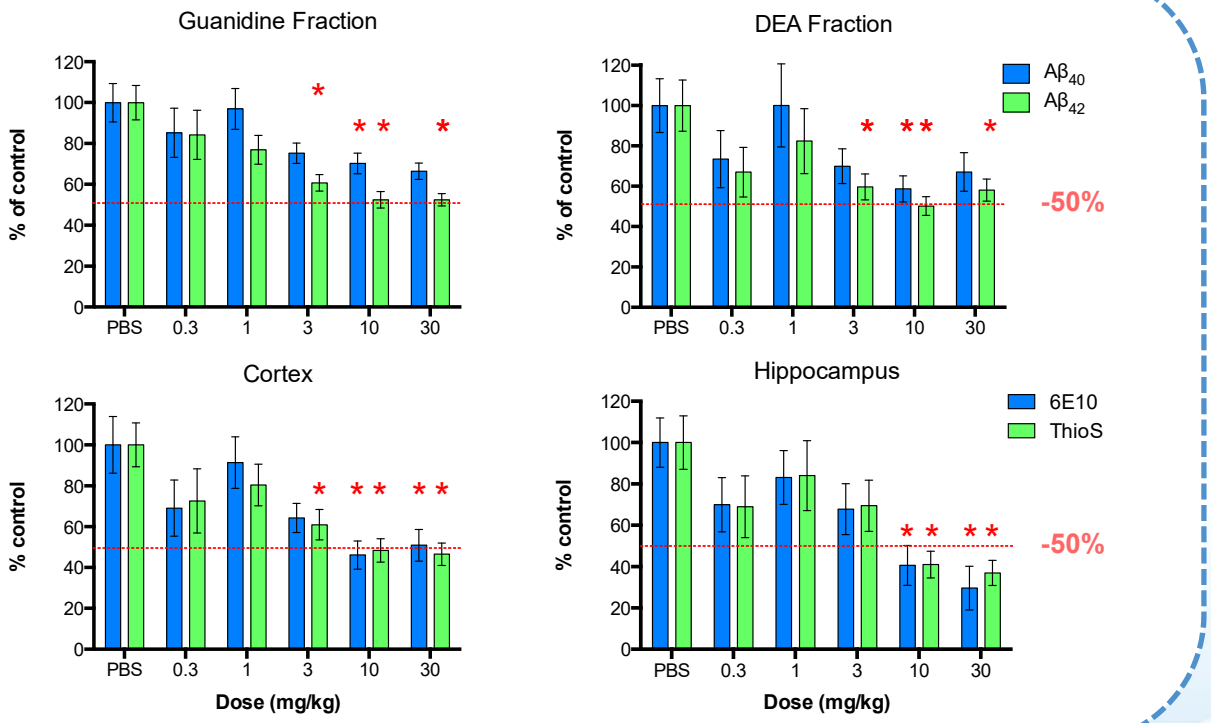
In vivo binding of aducanumab to amyloid deposits
Visualized with anti-human IHC



Pattern of amyloid deposition
Serial section visualized with pan-Aβ IHC

APP, amyloid precursor protein; IHC, immunohistochemistry.

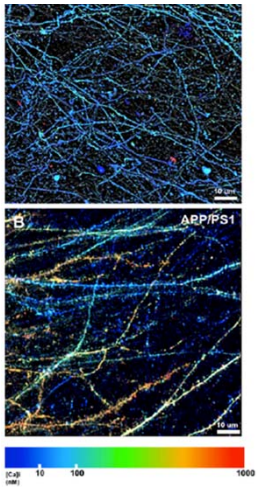
6-month aducanumab dosing reduces amyloid plaque in a dose-dependent manner in transgenic mice (Tg2576)

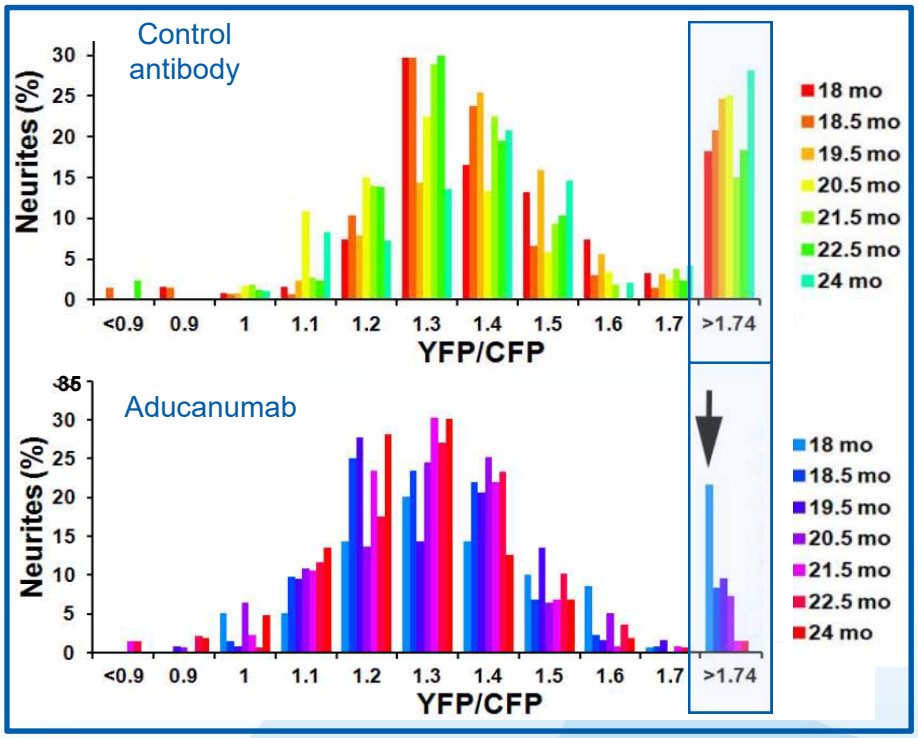


DEA, diethylamine; ThioS, thioflavin S.
*P<0.05 versus control.
Sevigny J, et al. Nature 2016;537:50–56.

Aducanumab restores neurite calcium levels in transgenic mice with amyloid plaques

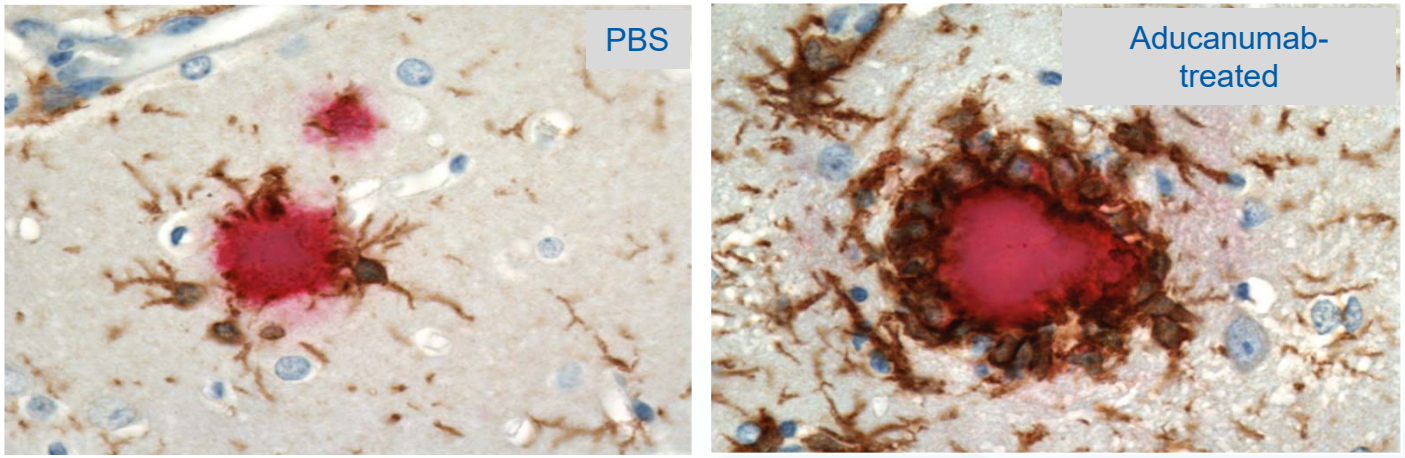
Multiphoton live imaging in Tg2576 mouse brain





YFP, yellow fluorescent protein; CFP, cyan fluorescent protein.
Kastenaka, KV. et al. Neurobiol. Dis. 2016;536:12549–12558.

Aducanumab recruits microglial cells and induces phagocytosis-mediated clearance of amyloid plaques in Tg2576 mice

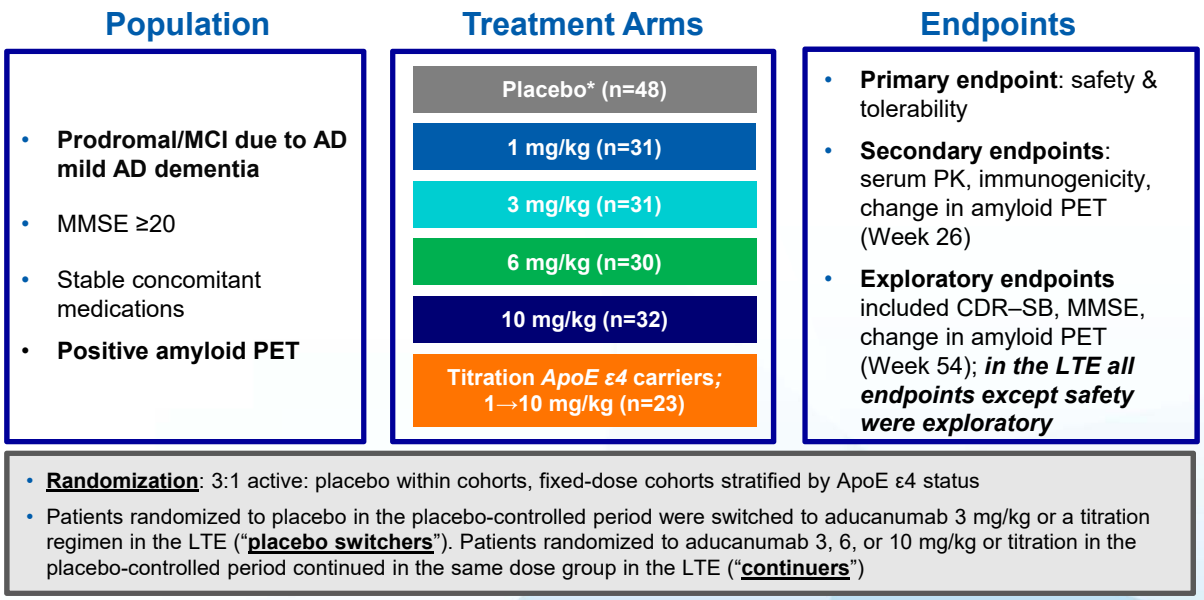


PBS, phosphate buffered saline; Iba-1, ionizing calcium-binding adaptor molecule 1.
Sevigny J, et al. Nature 2016;537:50–56.

Clinical learnings from the Phase 1b PRIME study

Aducanumab Phase 1b study (PRIME) design

- PRIME is an ongoing Phase 1b study assessing the safety, tolerability, PK and PD of aducanumab in patients with prodromal or mild Alzheimer's disease dementia
- 197 subjects randomized, 196 dosed; 12-month placebo-controlled period, ongoing LTE

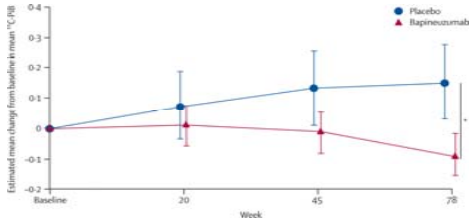


PK, pharmacokinetics; PD, pharmacodynamics; LTE, long-term extension; MCI, mild cognitive impairment; MMSE, Mini–Mental State Examination; PET, positron-emission tomography; CDR-SB, Clinical Dementia Rating-Sum of Boxes.
*Pooled placebo group.
ClinicalTrials.gov: https://clinicaltrials.gov/ct2/show/NCT03718819. Accessed October 24, 2018.

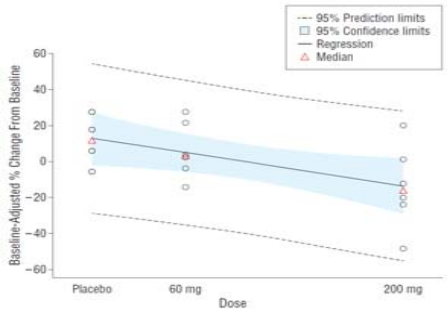
Target engagement

Amyloid plaque reduction as a measure of target engagement

Bapineuzumab[1]



Gantenerumab[2]

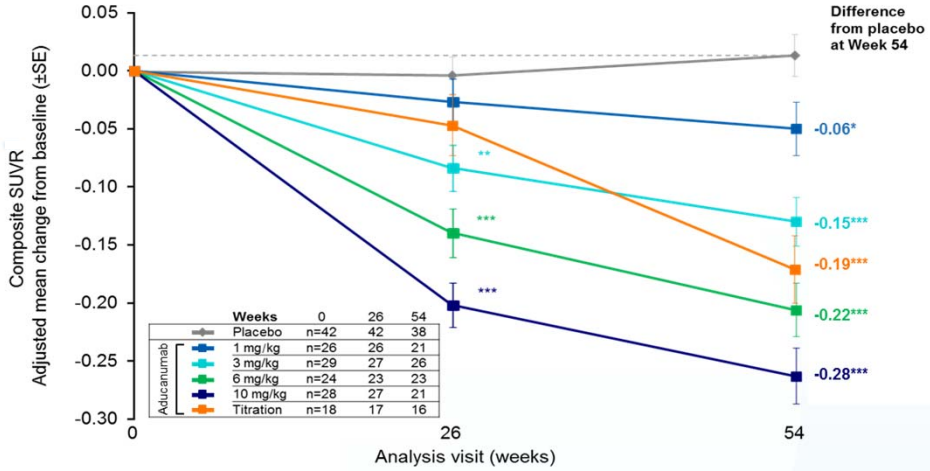


- Amyloid PET when the PRIME study started was a very new technology for multicenter clinical trials
- Two pioneering studies bapineuzumab (^{11}C-PiB PET) and gantenerumab moved the fields understanding on
  - Sample sizes
  - Placebo response
  - Analysis methodologies
- Aducanumab PRIME study
  - Screened all subjects for baseline levels of amyloid
  - >20 clinical sites
  - ^{18}F-AV-45 (Amyvid)
  - Larger sample sizes per arm

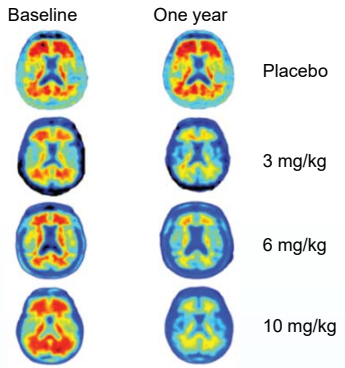
^{11}C-PiB PET, Pittsburgh compound B positron-emission tomography.
*Difference between patients in the placebo group and those in the bapineuzumab group at week 78= -0.24 (p=0.003).
1. Rinne et al. Lancet. 2010;9:363-372; 2. Ostrowitzki et al Arch Neurology. 2012;69:198-207.

Aducanumab target engagement: dose- and time-dependent reduction in amyloid plaque as measured by PET

Dose and time dependent reduction in composite SUVR (PET)[1]



Amyloid-β (Aβ) plaque reduction: example amyloid PET images[2]



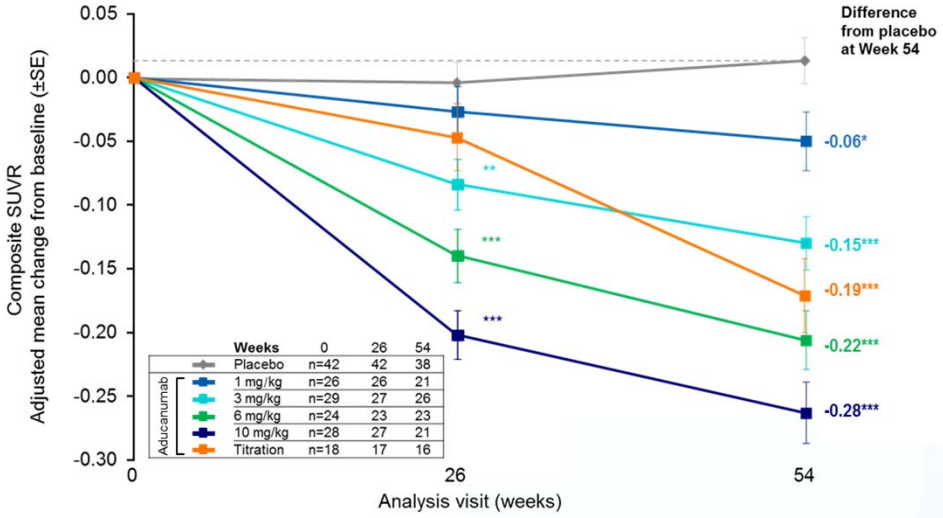
- Statistically significant reduction in amyloid plaque seen as early as 6 months
- No increase in placebo arms

ANCOVA, analysis of covariance; PET, positron-emission tomography; SE, standard error; SUVR, standard uptake value ratio.
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.

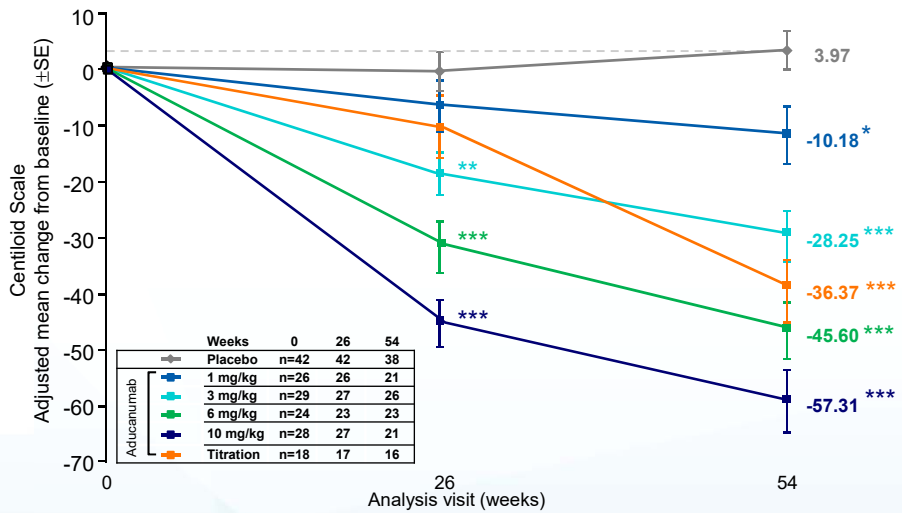
1. Viglietta et al. Aducanumab titration dosing regimen: 12-month interim analysis from PRIME, a randomized, double-blind, placebo-controlled Phase 1b study in patients with prodromal or mild Alzheimer's disease. Presented at the 9th edition of Clinical Trials on Alzheimer's Disease (CTAD), December 8–10, 2016, San Diego, CA, USA; 2. Sevigny J, et al. Nature. 2016;537:50–56.

Aducanumab target engagement: dose- and time-dependent reduction in amyloid plaque in SUVR and centiloid

Change in SUVR[1]



Change in centiloid[2]



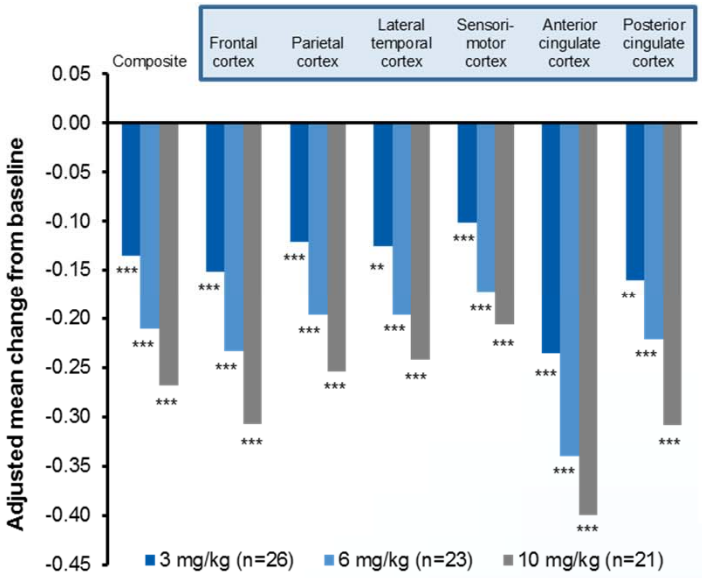
Standardization:

- Centiloid facilitates cross ligand / cross trial comparison

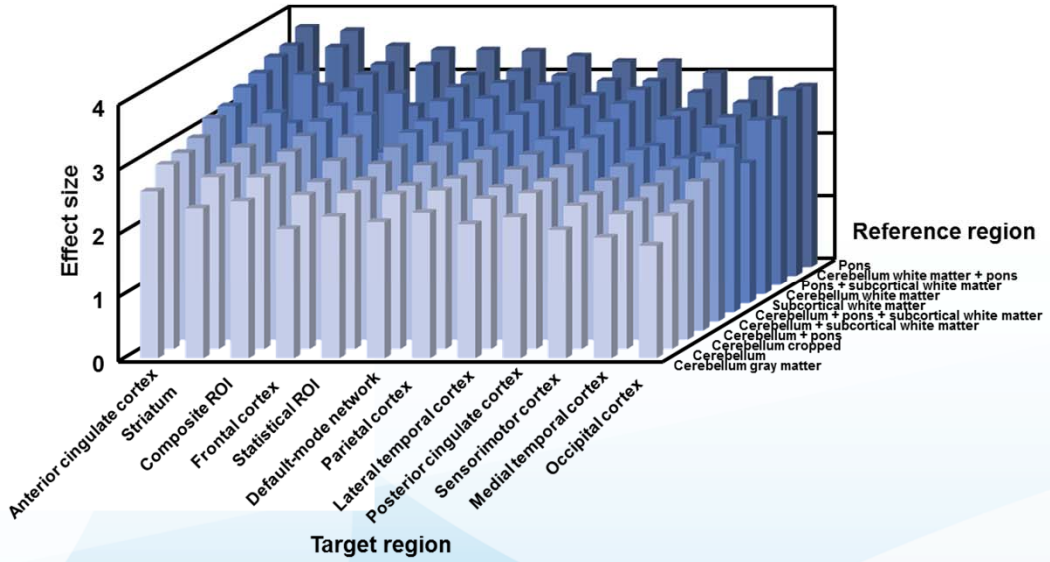
ANCOVA, analysis of covariance; SE, standard error; SUVR, standard uptake value ratio.
Nominal p values: * P<0.05; **P<0.01; ***P<0.001 vs placebo. Analyses based on observed data. ANCOVA for change from baseline with factors of treatment, laboratory ApoE ε4 status (carrier and non-carrier), and baseline 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. 1. Viglietta et al. Aducanumab titration dosing regimen: 12-month interim analysis from PRIME, a randomized, double-blind, placebo-controlled Phase 1b study in patients with prodromal or mild Alzheimer's disease. Presented at the 9th edition of Clinical Trials on Alzheimer's Disease (CTAD), December 8–10, 2016, San Diego, CA, USA Viglietta et al. Data presented at CTAD 2016; 2. Data on file.

Dose- and time-dependent reductions in SUVR observed with aducanumab regardless of reference/target regions

Aducanumab reduces amyloid plaque in regions anticipated to have amyloid

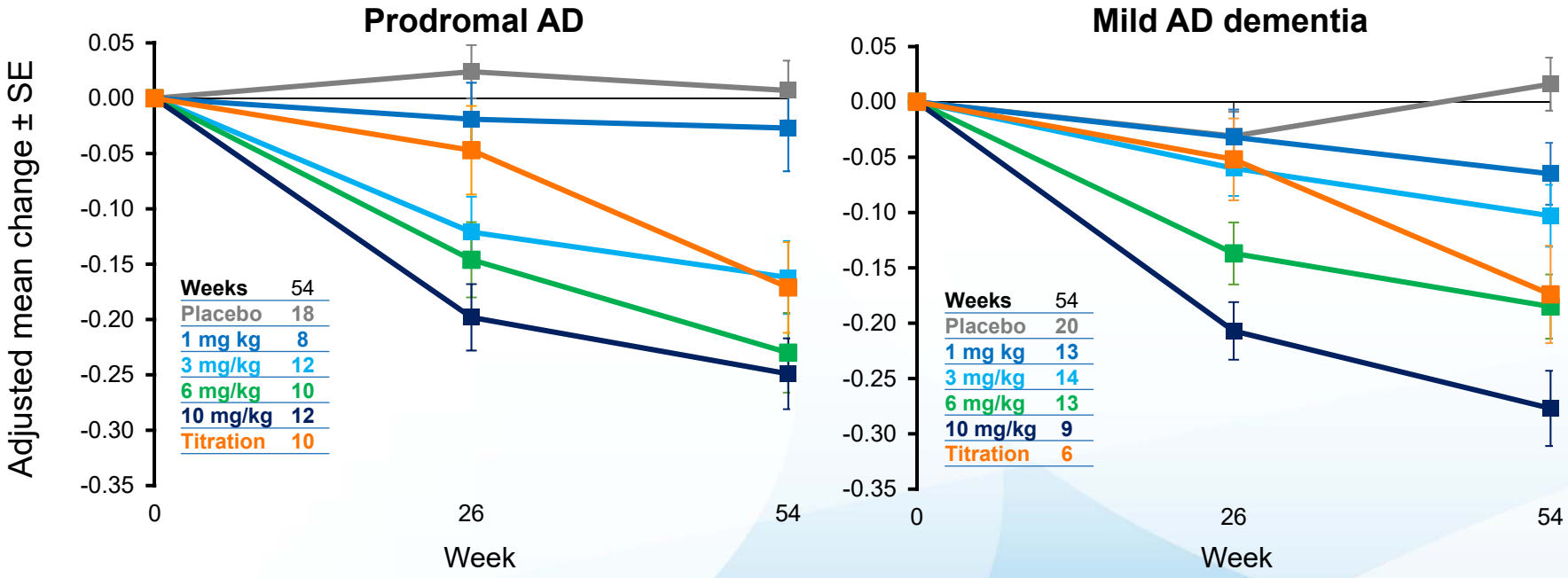


Effect size for each brain target region in 10 mg/kg aducanumab group by reference region at week 54



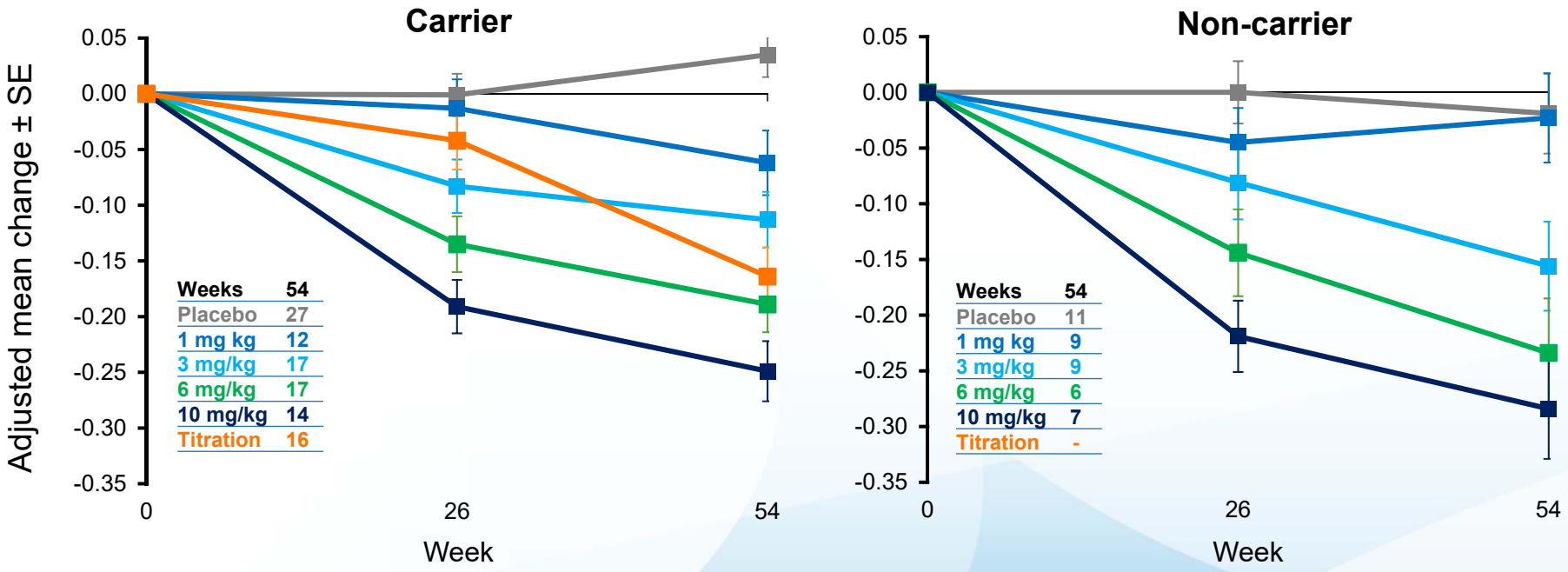
SUVR, standard uptake value ratio.
P<0.05; **P<0.01; ***P<0.001 vs placebo. Analyses based on observed data. ANCOVA for change from baseline with factors of treatment, laboratory ApoE ε4 status (carrier and non-carrier), and baseline composite SUVR. PD analysis population is defined as all randomized patients who received at least 1 dose of study medication and had at least 1 post-baseline assessment of the parameter.
Chiao P et al. J Nucl Med. 2018;pii: jnumed.118.209130. [Epub ahead of print]; Sevigny J et al. Nature. 2016;537:50-56.

Aducanumab reduction in amyloid plaque is equivalent across prodromal/MCI due to AD and Mild AD dementia



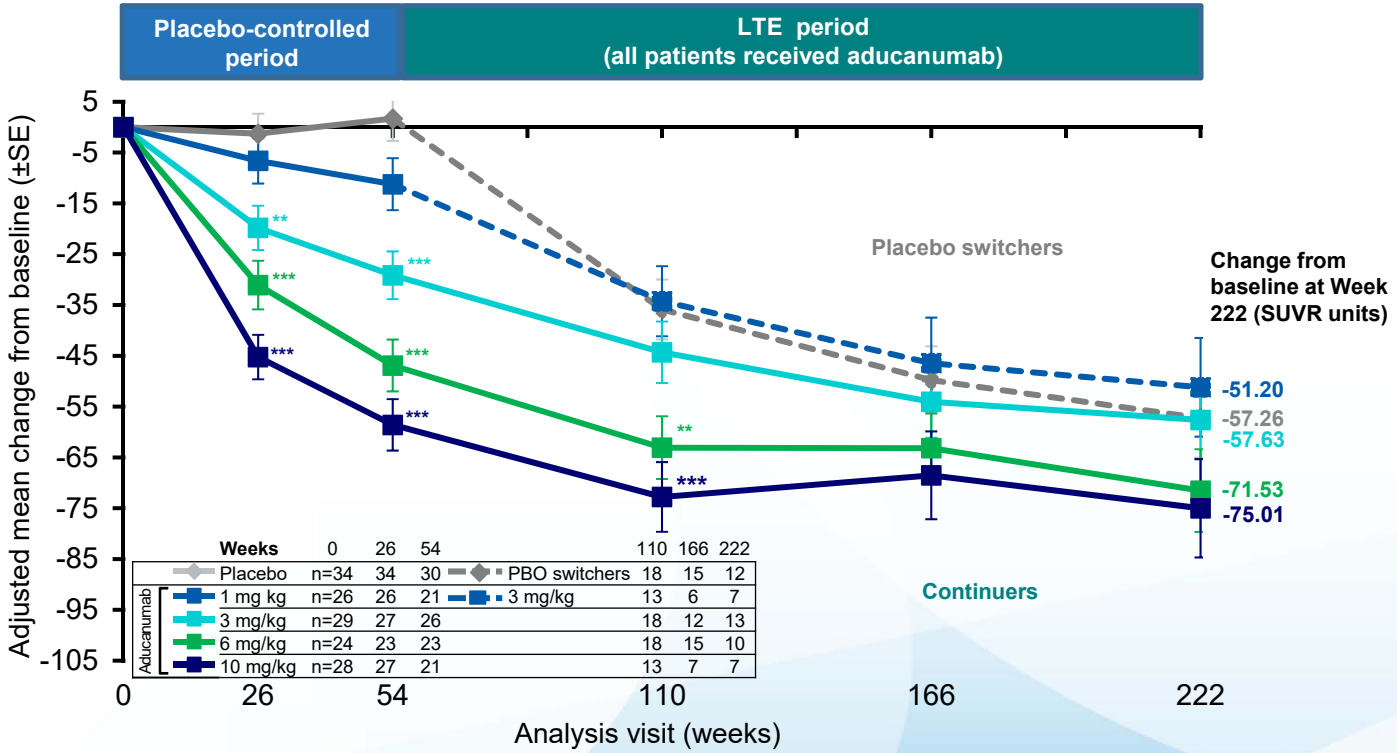
MCI, mild cognitive impairment; ANCOVA, analysis of covariance; SE, standard error.
Analysis based on ANCOVA model with factors of treatment, ApoE ε4 status (carrier/non-carrier) and baseline.
Data on file.

Aducanumab reduction in amyloid plaque is equivalent in ApoE ε4 carriers and non-carriers



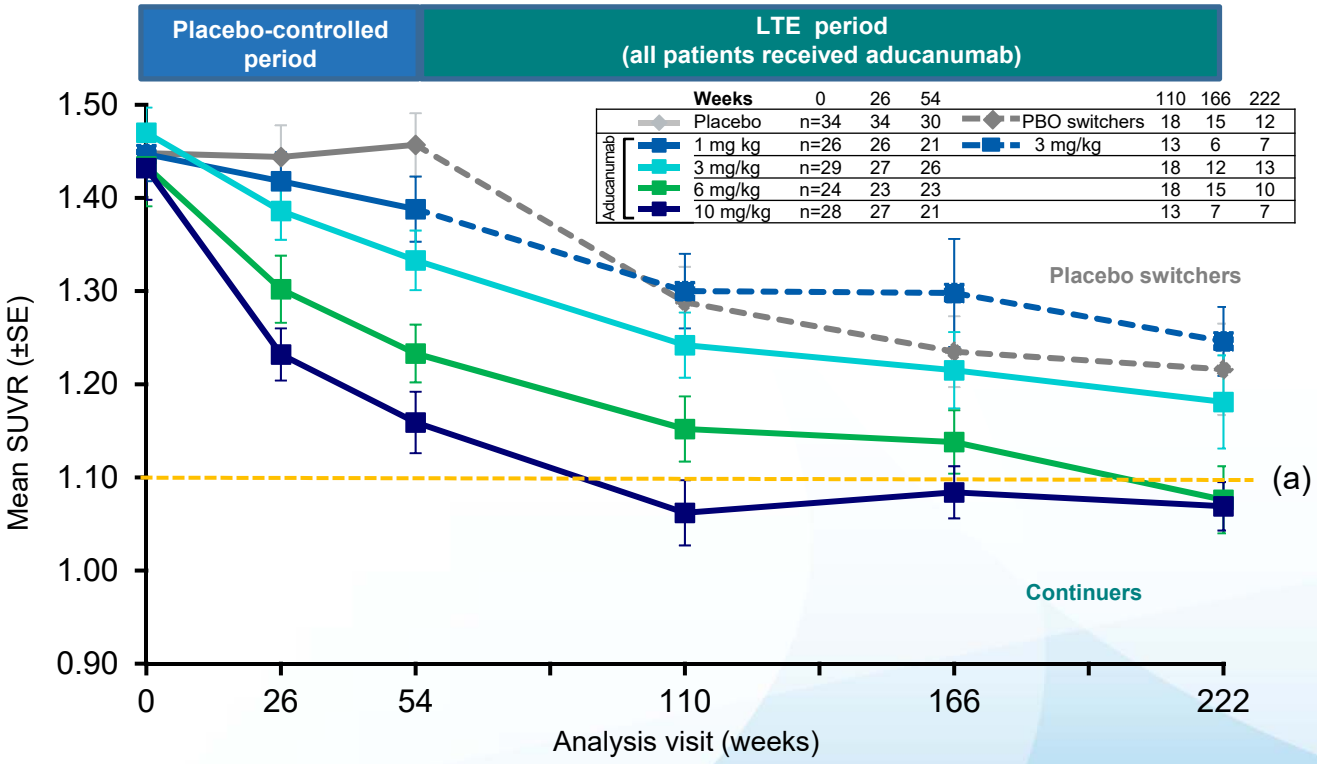
ANCOVA, analysis of covariance; SE, standard error.
Analysis based on ANCOVA model with factors of treatment and baseline.
Data on file.

Aducanumab continues to reduce amyloid plaque levels over 48 Months – by up to 75 centiloid units



LTE, long-term extension; MMRM, mixed model for repeated measures; PBO, placebo; SE, standard error, SUVR, standard uptake value ratio.
* P<0.05; ** P<0.01; *** P<0.001 vs PBO in the placebo-controlled period and vs PBO switchers in the LTE period.
Results based on MMRM, fitted with change from baseline as a dependent variable, and included fixed effects for categorical treatment, categorical visit and treatment-by-visit interaction, continuous baseline value, and laboratory ApoE ε4 status (carrier and non-carrier). Data on file.

Aducanumab reduction in amyloid plaque falls below a purported SUVR cut point for positive pathology



[a]The value of 1.10 is a purported quantitative cut-point that discriminates between positive and negative scans.[1]

LTE, long-term extension; SUVR, standardized uptake value ratio; SE, standard error.

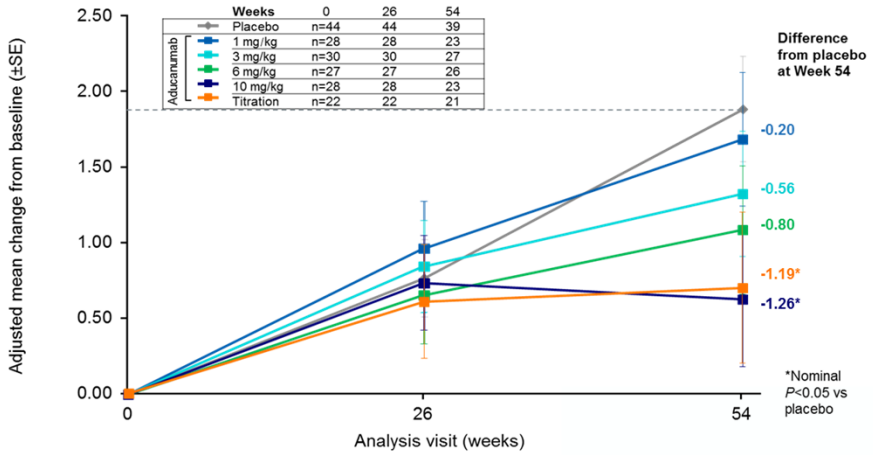
1. Joshi AD, et al. J Nucl Med. 2015;56:1736-1741.

Data on file.

Clinical endpoints
(Exploratory endpoints in Phase 1b study)

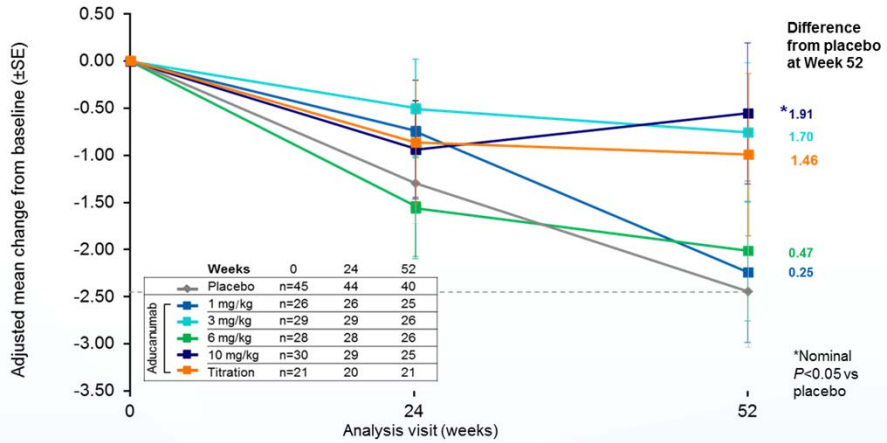
Clinical proof of concept: effect of aducanumab on clinical decline as measured by CDR-SB & MMSE

Change in CDR-SB



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 subjects who received at least 1 dose of study medication and had at least 1 post-baseline questionnaire assessment

Change in MMSE

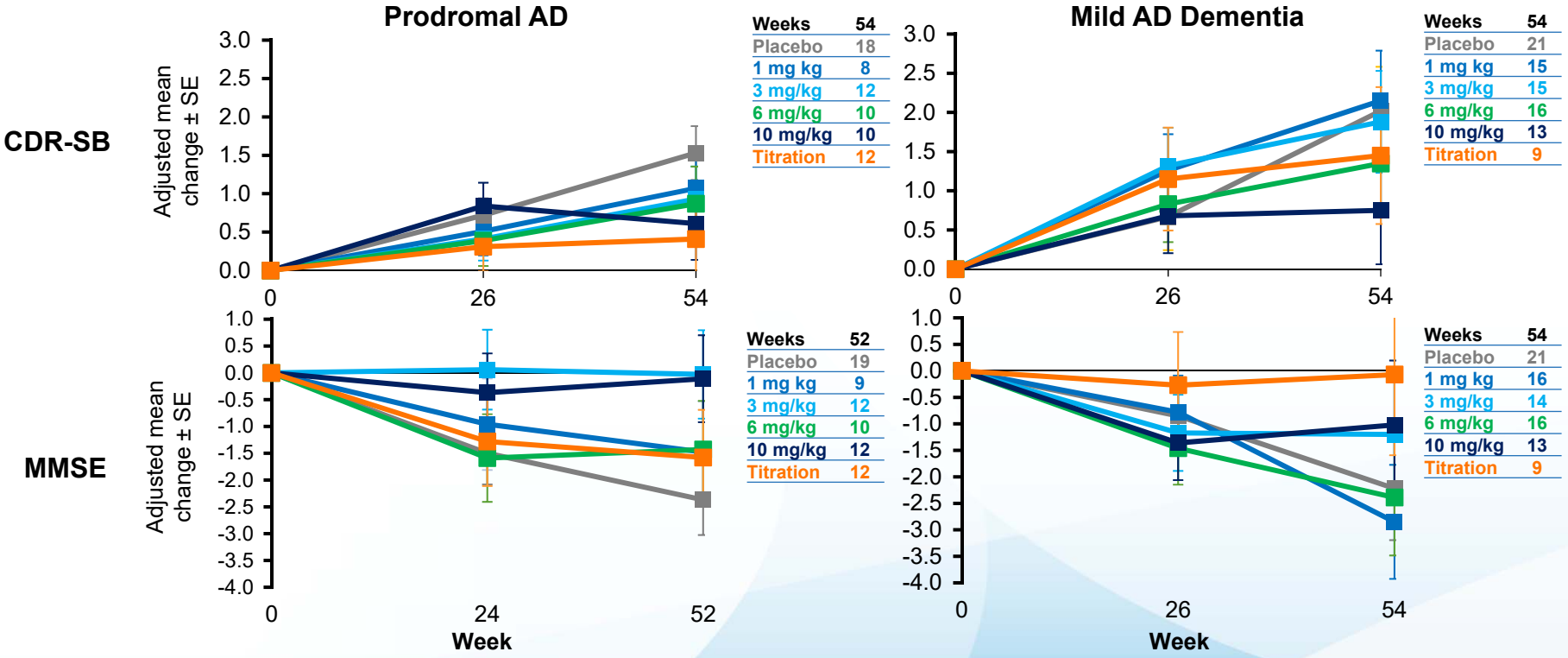


MMSE is an exploratory endpoint. Analyses based on observed data. ANCOVA for change from baseline with factors of treatment, laboratory ApoE ε4 status (carrier and non-carrier), and baseline MMSE. Efficacy analysis population is defined as all randomized patients who received at least 1 dose of study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

MMRM, mixed model for repeated measures. CDR-SB, Clinical Dementia Rating–Sum of Boxes; LTE, long-term extension; PBO, placebo; SE, standard error.

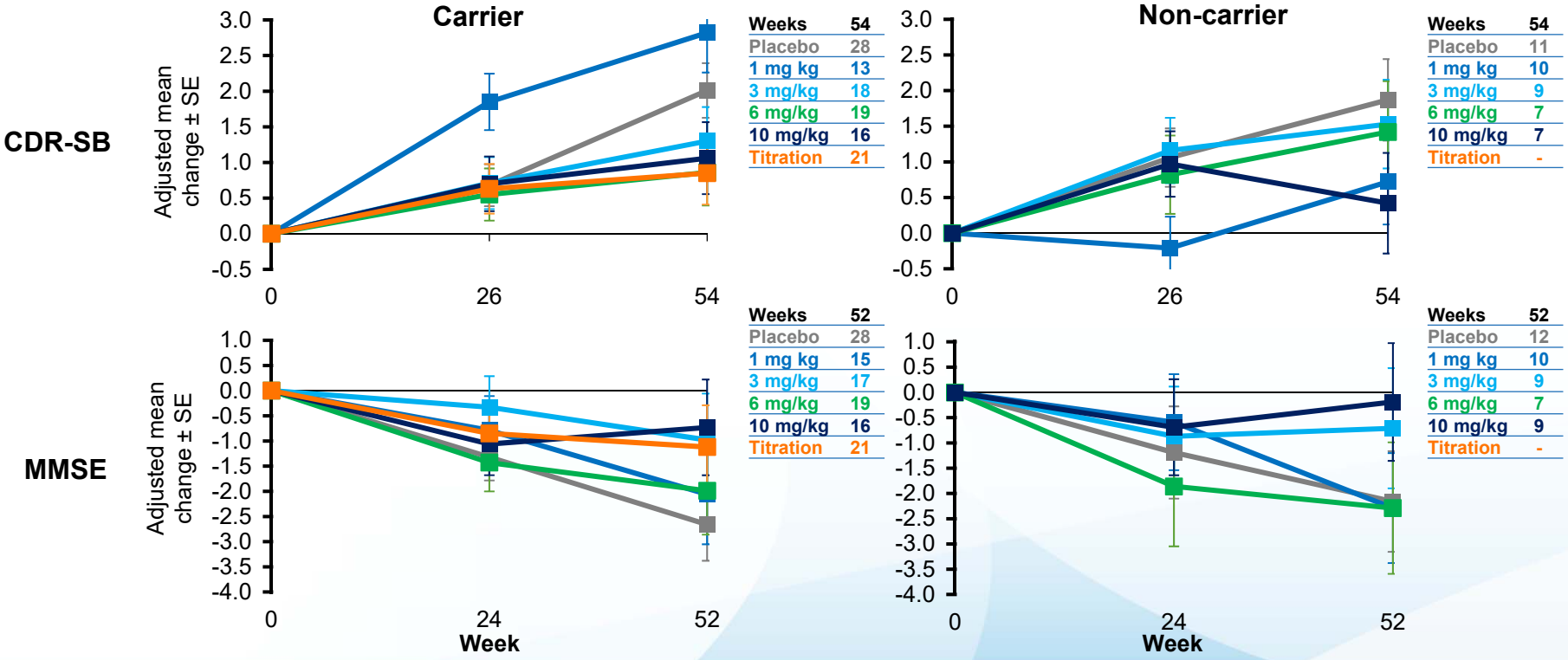
Viglietta et al. Aducanumab titration dosing regimen: 12-month interim analysis from PRIME, a randomized, double-blind, placebo-controlled Phase 1b study in patients with prodromal or mild Alzheimer's disease. Presented at the 9th edition of Clinical Trials on Alzheimer's Disease (CTAD), December 8–10, 2016, San Diego, CA, USA.

Clinical stage impacts disease progression in the placebo arms but does not impact treatment effect of aducanumab



MMSE, Mini–Mental State Examination; CDR-SB, Clinical Dementia Rating-Sum of Boxes; SE, standard error; ANCOVA, analysis of covariance.
Analysis based on ANCOVA model with factors of treatment, ApoE ε4 status (carrier/non-carrier) and baseline.
Data on file.

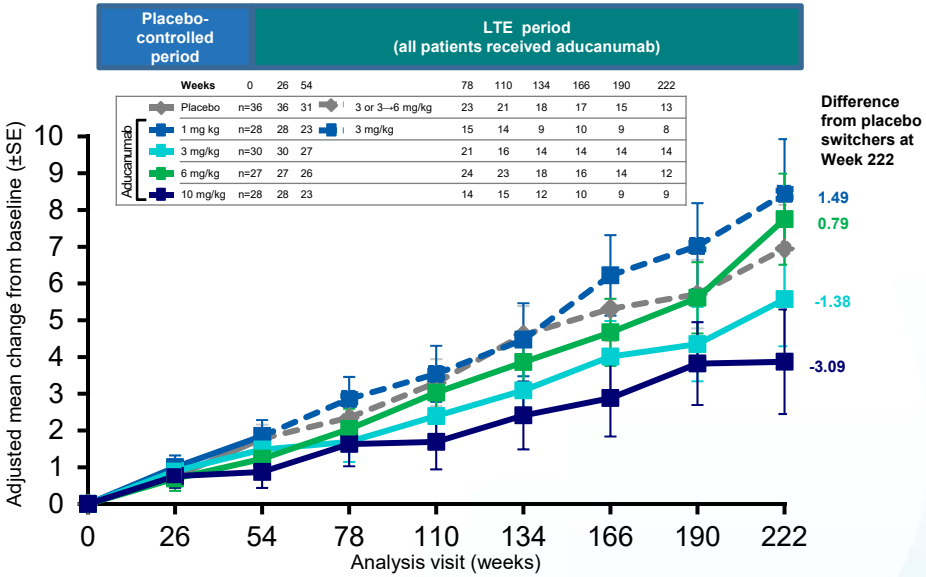
ApoE ε4 status does not impact disease progression or treatment effect with Aducanumab on CDR-SB and MMSE



MMSE, Mini–Mental State Examination; CDR-SB, Clinical Dementia Rating-Sum of Boxes; SE, standard error; ANCOVA, analysis of covariance
Analysis based on ANCOVA model with factors of treatment, ApoE E4 status (carrier/non-carrier) and baseline.
Data on file.

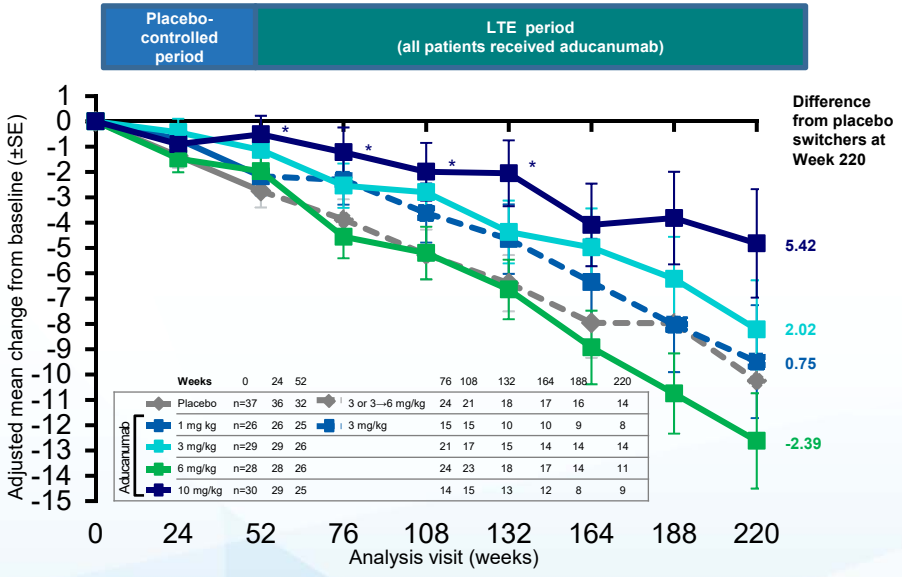
PRIME: Treatment up to 48 months CDR–SB & MMSE data suggests clinical benefit in patients continuing aducanumab

Change in CDR-SB



CDR-SB is an exploratory endpoint. Results based on MMRM, fitted with change from baseline as a dependent variable, and included fixed effects for categorical treatment, categorical visit and treatment-by-visit interaction, continuous baseline value, and laboratory ApoE ε4 status (carrier and non-carrier).

Change in MMSE



*P<0.05 (vs placebo [Week 52] or placebo switchers [Weeks 76,108,132,164,188 and 220]). MMSE is an exploratory endpoint. Results based on MMRM, fitted with change from baseline as a dependent variable, and included fixed effects for categorical treatment, categorical visit and treatment-by-visit interaction, continuous baseline value, and laboratory ApoE ε4 status (carrier and non-carrier).

MMRM, mixed model for repeated measures. CDR-SB, Clinical Dementia Rating–Sum of Boxes; LTE, long-term extension; PBO, placebo; SE, standard error.
Analysis based on ANCOVA model with factors of treatment, ApoE E4 status (carrier/non-carrier) and baseline.
Data on file.

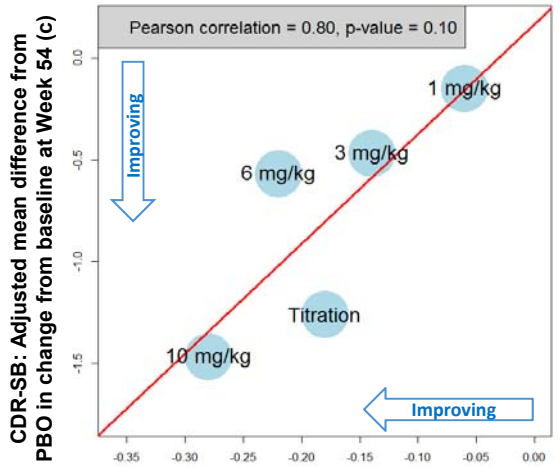
PRIME: Reduction in brain amyloid correlates with slowing of cognitive decline at the individual and group levels

At the Individual-subject Level
Reduction in brain amyloid is significantly correlated with slowing of cognitive decline as measured by CDR-SB in the 10 mg/kg group at Week 54

At the Group (Dose) Level
Treatment-induced reduction in brain amyloid is correlated with treatment-induced slowing of cognitive decline as measured by CDR-SB at Week 54

Correlation between changes in PET SUVR and CDR-SB at Week 54 adjusting for baseline PET SUVR (a)

	N	Pearson correlation	P-value
Placebo	37	-0.03	0.8854
1 mg/kg	21	0.03	0.9163
3 mg/kg	26	0.49	0.0119
6 mg/kg	23	0.24	0.2861
Titration	16	0.39	0.1485
10 mg/kg	19	0.64	0.0034

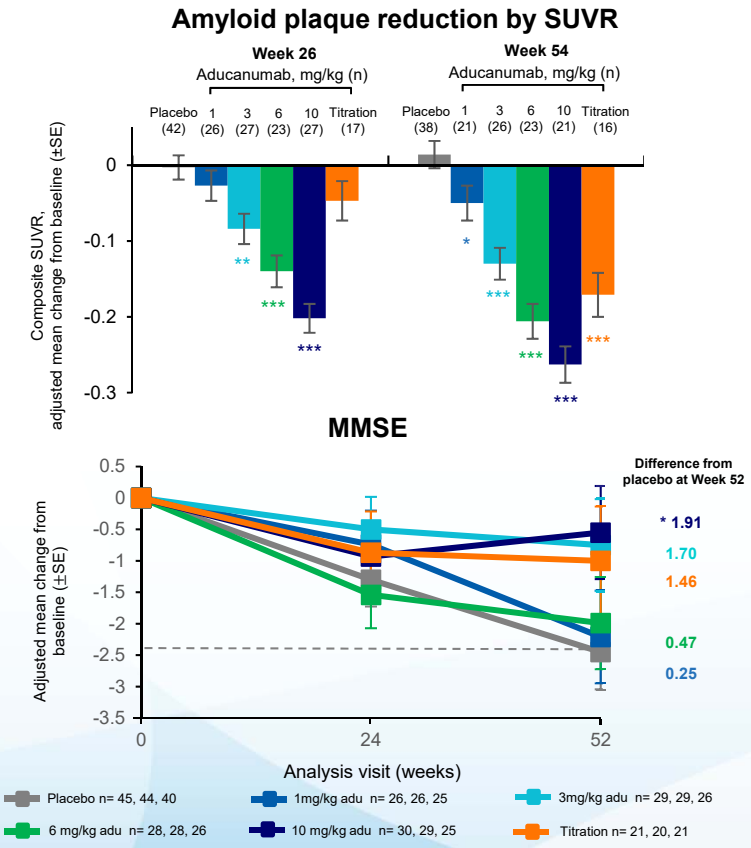


Amyloid PET SUVR: Adjusted mean difference from placebo in change from baseline at Week 54 (b)

Data on file. Analyses based on subjects who had changes from baseline at Week 54 in both amyloid PET SUVR and CDR-SB. Amyloid PET SUVR is calculated using whole cerebellum.
a. The partial correlations that adjusted for the baseline amyloid PET SUVR were presented.
b. Based on ANCOVA for change from baseline in PET SUVR, with factors of treatment, laboratory ApoE ε4 status (carrier and non-carrier) and baseline PET.
c. Based on ANCOVA for change from baseline in CDR-SB, with factors of treatment, laboratory ApoE ε4 status (carrier and non-carrier), baseline CDR-SB, and baseline PET.

What about the 6 mg/kg cohort?

- **PET performs as expected in the 6mg/kg cohort**
- **But 6 mg/kg does not perform as expected on the clinical endpoints – particularly MMSE**
- We have done an extensive review of the data
  - No detectable differences in baseline characteristics
  - Baseline MMSE and CDR-SB scores not different than other cohorts
  - Placebo decline of 6mg/kg cohort is consistent with other cohorts
  - No detectable enrollment, site/rater differences
    - Majority of data was collected prior to announcement of first results in 1, 3, and 10 mg/kg cohorts.
- These sample sizes are very small for clinical endpoints; PRIME was not powered to detect clinical effects
- The inconsistency is either due to chance alone, resulting from the small sample sizes, or caused by unknown or unobserved factors.
- In the phase 3 study, parallel group design and larger sample size should address similar inconsistencies

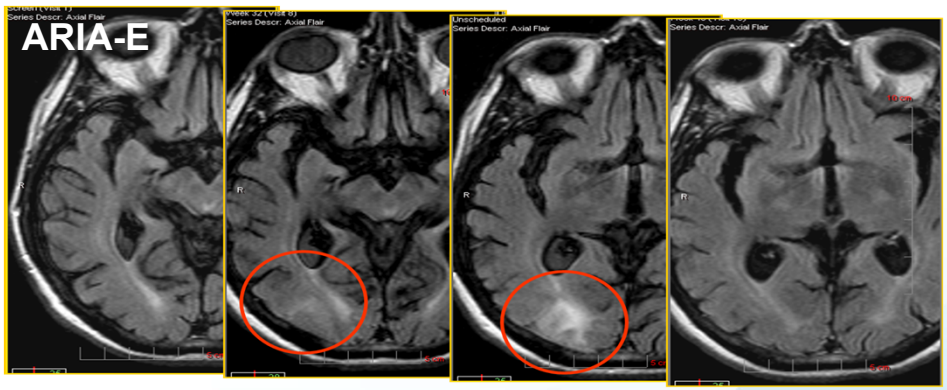


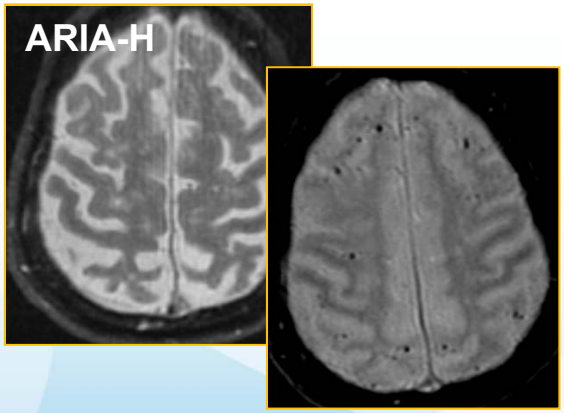
ANCOVA, analysis of covariance; ARIA-E, amyloid-related imaging abnormalities - vasogenic edema; CDR-SB, Clinical Dementia Rating–Sum of Boxes; MMSE, Mini-Mental State Examination; SE, standard error; SUVR, standard uptake value ratio. Nominal p values: * *P*<0.05; ** *P*<0.01; *** *P*<0.001 vs placebo. Analyses based on observed data. ANCOVA for change from baseline with factors of treatment, laboratory ApoE ε4 status (carrier and non-carrier), and baseline CDR-SB. Efficacy analysis population is defined as all randomized subjects who received at least 1 dose of study medication and had at least 1 post-baseline questionnaire assessment. 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 et al. Aducanumab titration dosing regimen: 12-month interim analysis from PRIME, a randomized, double-blind, placebo-controlled Phase 1b study in patients with prodromal or mild Alzheimer's disease. Presented at the 9th edition of Clinical Trials on Alzheimer's Disease (CTAD), December 8–10, 2016, San Diego, CA, USA.

Safety

ARIA (amyloid related imaging abnormalities)

- The term ARIA refers to a spectrum of MRI signal abnormalities observed in the clinical trials of amyloid lowering agents.
- Image presentation as vasogenic edema (ARIA-E) or deposition of heme products (ARIA-H)
- Spontaneous ARIA-like events can occur in untreated AD and CAA
- The mechanism leading to ARIA are not fully elucidated
    - Putative pathophysiological basis thought to be increased vascular permeability triggered by removal of parenchymal/ vascular amyloid





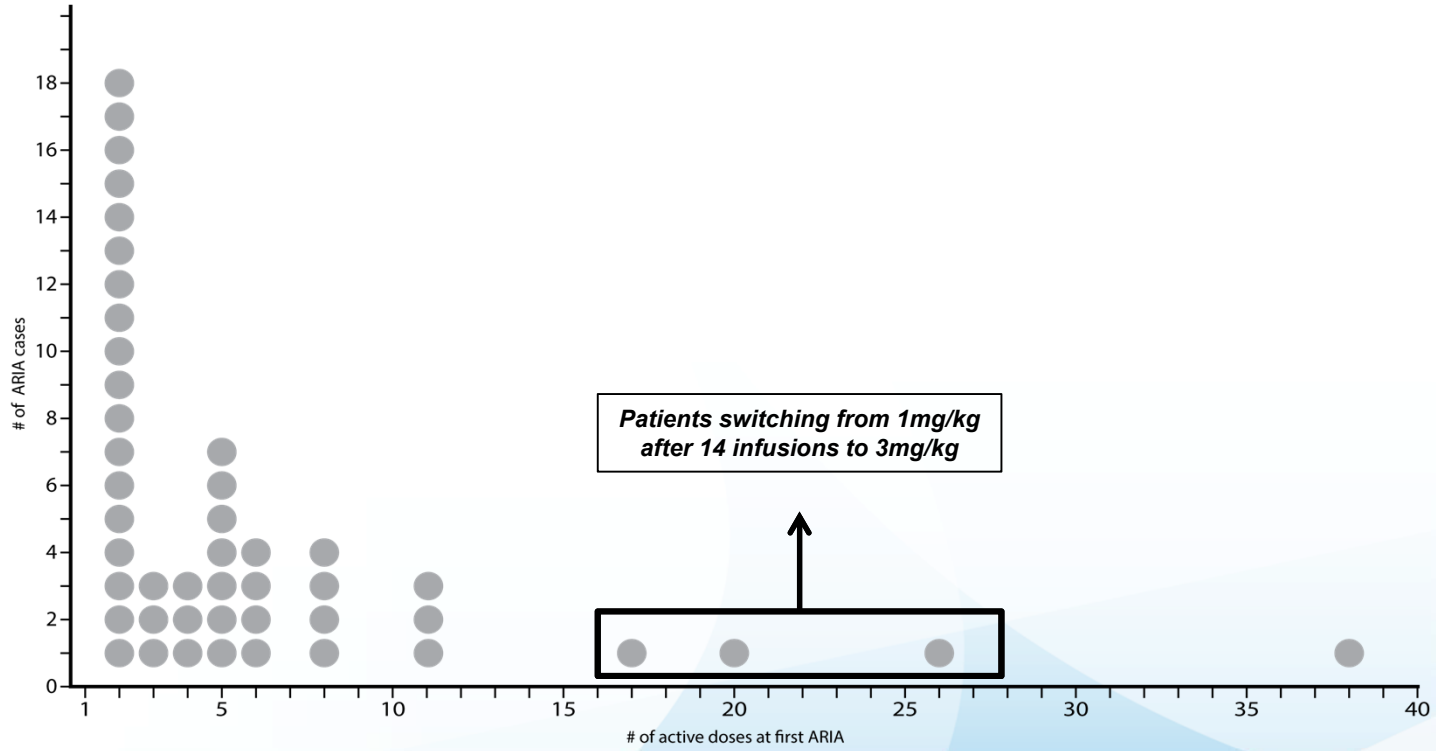
ARIA, amyloid related imaging abnormalities; CAA, Cerebral Amyloid Angiopathy.
Sperling R et al. Alzheimers Dement. 2011;7:367-385.

ARIA characteristics in PRIME

- Since the start of the PRIME study, ARIA-E has been observed in 46 of the 185 patients doses with aducanumab, with a cumulative incidence of 25% over the course of the study
- Of the 46 patients with ARIA-E (± ARIA-H), 28 (61%) were asymptomatic and 18 (39%) had associated symptoms, which were typically mild
- ARIA-E resolved on MRI in 44 of 46 patients and was ongoing in 2 patients at the time of withdrawal. In most cases resolving as assessed by MRI 4-12 weeks after onset
- 8 patients experienced more than one event of ARIA-E (recurrent ARIA-E) which was similar to initial events
- The incidence of ARIA-E in fixed dose cohorts was dose-dependent and occurred more frequently in ApoE ε4 carriers
- The incidence of ARIA-E during the placebo-controlled period was lower in ApoE ε4 carriers receiving aducanumab titrated to 10mg/kg (35%) than in ApoE e4 carriers receiving fixed doses of 6mg/kg (43%) or 10mg/kg (55%) of aducanumab
- The incidence of ARIA-H not accompanied by ARIA-E in the placebo-controlled period was low and similar across dose groups

ARIA-E, amyloid-related imaging abnormalities - vasogenic edema; ARIA-H, amyloid-related imaging abnormalities – haemosiderin.
Data on file.

ARIA-E tends to occur early in the course of treatment with aducanumab



ARIA-E, amyloid-related imaging abnormalities - vasogenic edema.
Data on file.

What we will learn (Phase 3)

Aducanumab Phase 3 studies ENGAGE & EMERGE

Studies	Two 18-month, randomized, double-blind, placebo-controlled, Phase 3 studies
Geography	~360 sites in 20 countries
Population	▪ MCI due to AD + mild AD dementia • MMSE 24-30, CDR-G 0.5, RBANS ≤ 85, enriched using Amyloid PET
Doses	▪ Two dose levels (low & high) and placebo, randomized 1:1:1
Duration	▪ 18 months; followed by long-term extension
Primary endpoint	▪ CDR sum of boxes
Other endpoints	▪ Secondary: MMSE, ADAS-Cog 13, ADCS-ADL-MCI ▪ Biomarkers: Aβ PET, tf-MRI, ASL-MRI, PBMC, blood-based biomarkers ▪ Sub-studies: Amyloid PET, Tau PET, CSF disease-related markers
Sample size	▪ ~1605 per study

Strong engagement and high interest of clinical sites/community in aducanumab

- ~12,500 patients screened
- Enrollment has completed July 2018

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); ASL-MRI, arterial spin labelling MRI; fMRI, functional MRI; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; PBMC, peripheral blood mononuclear cells; PET, positron-emission tomography; RBANS, Repeatable Battery for Assessment of Neuropsychological Status.

ClinicalTrials.gov: https://clinicaltrials.gov/ct2/show/NCT02477800. Accessed October 24, 2018; ClinicalTrials.gov: https://clinicaltrials.gov/ct2/show/NCT02484547. Accessed October 24, 2018; Data on file.

With thanks!

Patients, their caregivers, our Investigators and staff at the clinical trial sites

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