Therapeutic Reversal of Amyloid and Tau Pathologies in Alzheimer's Disease

and how it translates into slowed clinical decline

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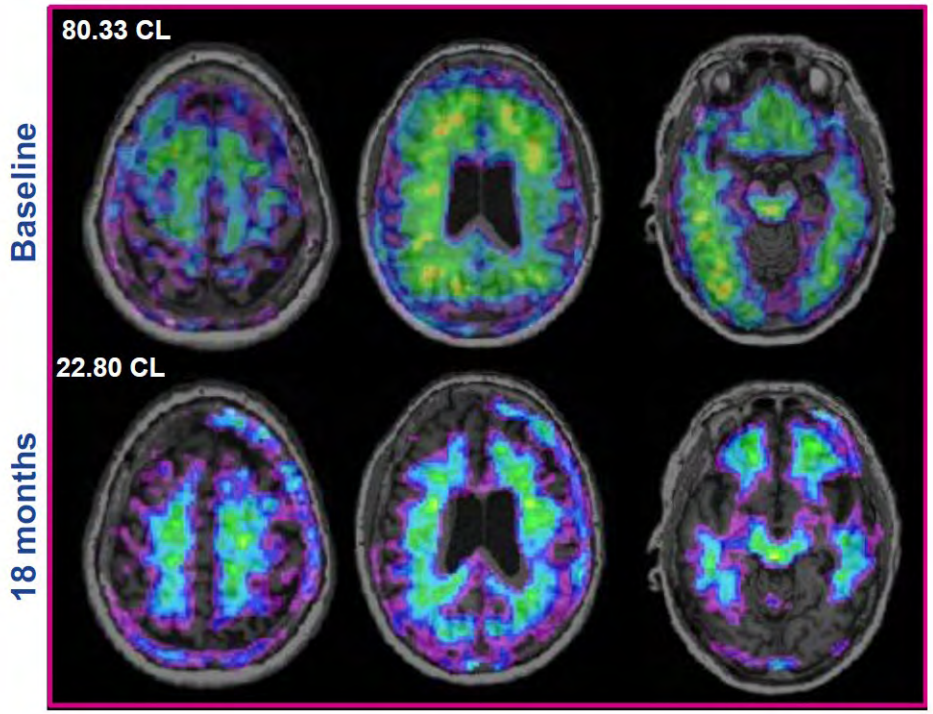
neurimmune

Disclosures

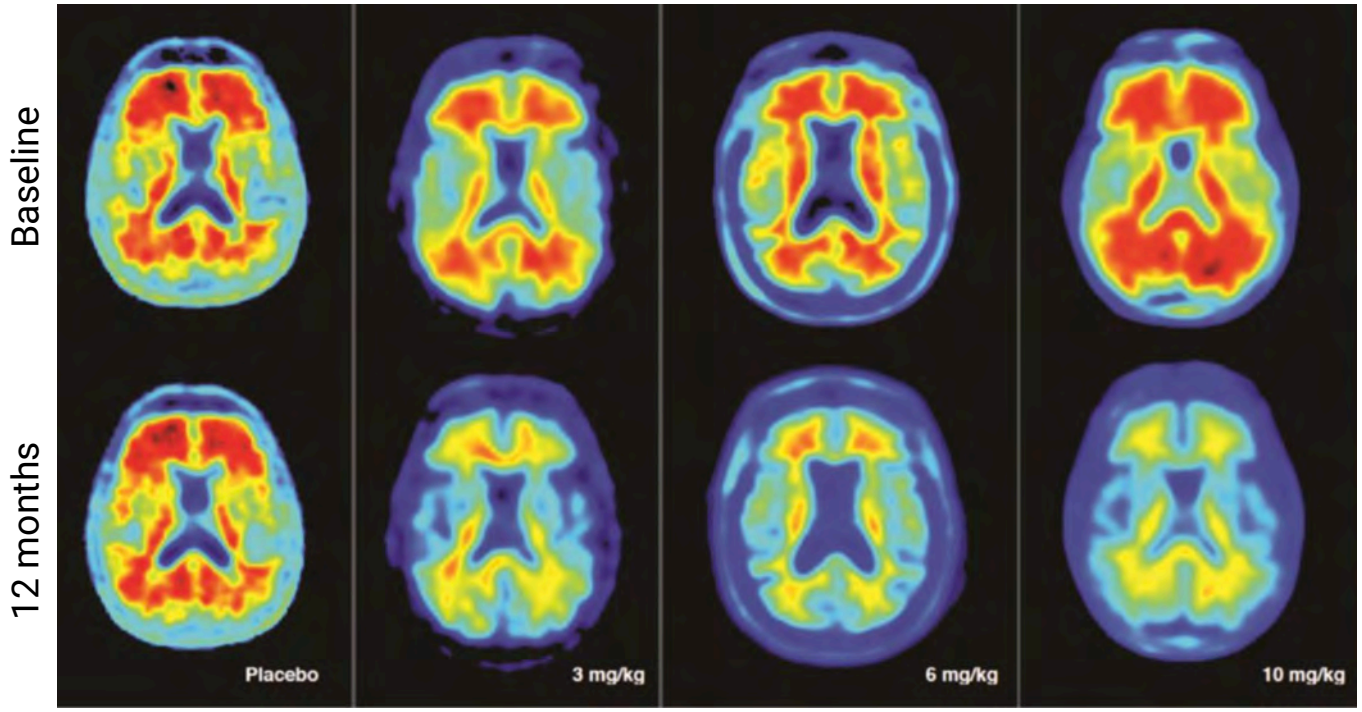
- Employee and shareholder of Neurimmune, a University of Zurich spin-off company.
- Inventor on patent families relating to aducanumab.
- Neurimmune licensed rights in aducanumab to Biogen.

Amyloid depletion is becoming a clinical reality

Lecanemab



Aducanumab



Amyloid-PET in Alzheimer's disease before and during treatment.

van Dyck *et al., CTAD* 2022 (https://www.eisai.com/ir/)
Sevigny *et al., Nature* 2016

Immunization with amyloid-β attenuates Alzheimer-disease-like pathology in the PDAPP mouse

Dale Schenk, Robin Barbour, Whitney Dunn, Grace Gordon, Henry Grajeda, Teresa Guido, Kang Hu, Jiping Huang, Kelly Johnson-Wood, Karen Khan, Dora Kholodenko, Mike Lee, Zhenmei Liao, Ivan Lieberburg, Ruth Motter, Linda Mutter, Ferdie Soriano, George Shopp, Nicki Vasquez, Christopher Vandevert, Shannan Walker, Mark Wogulis, Ted Yednock, Dora Games & Peter Seubert

Elan Pharmaceuticals, 800 Gateway Boulevard, South San Francisco, California 94080, USA

NATURE | VOL 400 | 8 JULY 1999 | www.nature.com

Neuron, Vol. 38, 547–554, May 22, 2003, Copyright ©2003 by Cell Press

Antibodies against β-Amyloid Slow Cognitive Decline in Alzheimer's Disease

Christoph Hock,* Uwe Konietzko, Johannes R. Streffer, Jay Tracy, Andri Signorell, Britta Müller-Tillmanns, Ulrike Lemke, Katharina Henke, Eva Moritz, Esmeralda Garcia, M. Axel Wollmer, Daniel Umbricht, Dominique J.F. de Quervain, Marc Hofmann, Alessia Maddalena, Andreas Papassotiropoulos, and Roger M. Nitsch*

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doi:10.1038/nature19323

The antibody aducanumab reduces Aβ plaques in Alzheimer's disease

Jeff Sevigny[1]*, Ping Chiao[1]*, Thierry Bussière[1]*, Paul H. Weinreb[1]*, Leslie Williams[1], Marcel Maier[2], Robert Dunstan[1], Stephen Salloway[3], Tianle Chen[1], Yan Ling[1], John O'Gorman[1], Fang Qian[1], Mahin Arastu[1], Mingwei Li[1], Sowmya Chollate[1], Melanie S. Brennan[1], Omar Quintero-Monzon[1], Robert H. Scannevin[1], H. Moore Arnold[1], Thomas Engber[1], Kenneth Rhodes[1], James Ferrero[1], Yaming Hang[1], Alvydas Mikulskis[1], Jan Grimm[2], Christoph Hock[2,4], Roger M. Nitsch[2,4]§ & Alfred Sandrock[1]§

50 | NATURE | VOL 537 | 1 SEPTEMBER 2016

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 6, 2021 VOL. 384 NO. 18

Donanemab in Early Alzheimer's Disease

Mark A. Mintun, M.D., Albert C. Lo, M.D., Ph.D., Cynthia Duggan Evans, Ph.D., Alette M. Wessels, Ph.D., Paul A. Ardayfio, Ph.D., Scott W. Andersen, M.S., Sergey Shcherbinin, Ph.D., JonDavid Sparks, Ph.D., John R. Sims, M.D., Miroslaw Brys, M.D., Ph.D., Liana G. Apostolova, M.D., Stephen P. Salloway, M.D., and Daniel M. Skovronsky, M.D., Ph.D.

The NEW ENGLAND JOURNAL of MEDICINE

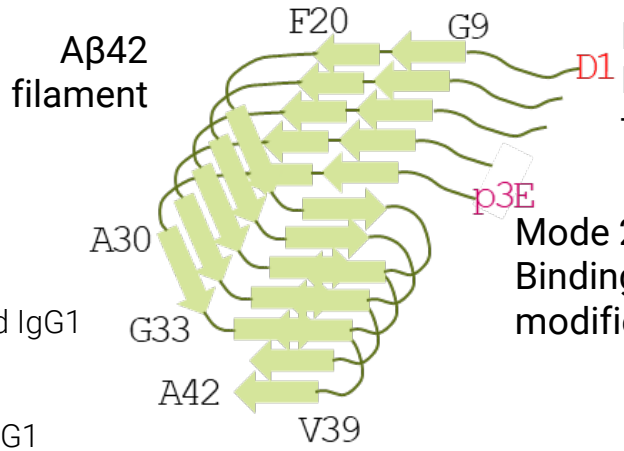
ORIGINAL ARTICLE

Lecanemab in Early Alzheimer's Disease

C.H. van Dyck, C.J. Swanson, P. Aisen, R.J. Bateman, C. Chen, M. Gee, M. Kanekiyo, D. Li, L. Reyderman, S. Cohen, L. Froelich, S. Katayama, M. Sabbagh, B. Vellas, D. Watson, S. Dhadda, M. Irizarry, L.D. Kramer, and T. Iwatsubo

Lecanemab, Aducanumab and Donanemab target the Aβ N-terminus

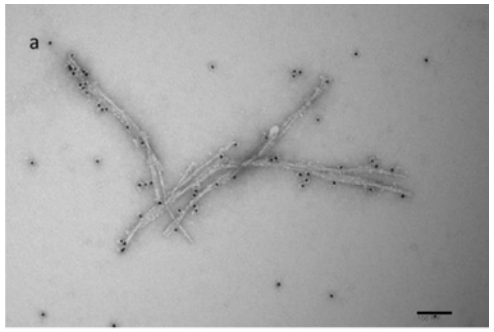
Aβ aggregate selectivity - no Aβ monomer binding



Mode 1:
High-avidity binding
to exposed N-termini

Mode 2:
Binding to post-translationally
modified $Aβ_{pE3}$ N-termini

Aβ42 fibril binding



Example: Aducanumab

Lecanemab A2-S8 humanized IgG1

Aducanumab E3-D7 human IgG1

N DAEFRHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMVGGVVIA C

1 β1 β2 β3 β4 β5 42

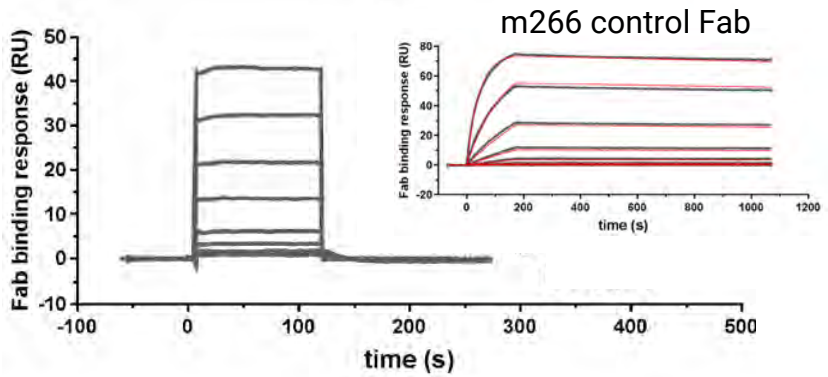
hydrolysis & pyroglutamate formation

N pEFRHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMVGGVVIA C

42

Donanemab pE3-D7 humanized IgG1

>10,000-fold selectivity over Aβ monomer



Aducanumab Fab rapid offrate
indicates absent monomer binding

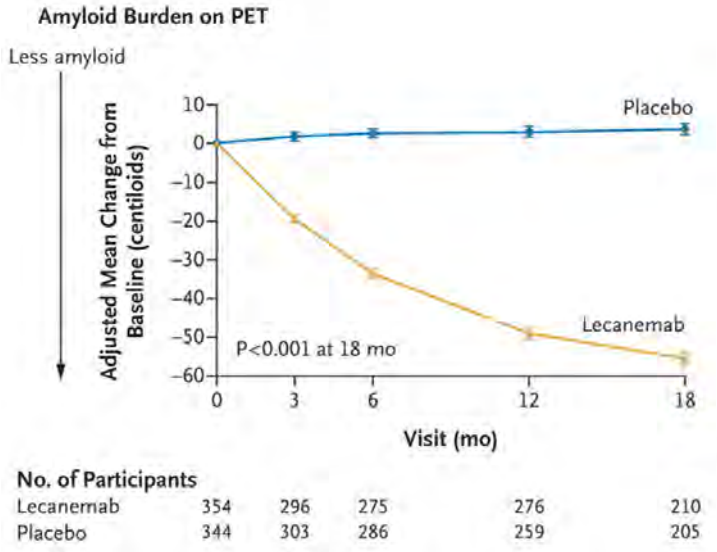
Yang *et al., Science* 2022; Bahri *et al., PNAS* 2022; Plotkin *et al., Neurobiol. Dis.*, 2020; Arndt JW *et al., Sci. Rep.* 2018; Greiner *et al., Science* 2017; Colvin *et al., J. Am. Chem. Soc.* 2015 ; Osswald, *SEB Nordic Healthcare Seminar* 2022; Oswald *et al. Bioartic Company Presentation Nov.2021*; Bohrmann *et al., J. Alzheimers Dis.* 2012; DeMattos *et al., Neuron* 2012.

Dose- and time-dependent amyloid depletion in clinical trials with a total of more than 6000 patients

Amyloid removal down to amyloid-negative levels within 12 to 18 months

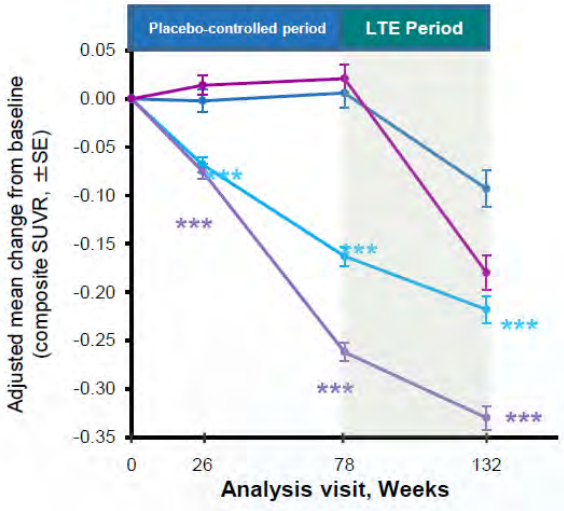
Lecanemab

CLARITY AD

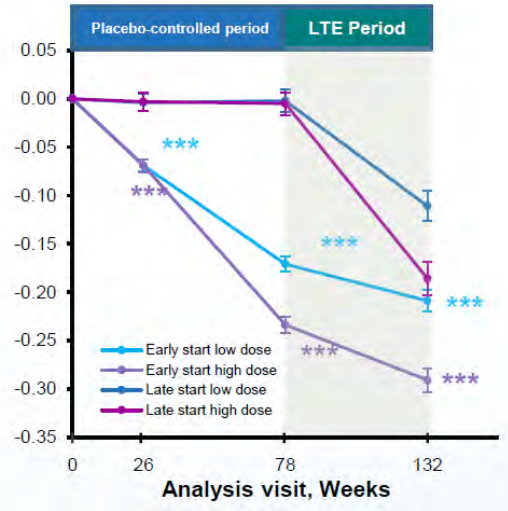


Aducanumab

EMERGE

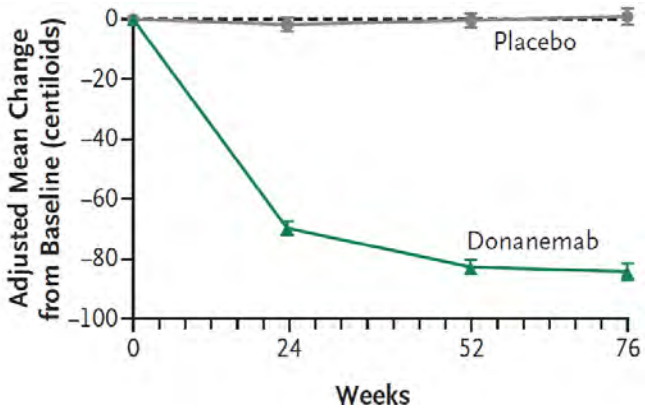


ENGAGE



Donanemab

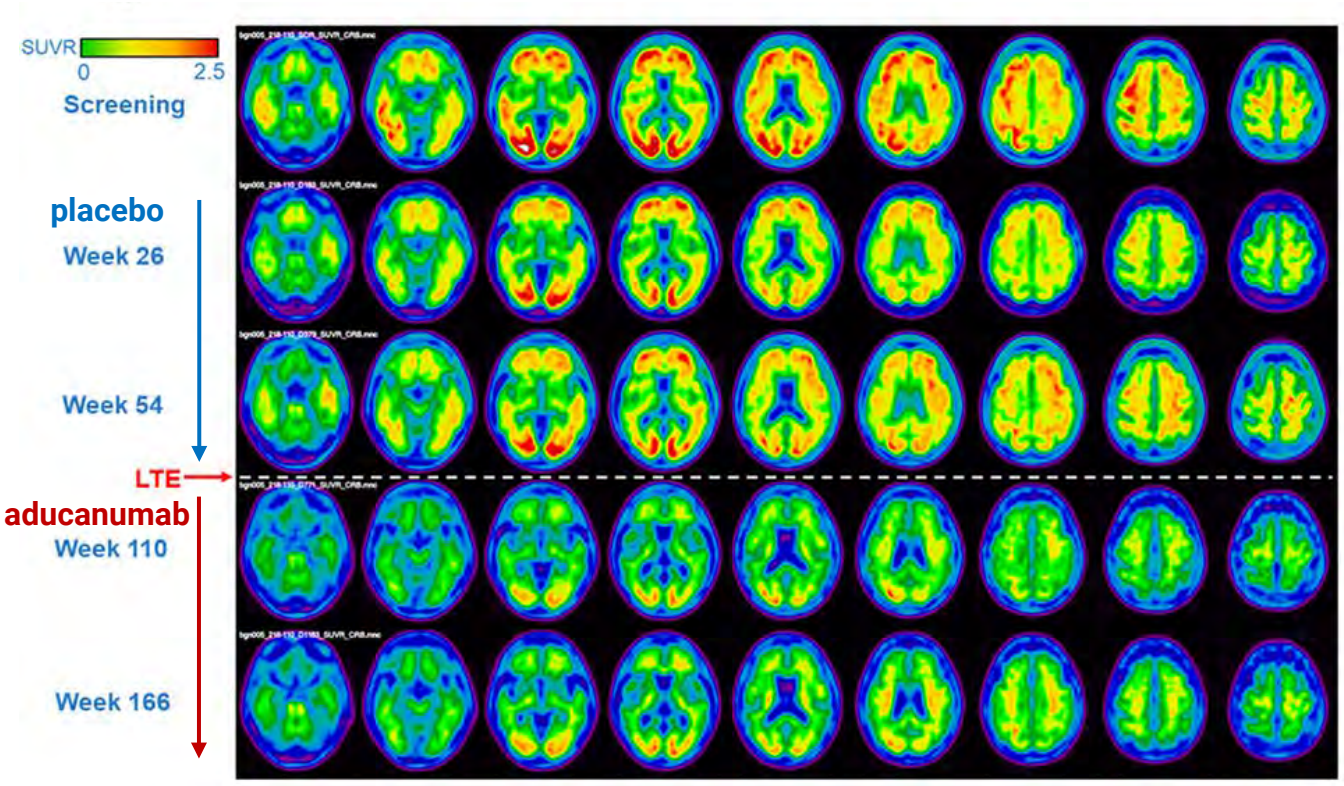
TRAILBLAZER-ALZ



Van Dyck *et al., NEJM 2022;* Budd Haeberlein *et al., JPAD* 2022; Budd Haeberlein *et al., AD/PD* 2021; Mintun *et al., NEJM* 2021

Neuropathology of amyloid depletion

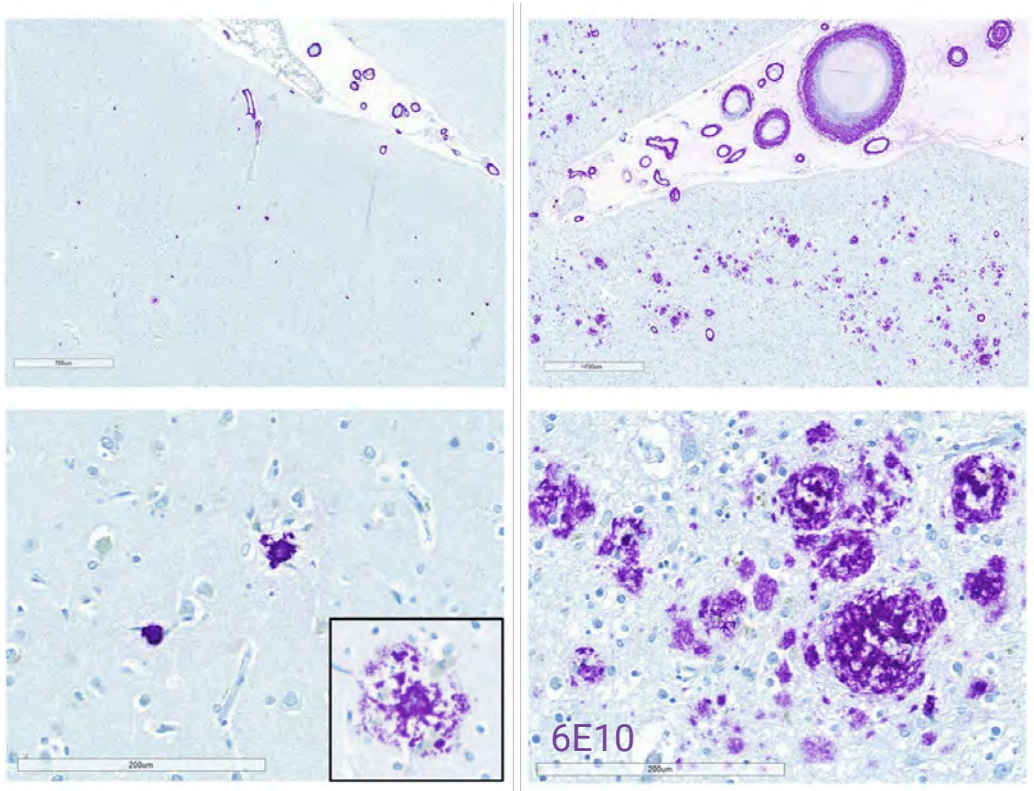
Amyloid PET during placebo and aducanumab LTE



widespread amyloid plaque removal,
moth-eaten residual plaques, preserved CAA

AD aducanumab-treated

AD untreated



32 monthly doses of aducanumab during LTE in an 84-year-old woman following 1 year of placebo

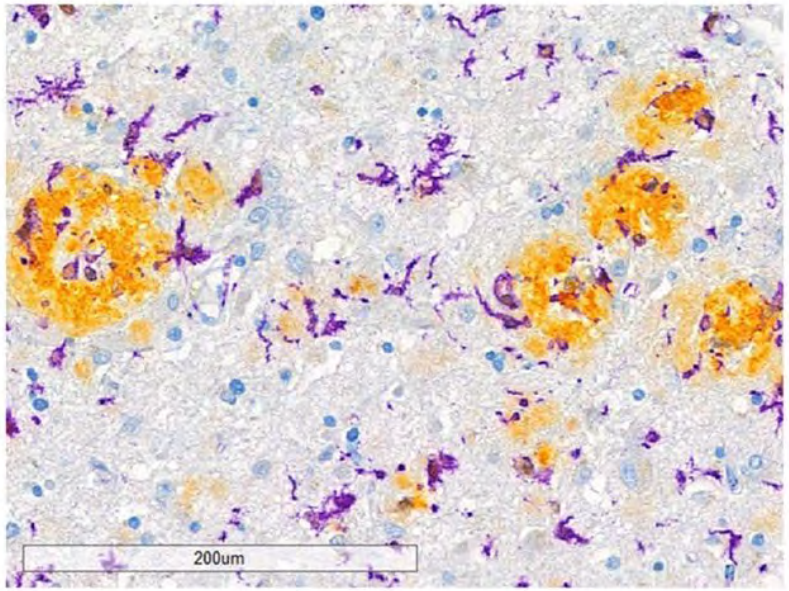
Plowey *et al., Acta Neuropathol.* 2022

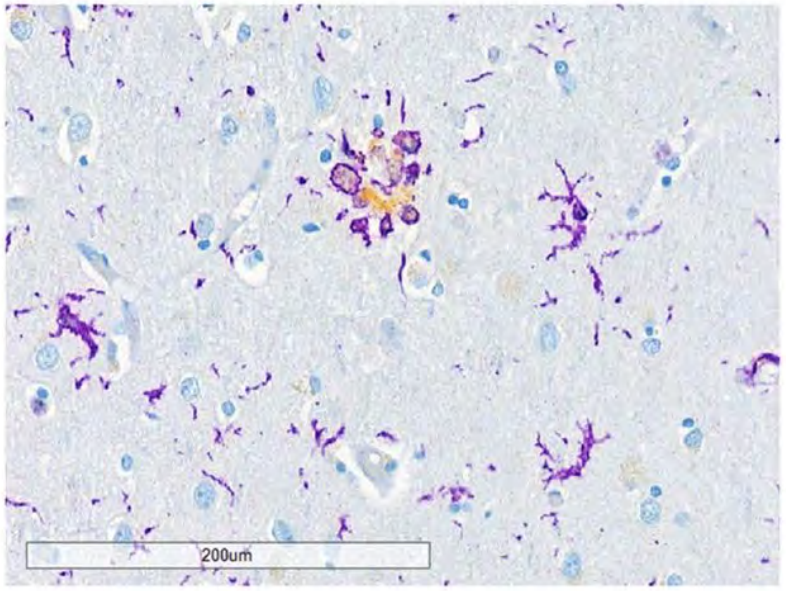
Amyloid depletion via FcγR–mediated microglia engagement

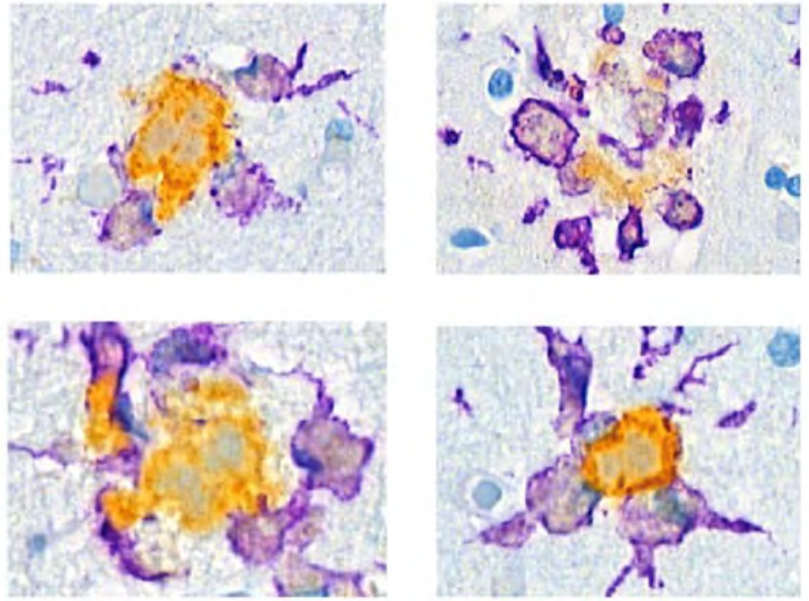
untreated AD

aducanumab-treated AD

aducanumab-treated AD







6E10 amyloid & IBA1 microglia

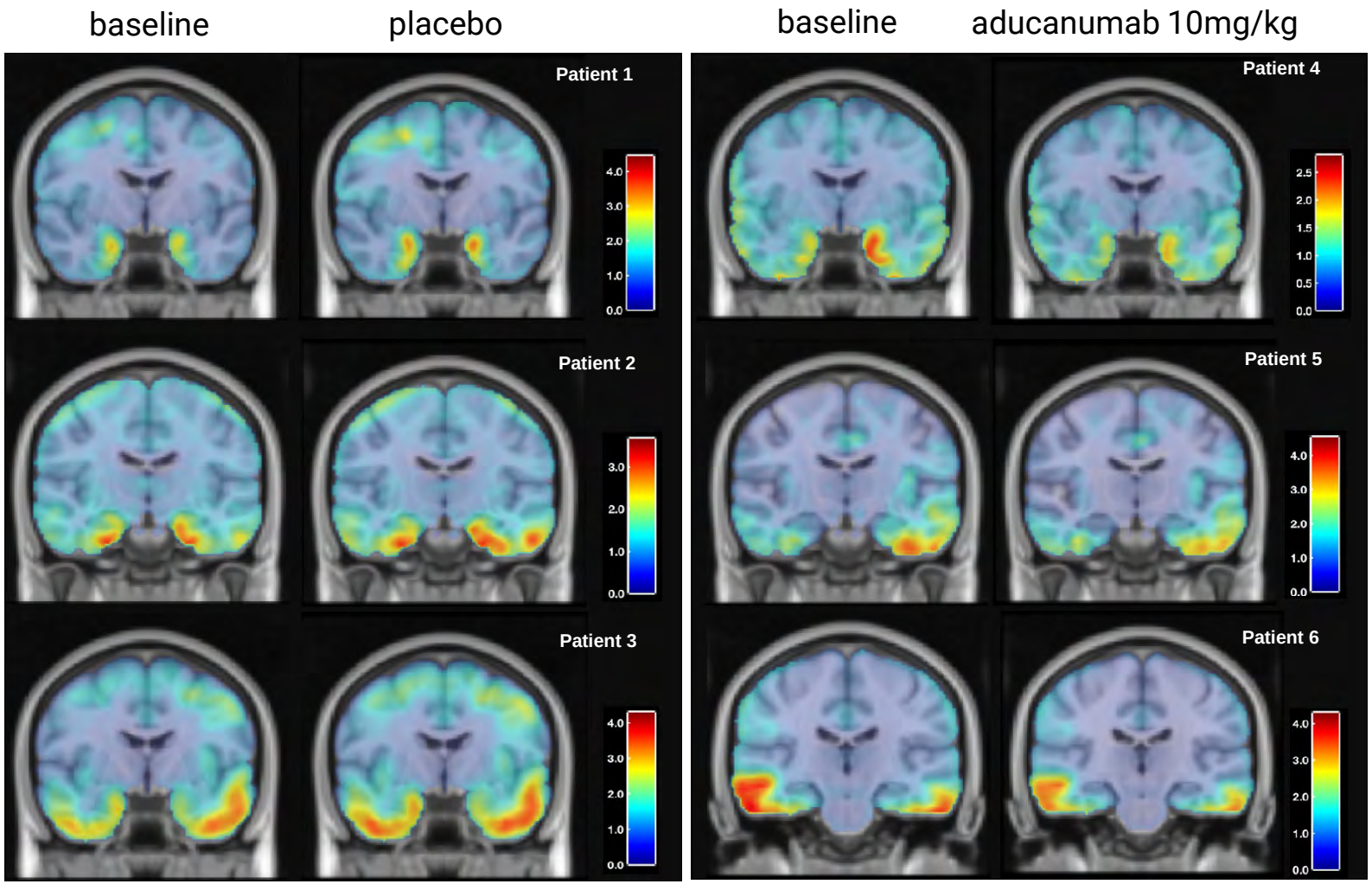
phagocytosing reactive microglia

Aducanumab PRIME LTE autopsy case. 84-yr woman 32 monthly doses in LTE.

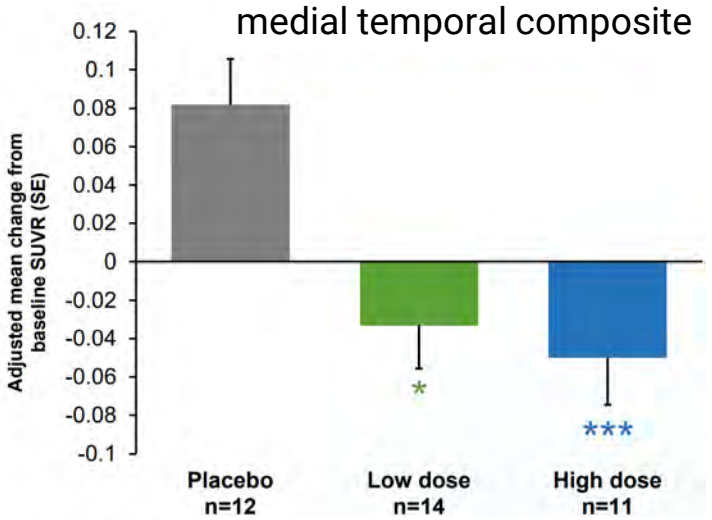
Similar autopsy findings in an AD patient who received lecanemab long-term treatment.

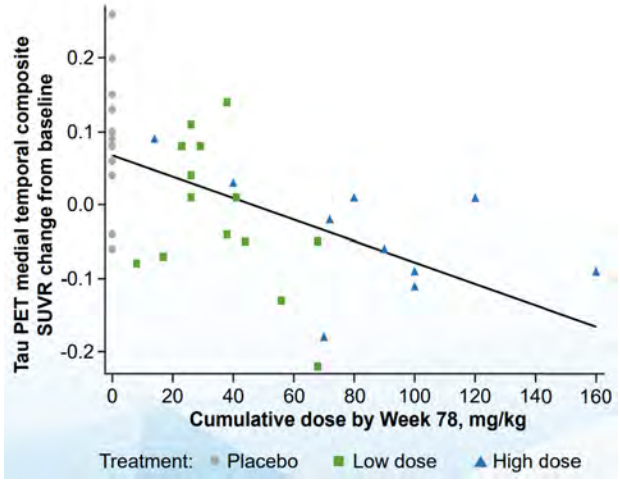
Plowey *et al., Acta Neuropathol.* 2022
Honig *et al., Poster AAIC* 2022

Reduced tau pathology



^{18}F-MK-6420 tau-PET in representative patients





*p<0.05; ***p<0.0001 vs. placebo

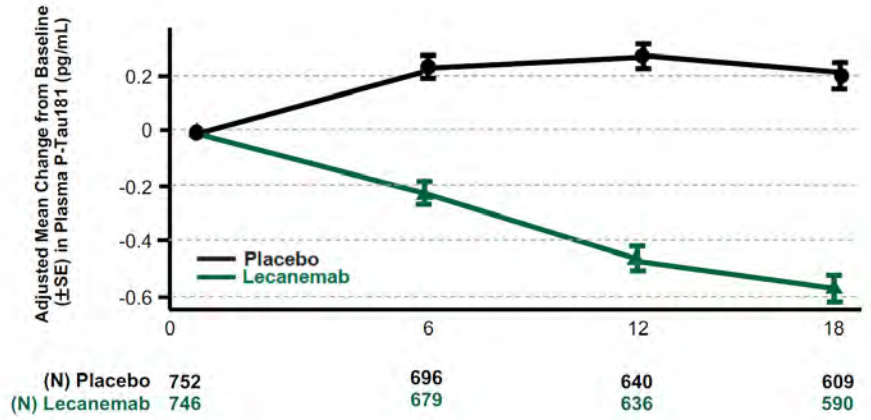
S. Budd Haeberlein *et al., CTAD* 2019; FDA prescribing information, Ref ID: 4822820

Reductions in plasma p-Tau

consistent with reductions in Tau PET imaging and CSF p-Tau

Lecanemab
Clarity AD

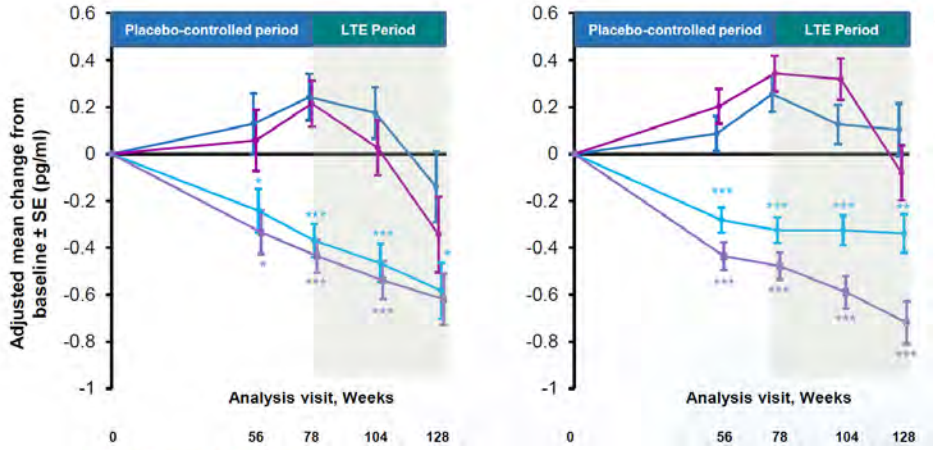
plasma p-Tau181



Bateman *et al., CTAD* 2022
Van Dyck *et al., NEJM* 2022

Aducanumab
EMERGE ENGAGE

plasma p-Tau181

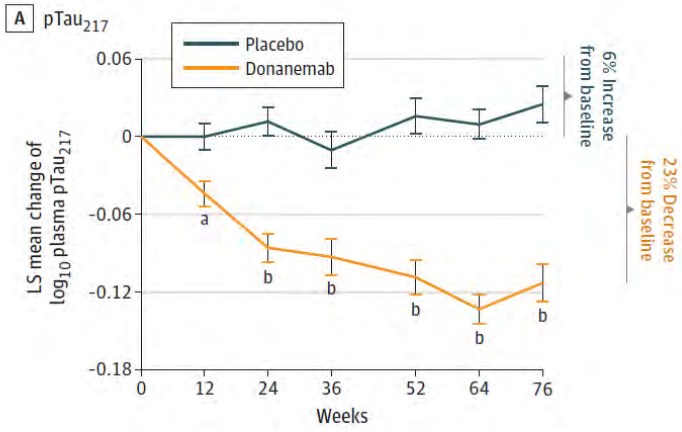


Late start low dose
Late start high dose
Early start low dose
Early start high dose

Budd Haeberlein *et al., AD/PD* 2021
Budd Haeberlein *et al., JPAD* 2022

Donanemab
TRAILBLAZER-ALZ

plasma p-Tau217

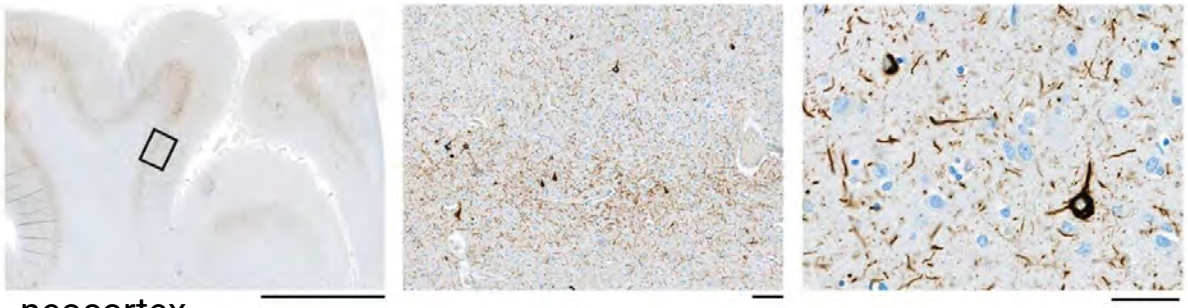


Mintun *et al., NEJM* 2021

Amyloid depletion is associated with low tau pathology

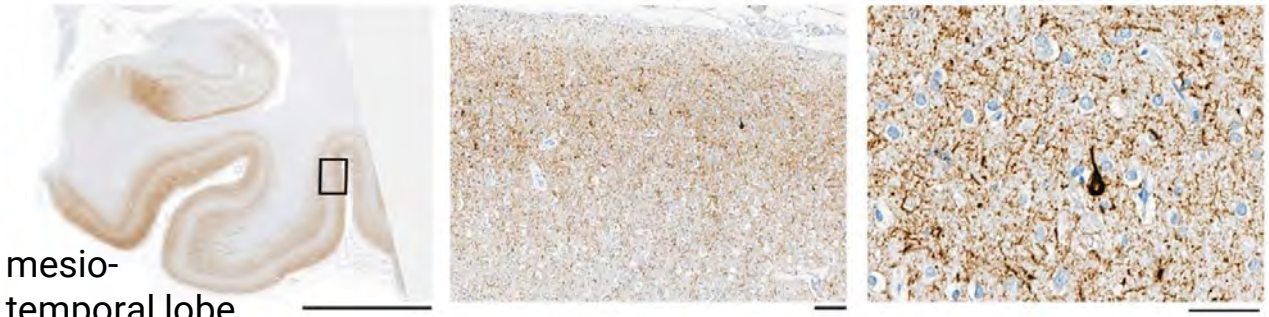
Phosphorylated pTau (40E8 staining)

aducanumab-treated AD



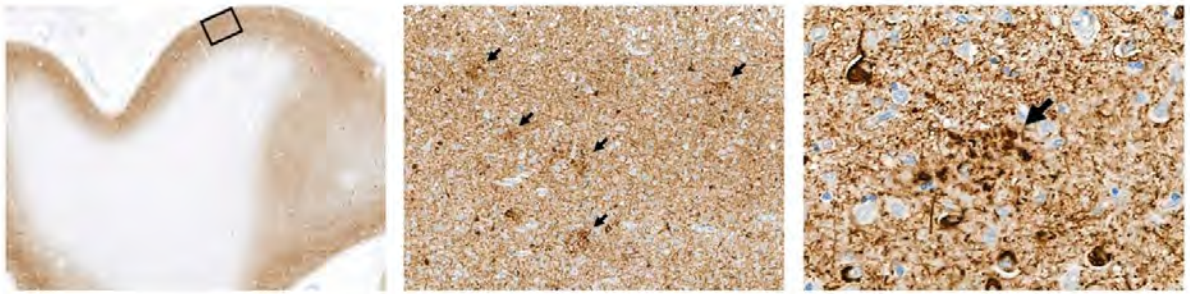
neocortex

aducanumab-treated AD

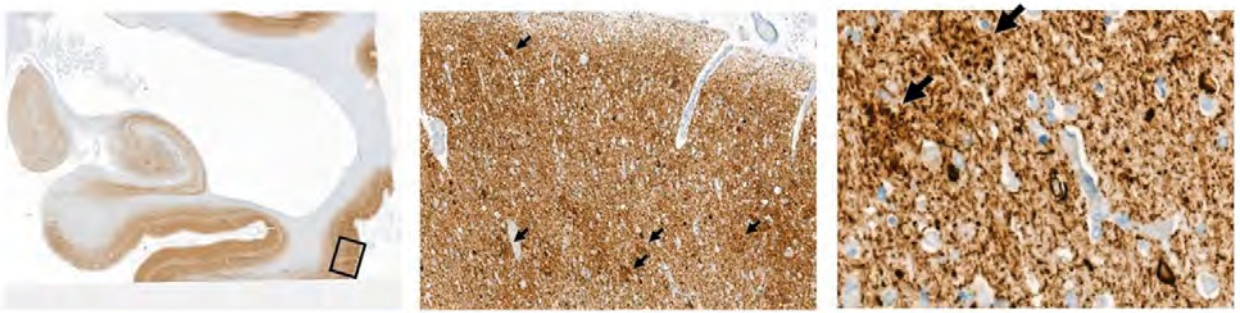


mesio-temporal lobe

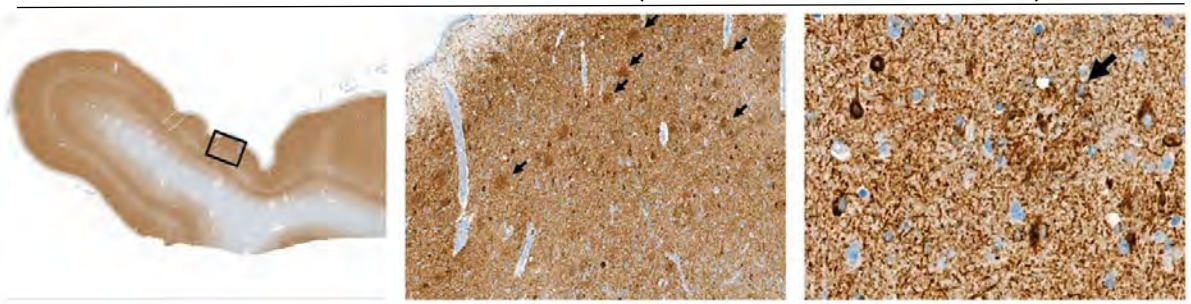
untreated HIGH AD case (Yale ADRC)



untreated HIGH AD (Yale ADRC)



untreated HIGH AD (Netherlands Brain Bank)



84-yr woman with 32 monthly doses of aducanumab:
sparse neuritic plaques (↙)
Scale bars: 5mm, 50µm & 100µm;

Similar autopsy findings in a lecanemab-treated AD patient.

Plowey *et al., Acta Neuropathol.* 2022
Honig *et al., Poster AAIC* 2022

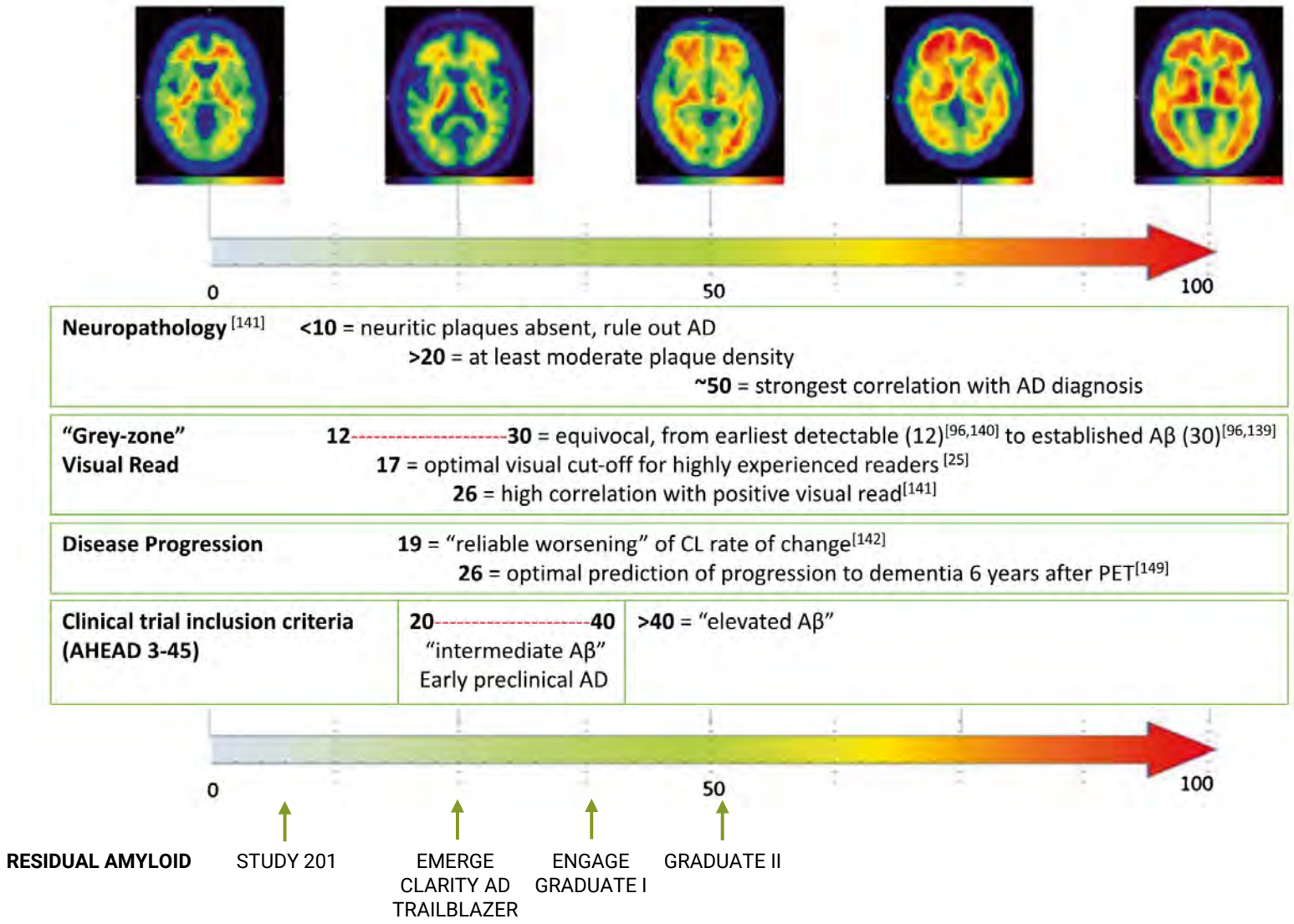
Substantial amyloid depletion is associated with slowed CDR-SB decline

Trial	Antibody	Duration (yrs)	Baseline amyloid (centiloids)	Residual amyloid (centiloids)	CDR-SB (Δ vs placebo)
EMERGE (Ph3)	Aducanumab	1.5	85	25	-22% (-0.39; p=0.012)
CLARITY AD (Ph3)	Lecanemab	1.5	78	23	-27% (-0.45; p=0.00005)
Study 201 (Ph2)	Lecanemab	1.5	75	6	-26% (p=0.125)
TRAILBLAZER-ALZ (Ph2)	Donanemab	1.5	108	23	-23% (-0.36)
Negative					
ENGAGE (Ph3)	Aducanumab	1.5	91	37	2% (+0.03; p=0.833)
GRADUATE I (Ph3)	Gantenerumab	2.25	92	34	-8% (-0.31; p=0.054)
GRADUATE II (Ph3)	Gantenerumab	2.25	98	51	-6% (-0.19; p=0.2998)

-22% to -27% slowed decline at 18 months

Sevigny *et al., Nature* 2016; Budd Haeberlein *et al., J Prev Alz Dis* 2022; Budd Haeberlein *et al., AD/PD* 2021; Castrillo-Viguera *et al., CTAD* 2021; clinicaltrials.gov; Van Dyck *et al., NEJM 2022;* Swanson *et al., Alzheimer's Res Ther.* 2021, Biogen news releases July 25, 2018 & Sept 27, 2022 *https://investors.biogen.com*, Mintun *et al.,* NEJM 2021; Bateman *et al., CTAD* 2022.

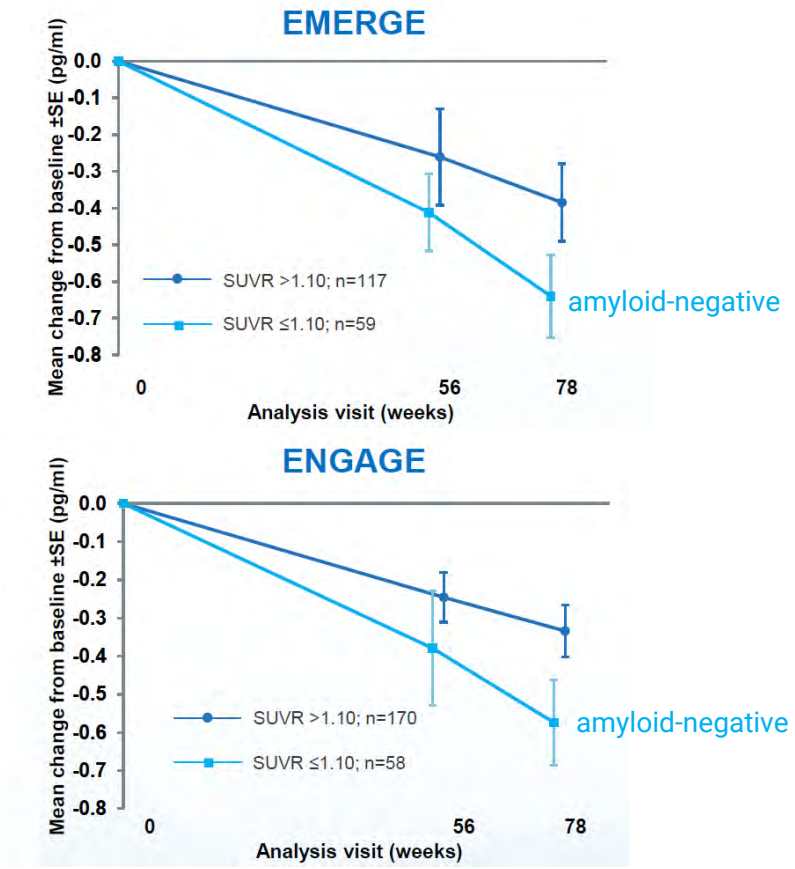
Residual amyloid burden following amyloid depletion in clinical trials



adapted from Pemberton *et al., EJNMMI* 2022

Amyloid-negative patients had greater p-Tau reductions and a more stable clinical trajectory during the gap period

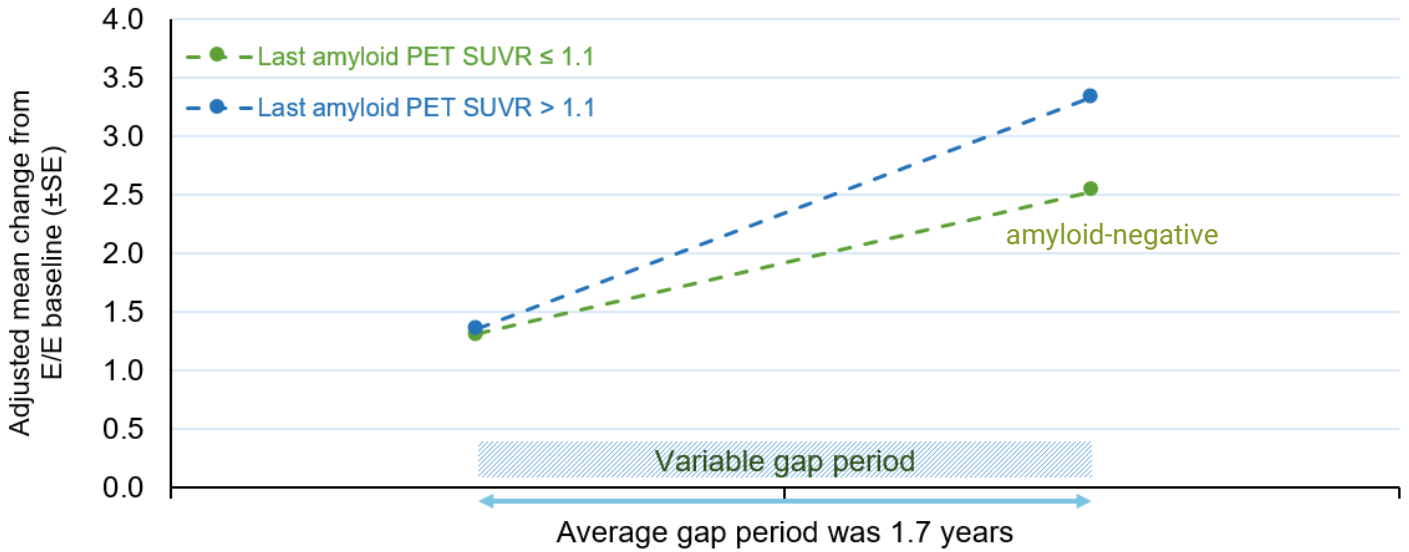
plasma p-Tau181



Change from baseline amyloid PET composite SUVR correlated with reductions of plasma p-Tau181 ($p<0.0001$)

CDR-SB

Change from baseline to end of Phase 3 and EMBARK baseline



	End of E/E*	EMBARK baseline
SUVR ≤ 1.1	n=125	121
SUVR > 1.1	n=228	223

*Study duration ranged from 0.6 – 3.5 years

Hansson *et al., CTAD* 2021
Budd Haeberlein *et al., JSDR* 2022

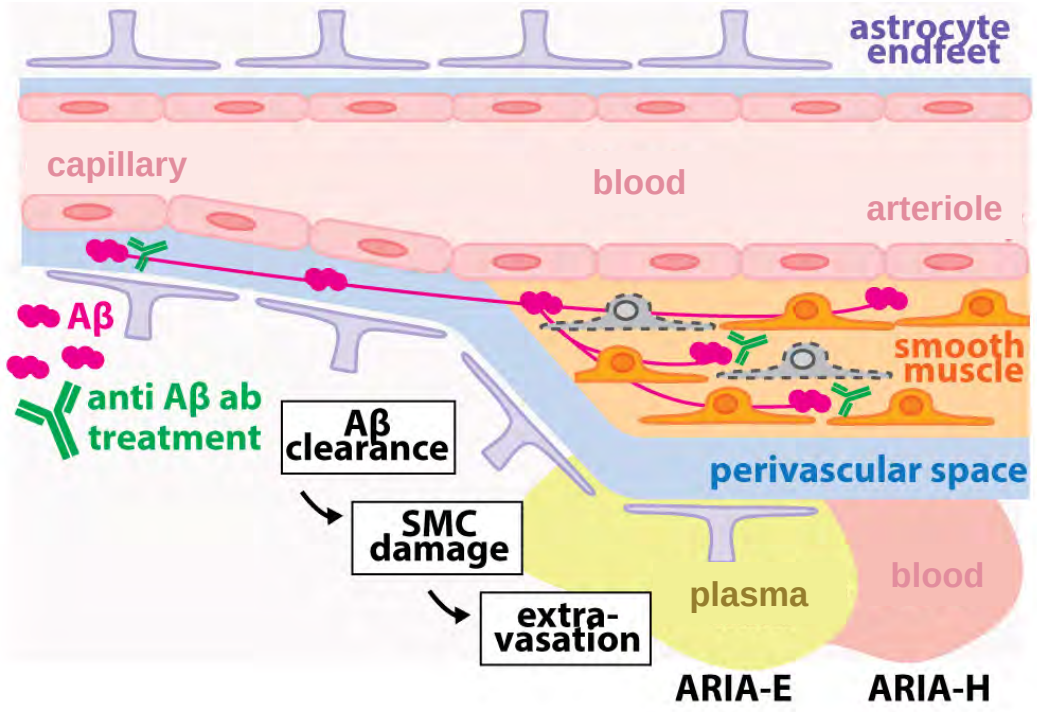
Upcoming readouts in ongoing clinical trials

Results pending				Estimated primary completion date
TRAILBLAZER-ALZ2 (Ph 3)	1800	Donanemab	1.5	Apr 2023
EMBARK (Ph 3b)	2400	Aducanumab	2 – 8	Oct 2023
ENVISION (Ph 4)	1512	Aducanumab	1.5	Dec 2025
TRAILBLAZER-ALZ5 (Ph 3)	1500	Donanemab	1.5	Apr 2027

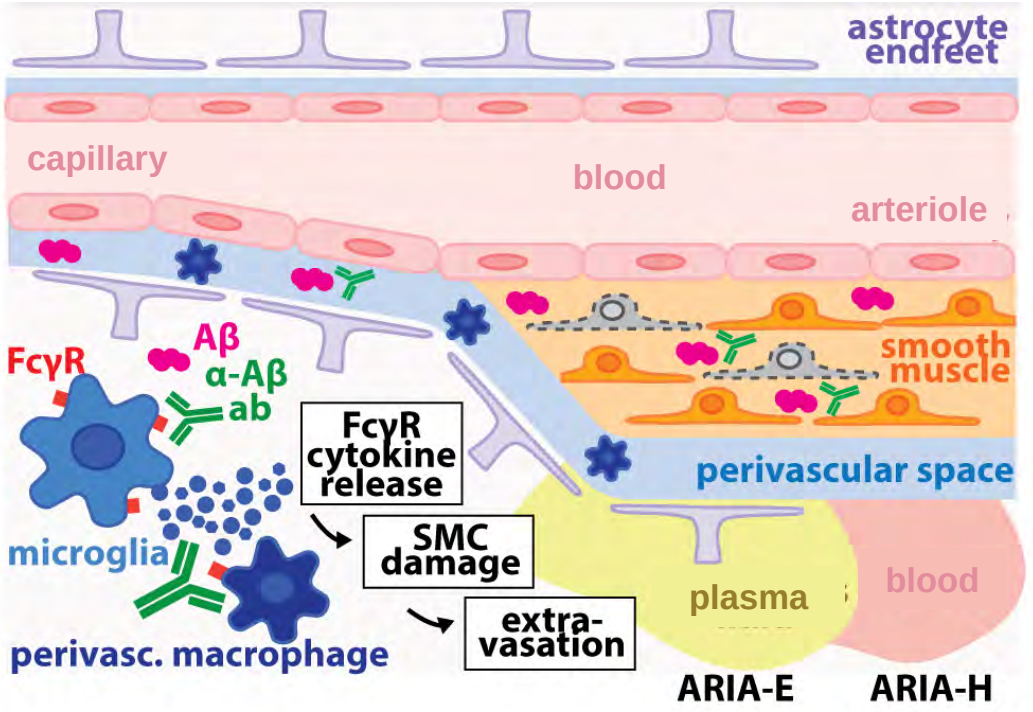
Clinicaltrials.gov

ARIA biology: possible mechanisms

vascular effusion



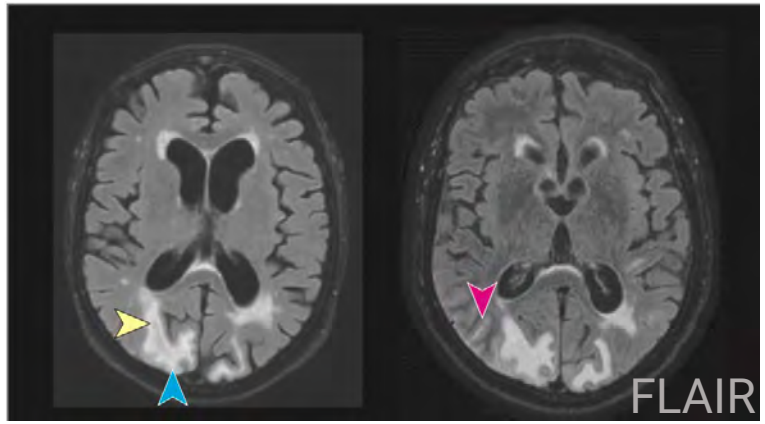
inflammation



Modified from Sperling *et al.*,

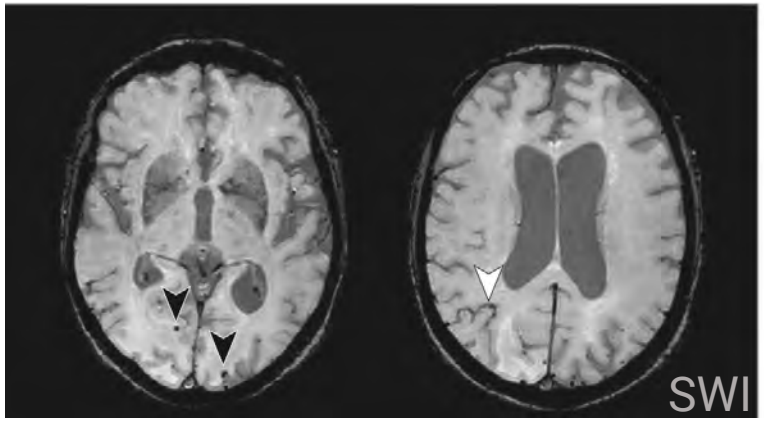
Adverse Reactions

ARIA-E



possible continuum

ARIA-H



ARIA-E
- **MRI:** parenchymal edema, sulcal effusion, gyral swelling
- **Incidence**: 11-35% at early stages of treatment, transient
- **Risk factors:** dosage, ApoEε4, microhemorrhages

ARIA-H
- **MRI:** microhemorrhages, superficial siderosis
- **Incidence:** 17-21% at early stages of treatment
- **Risk factors**: ARIA-E, APOEε4, microhemorrhages,

Symptomatic ARIA-E or H
- **Symptomatic:** 2.8-8.4% of treated patients
- **Common symptoms**: headache, confusion, dizziness, visual disturbance, nausea
- **Serious symptoms or macrohemorrhages:** 0.3-0.7% of treated patients
- **Management:** MRI monitoring, down-dosing, anti-inflammatory

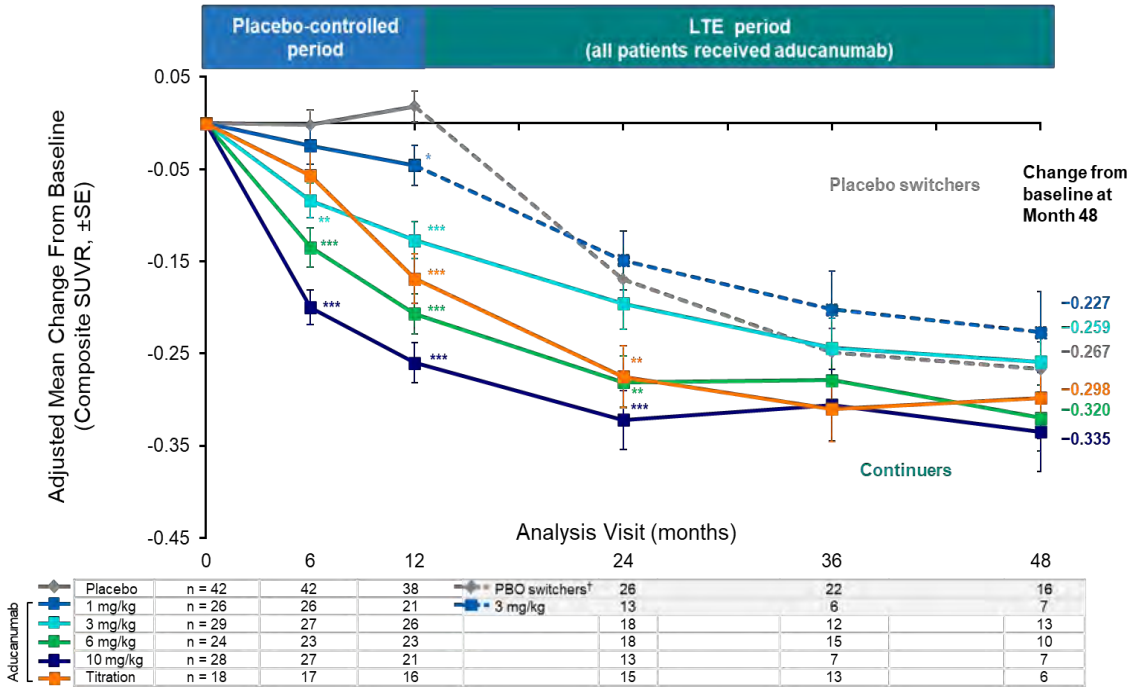
Immune reactions
- **Infusion reactions:** <0.01% - 26.4%
- **Anti-drug antibodies:** 0% - 90%

Images: Filippi *et al., JAMA Neurol.* 2022; Salloway *et al., JAMA Neurol* . 2021; FDA prescribing information, Ref ID: 4822820; Swanson *et al., Alzheimer's Res. Ther.* 2021; Mintun *et al., NEJM* 2021; Landry *et al.*, AAIC 2022; Van Dyck *et al., NEJM 2022 ;*

Four-year aducanumab data suggest continuous treatment effects

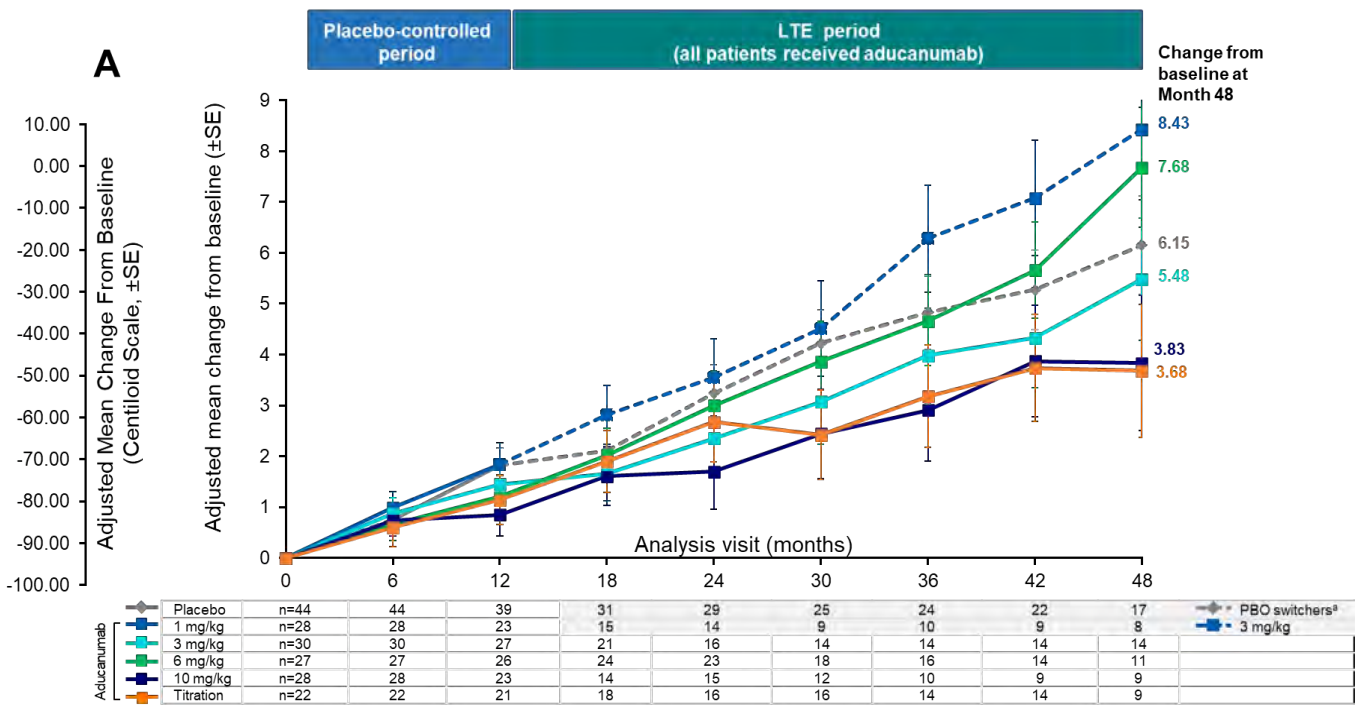
Sustained amyloid reduction over 4 years

Amyloid PET



Continued slowing of disease-progression over 4 years

CDR-SB



Slowed CDR-SB progression by 4.5 points in 10mg/kg vs. 1-3 mg/kg groups after 4 years of aducanumab

- Eligible PRIME LTE subjects had the opportunity to join the EMBARK study cohort with ~8 years of observation and ~6 years of treatment

Castrillo-Viguera *et al., in preparation*; Budd Haeberlein *et al., JSDR* 2022

Amyloid removal expected to flatten progression trajectories: increasing clinical benefit with time

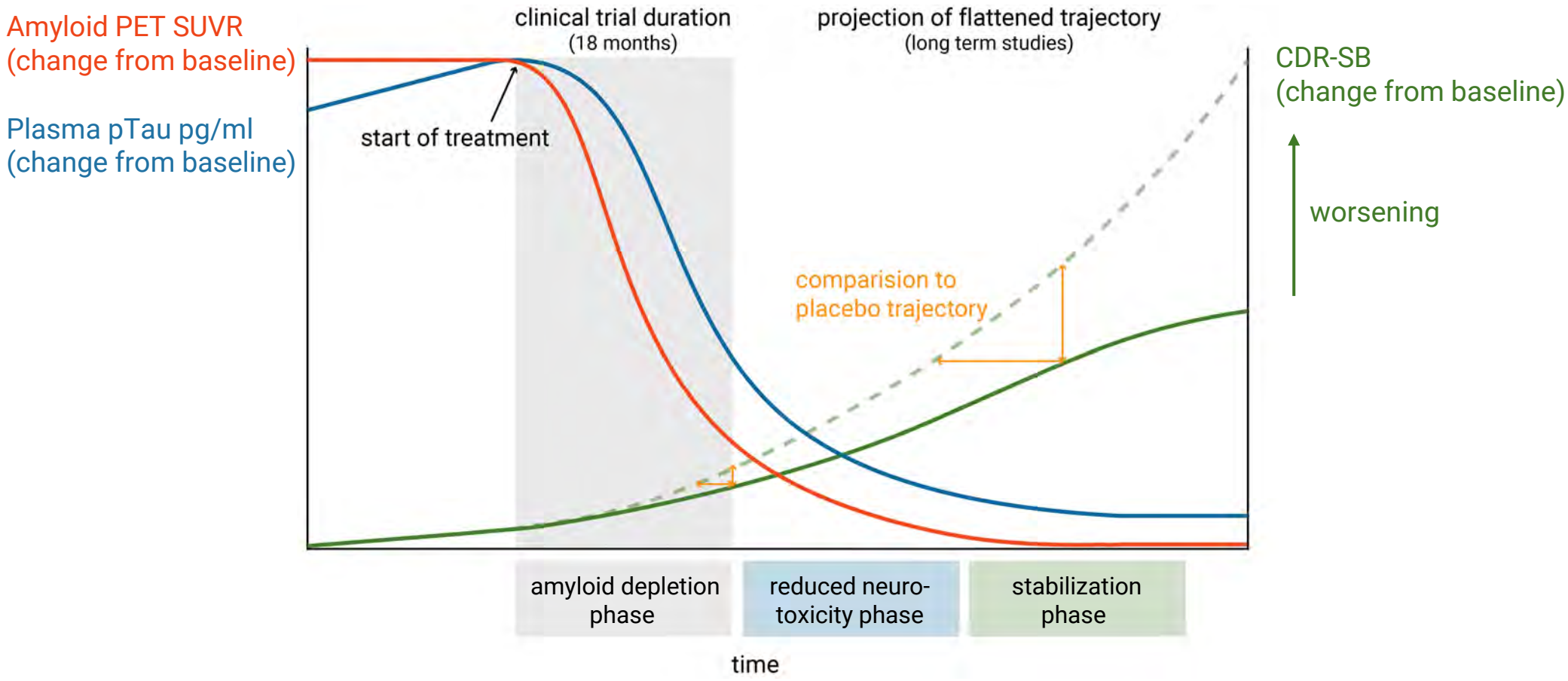


Illustration based on modeling, simulations and illustrations:

Cummings *et al., J Prev Alzheimers Dis.* 2017; Asuncao *et al., Alzheimer's Res. Ther.* 2022; Kühnel *et al., Stat. Med.* 2021; Tahami Monfared *et al., Neurol. Ther.* 2022; Doodey *et al., Alzforum* 2022: alzforum.org/news/conference-coverage/could-benefit-plaque-removal-grow-time

Conclusions

- Amyloid depletion is becoming a clinical reality for disease modification in Alzheimer’s disease.
- Amyloid depletion reduces tau pathology.
- Dose and treatment duration are key elements for amyloid depletion rates and clinical outcomes.
- Residual amyloid burden following amyloid depletion is associated with clinical effect size.
- Clinical effect sizes are expected to increase with time.
- Real-world data are needed to establish the impact of amyloid depletion on disease progression trajectories.

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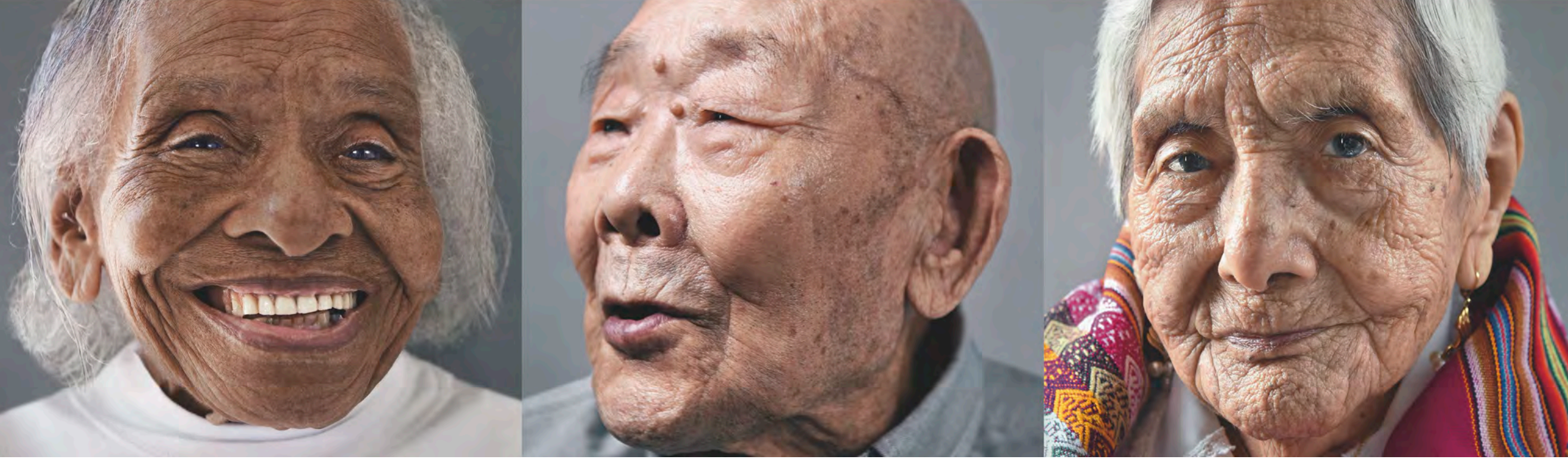

Thank you.

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neurimmune