Trailblazer-ALZ Study: Dynamics of Amyloid Reduction After Donanemab Treatment

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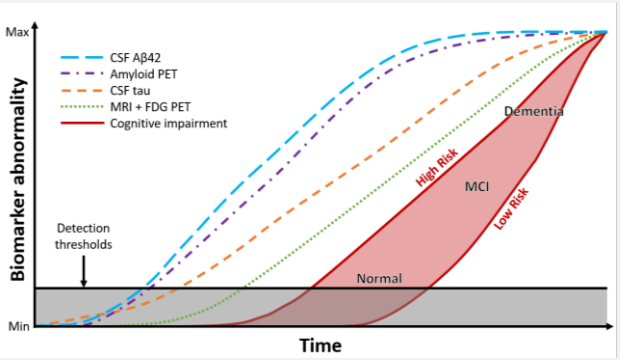
Disclosures

- John R. Sims is an employee of Eli Lilly and Company.
- All co-authors are employees of either Eli Lilly and Company or Avid Radiopharmaceuticals, a wholly owned subsidiary of Eli Lilly and Company.
- Amyvid (Florbetapir F 18) was developed at Avid Radiopharmaceuticals and is marketed by Eli Lilly and Company as a radioactive diagnostic agent for Positron Emission Tomography (PET) imaging of the brain to estimate β-amyloid neuritic plaque density; safety and effectiveness of Amyvid (Florbetapir F 18) has not been established for predicting development of dementia or other neurologic conditions and monitoring responses to therapies.
- Tauvid (Flortaucipir F 18) is approved for use with PET imaging of the brain to estimate the density and distribution of aggregated tau neurofibrillary tangles in adult patients with cognitive impairment who are being evaluated for Alzheimer's disease.
- All discussions refer to investigational purposes only.

Background

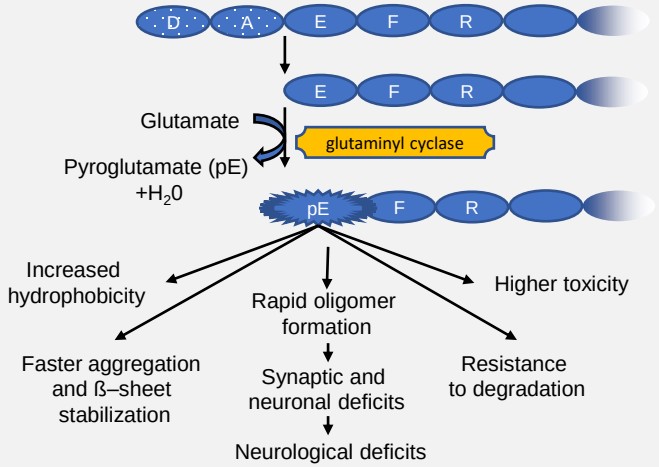
Accumulation of amyloid-β peptide in the form of amyloid plaques is an early and essential event in the onset of Alzheimer's disease (AD)



Adapted from Selkoe & Hardy EMBO, 2016

Donanemab is an immunoglobulin G1 antibody specific for an N-terminal pyroglutamate amyloid-β epitope that is present only in mature brain amyloid plaques

Formation of N3 pyroglutamate:

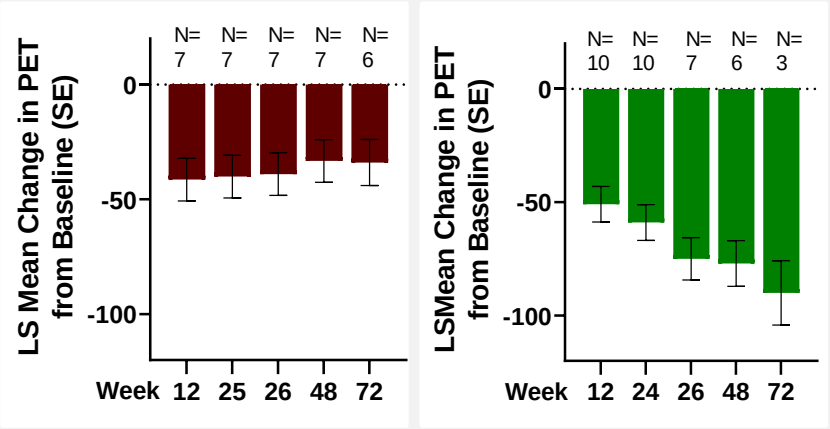


Adapted from Jawhar et al. J Biol Chem, 2011

In Phase 1, donanemab significantly reduced amyloid plaque, even with a single dose, in participants with amyloid positive AD

Single dose
LY20 mg/kg

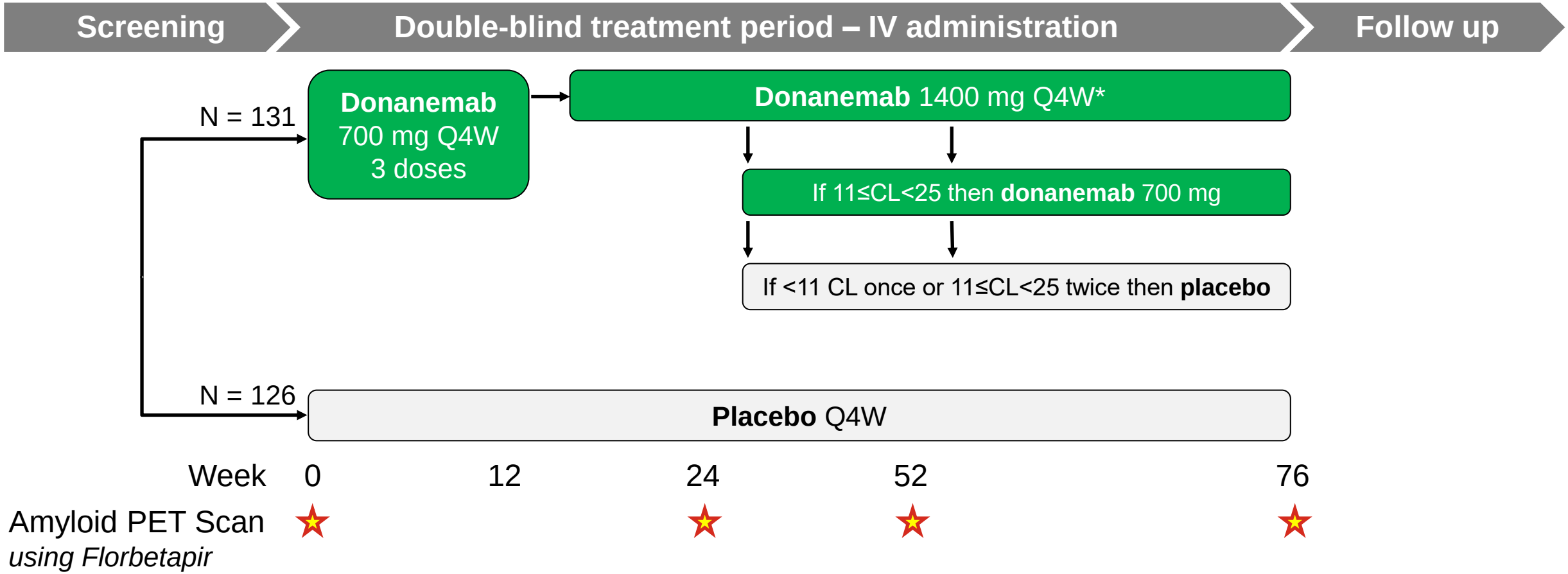
Q4W dosing
LY20 mg/kg



Lowe et al. CTAD, 2019

Q4W = every 4 weeks

TRAILBLAZER-ALZ study design & dose changes based on amyloid-β plaque removal



*If ARIA-E occurred with the first three doses, the dose was not increased

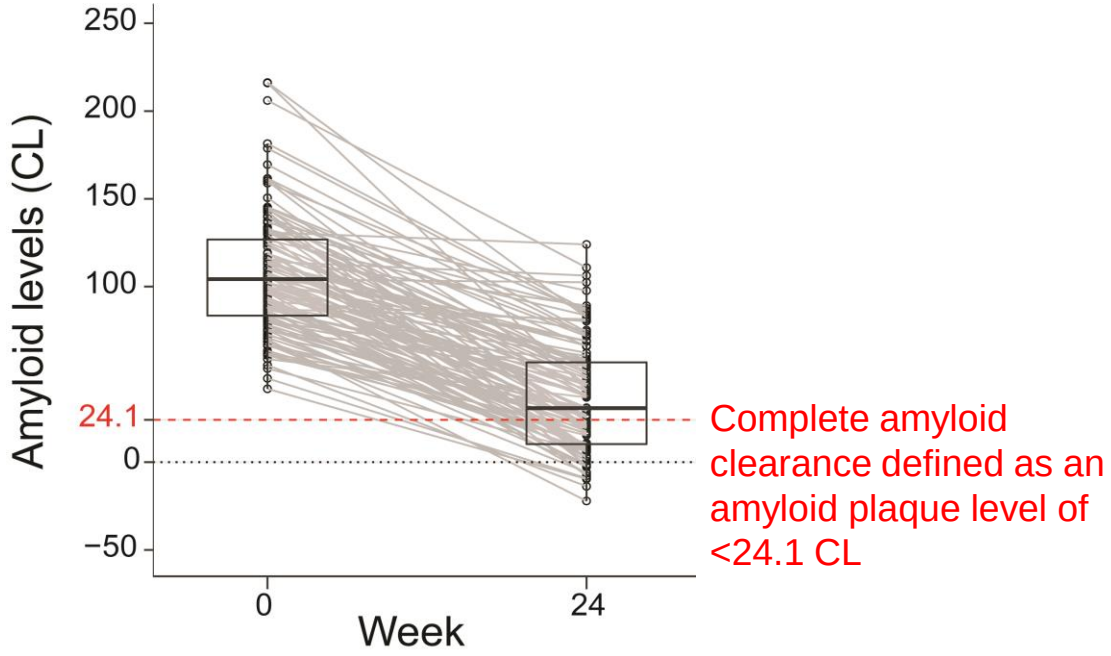
Dose reductions were blinded to sites and participants

ARIA-E = Amyloid-Related Imaging Abnormalities with Edema or Effusions; CL = Centiloids; IV = intravenous; N = number of participants; PET = Positron Emission Tomography; Q4W = every 4 weeks

Mintun et al. NEJM, 2021

Donanemab results in rapid 24-week amyloid reduction; the rate is directly proportional to the amount of baseline amyloid

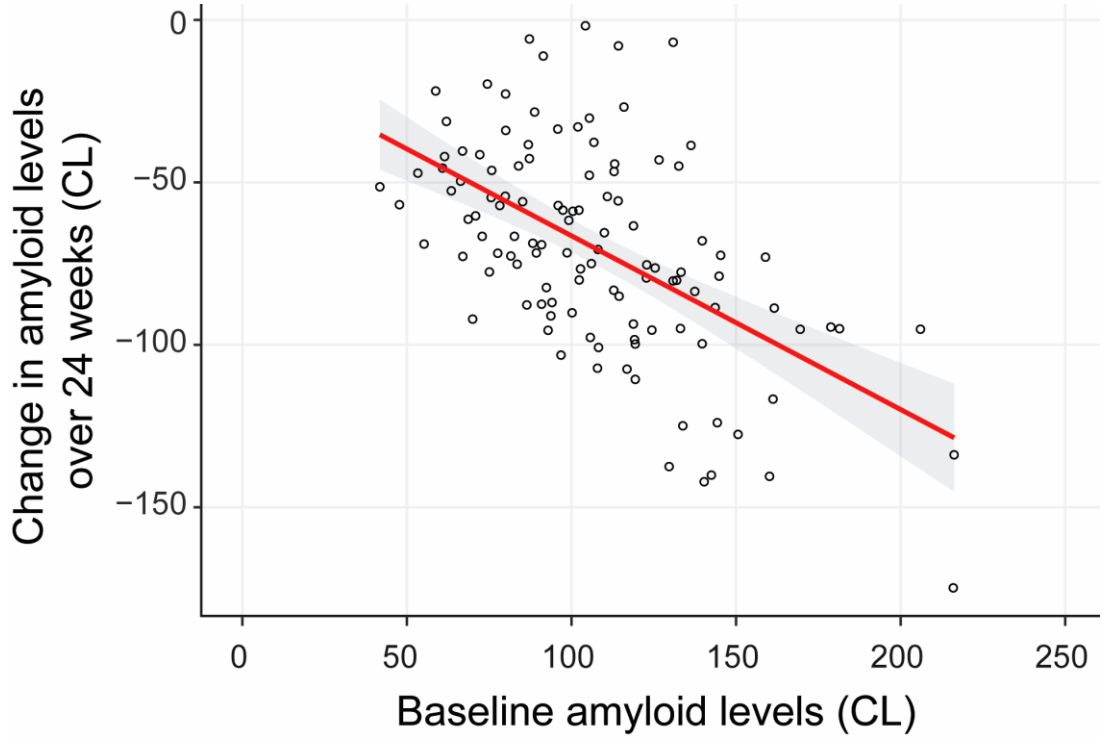
Donanemab induces a rapid amyloid plaque reduction in essentially all participants



Complete amyloid clearance defined as an amyloid plaque level of <24.1 CL

Amyloid plaque reduction at 24 weeks			
N	**Minimum**	**Maximum**	**Average rate**
115	**-1.8 CL**	**-174.8 CL**	**-2.9 CL/week**

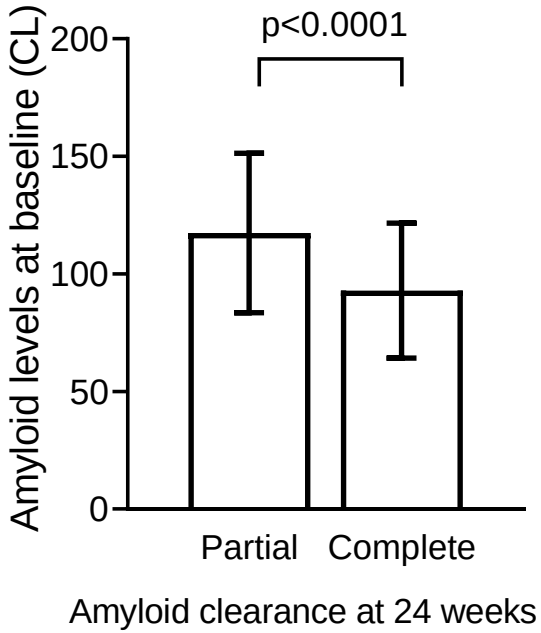
Amyloid plaque reduction is associated with baseline amyloid plaque level



CL = Centiloids

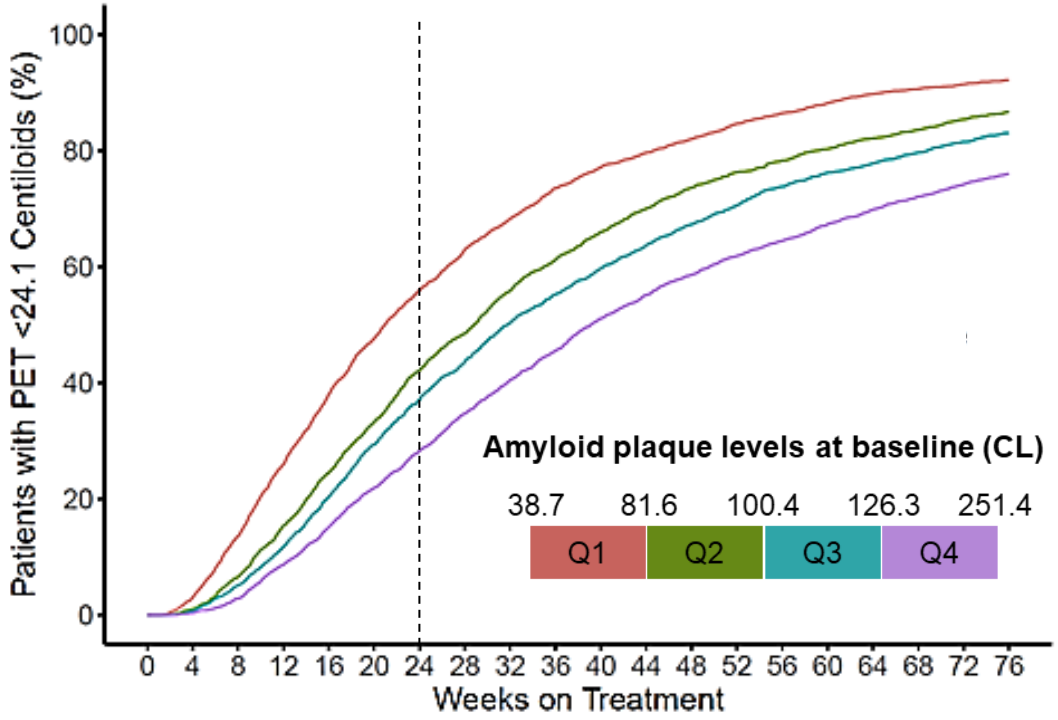
Lower amyloid plaque levels at baseline lead to earlier complete amyloid clearance

Participants with complete amyloid clearance at 24 weeks had lower baseline amyloid plaque levels



Complete amyloid clearance defined as an amyloid plaque level of <24.1 CL

Using treatment exposure-response model, participants with lower amyloid plaque baseline levels achieved complete amyloid clearance faster

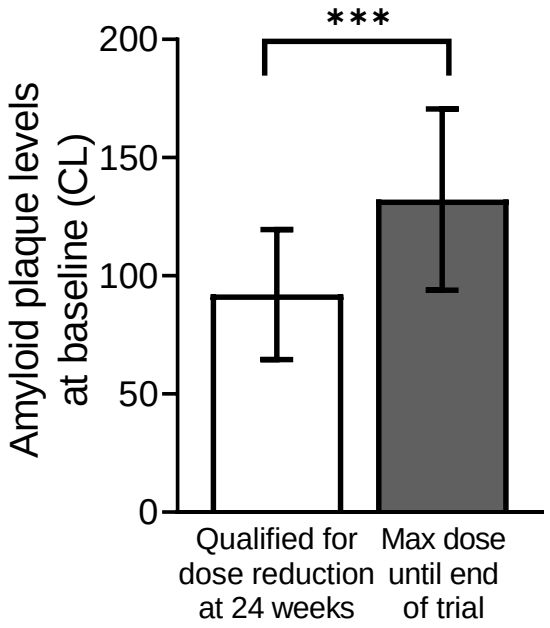


Percentage of participants achieving <24.1 Centiloid units by duration of treatment and by Q of baseline PET assessed using treatment exposure-response model.

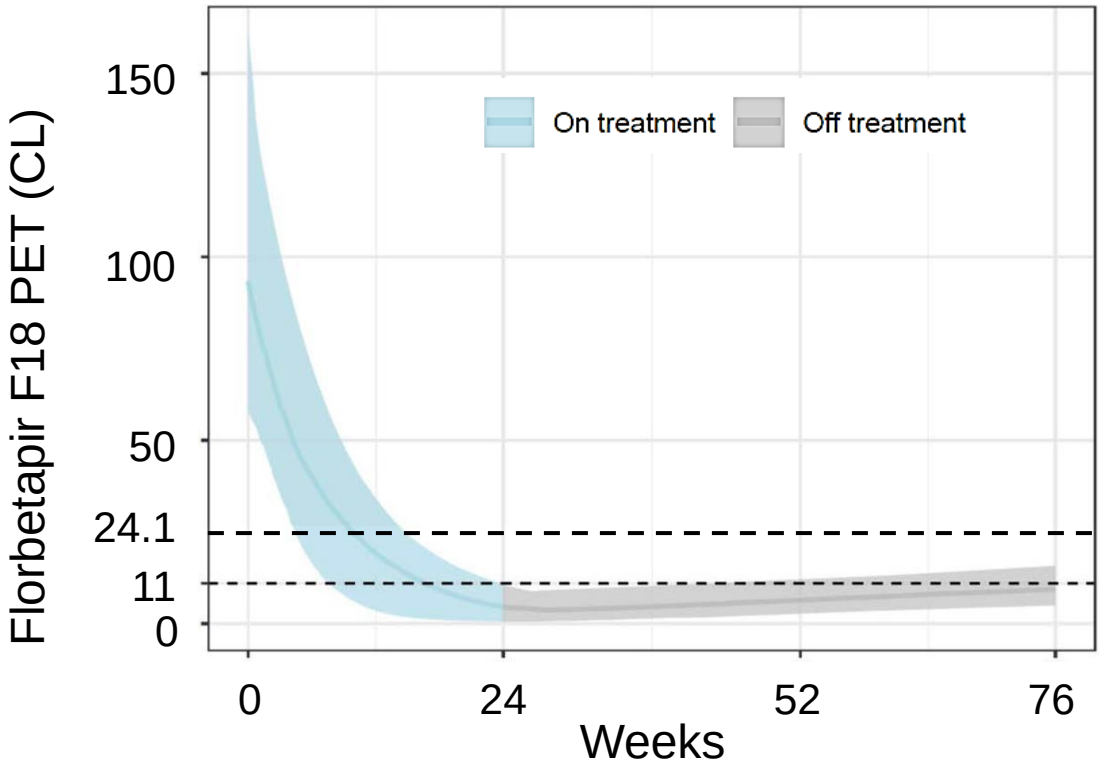
Bars show mean +/- standard deviation
CL = Centiloids; PET = Positron Emission Tomography; Q = quartile

Dosing depends on baseline amyloid plaque levels, and stopping treatment does not result in significant amyloid reaccumulation over 1 year

Participants with lower amyloid plaque baseline levels qualified for dose reduction earlier



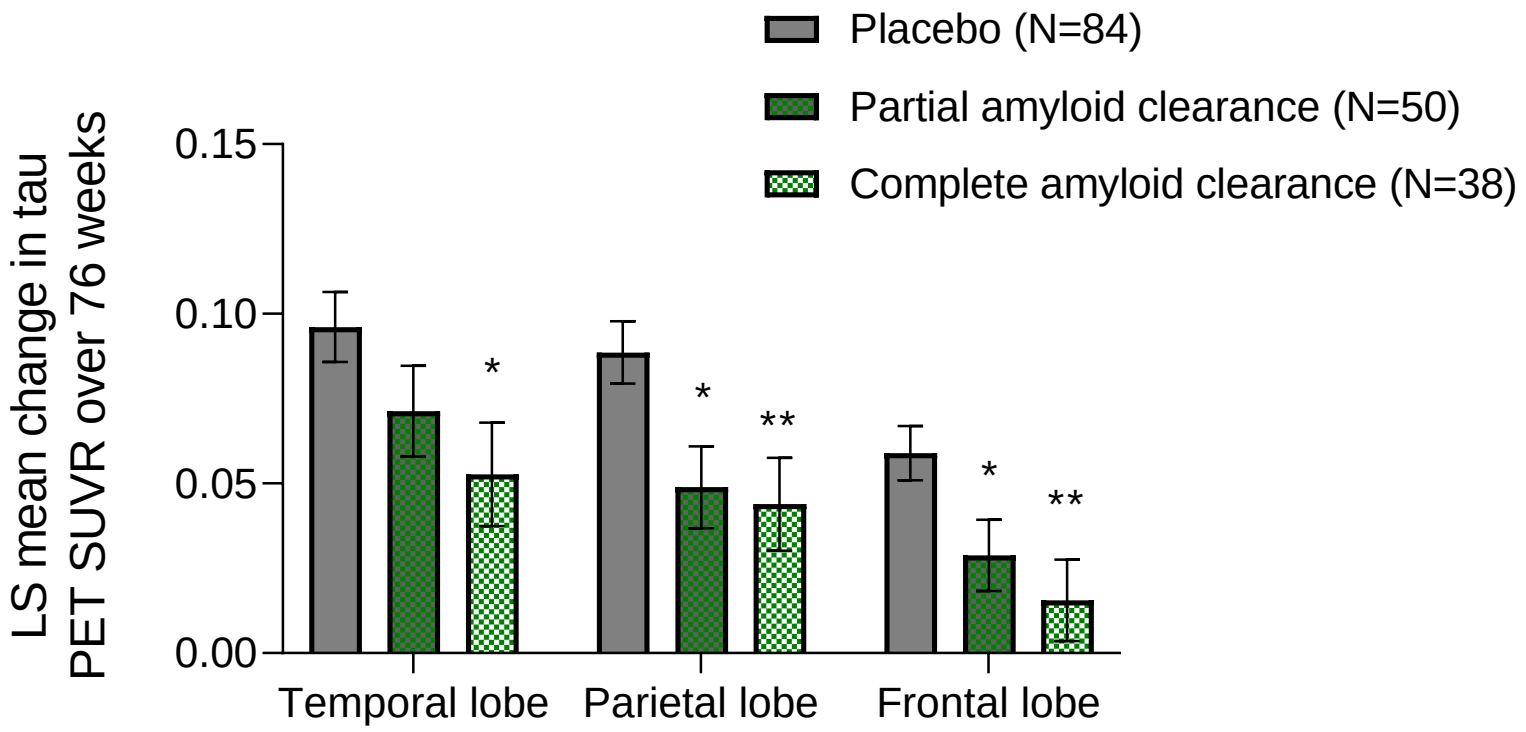
Exposure-response model of amyloid plaque level over time



Data suggests >14 years before plaque reaccumulates to baseline levels

Bars show mean +/- standard deviation
CL = Centiloids; Max = maximum; PET = Positron Emission Tomography;
*** p<0.001

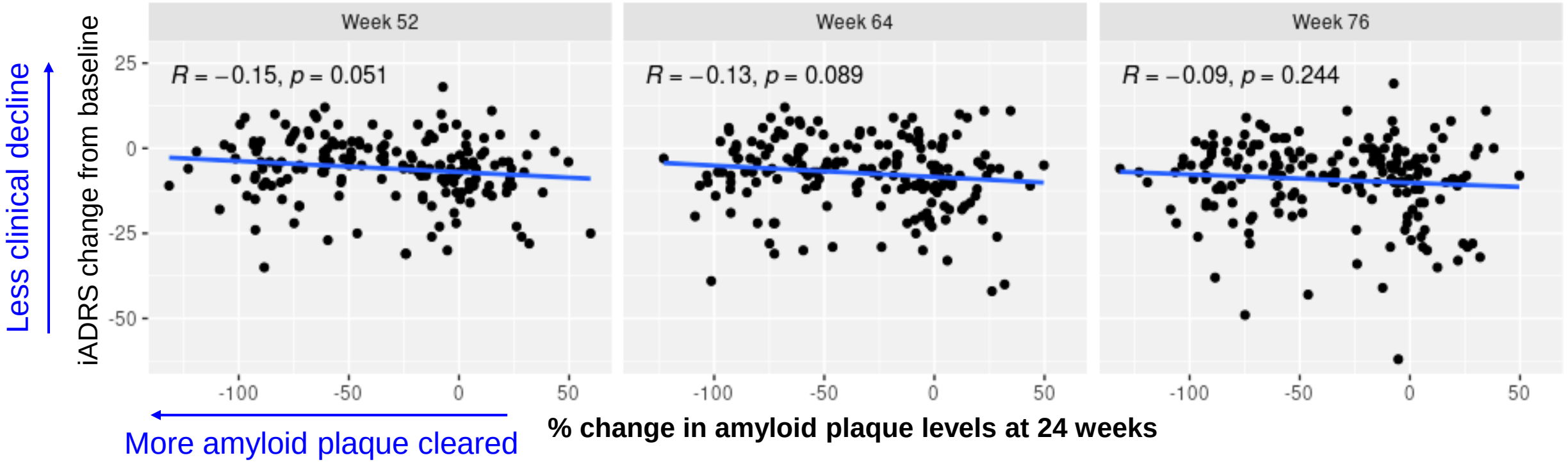
Donanemab decreased tau accumulation over 76 weeks with less accumulation in participants with complete amyloid plaque clearance at 24 weeks



- Complete amyloid clearance defined as an amyloid plaque level of <24.1 CL
- All participants underwent flortaucipir PET scans at baseline and 76 weeks
- Participants receiving donanemab are designated as having partial or complete amyloid clearance based on the amyloid plaque level at 24 weeks

Bars show mean +/- standard error
Footnote:cortical tau level was measured using regional tau SUVR with cere-crus as reference region
LS = least square; PET = Positron Emission Tomography; SUVR = Standardized Uptake Value Ratio;
*p<0.05; **p<0.01 vs. placebo

Greater amyloid plaque clearance at 24 weeks is associated with less clinical decline



- Participants completed clinical scales comprising the iADRS endpoint at weeks 52, 64, and 76
- Pooled data from placebo and donanemab-treated groups
- Similar but slightly less robust pattern is seen with absolute amyloid PET level achieved at 24 weeks

iADRS = Integrated Alzheimer's Disease Rating Scale;
PET = Positron Emission Tomography; R = correlation coefficient

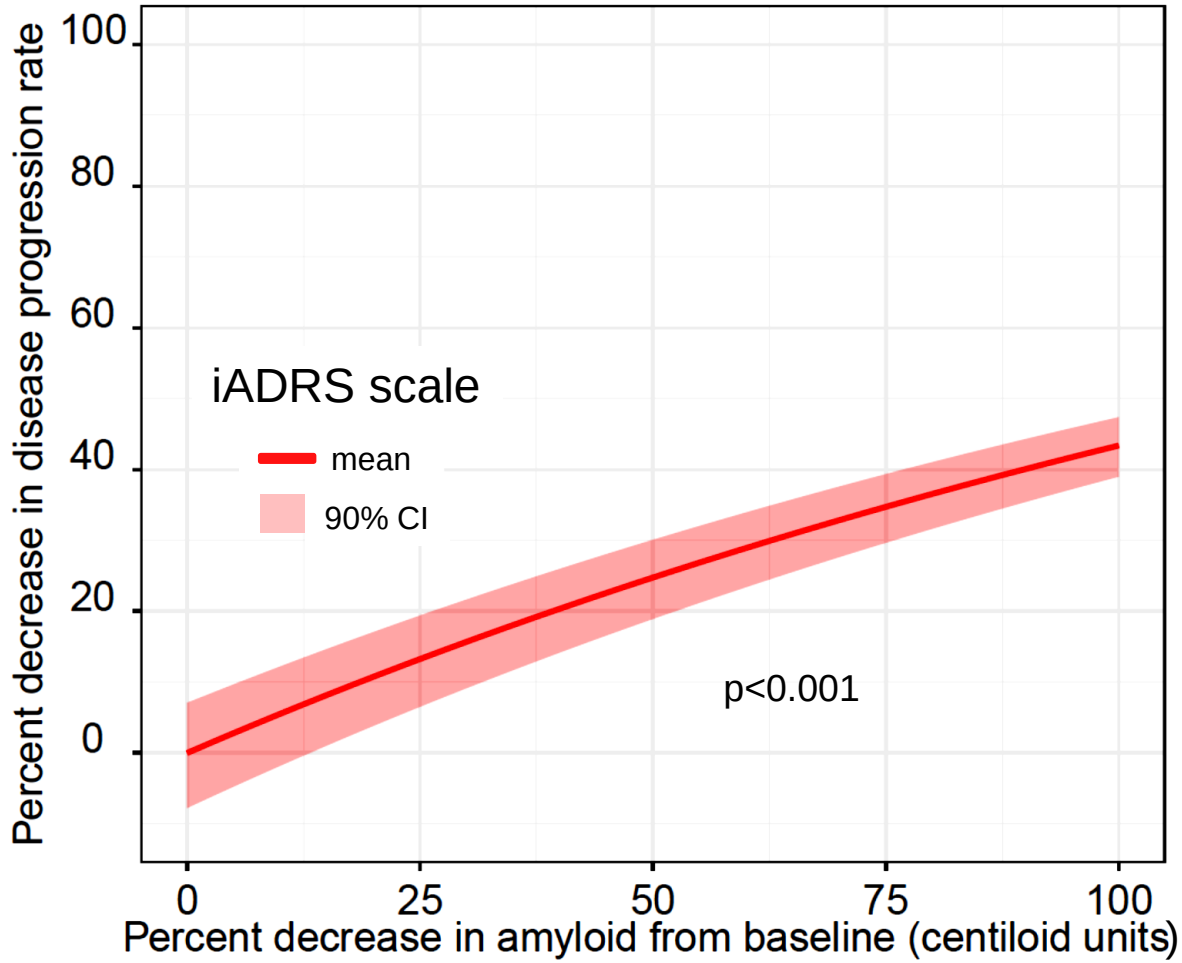
Direct relationship between decrease in amyloid plaque and slowing in disease progression rate

Conrado (PK/PET/iADRS) Model

An updated Alzheimer's disease progression model: incorporating non-linearity, beta regression, and a third-level random effect in NONMEM.

Conrado DJ et al. J Pharmacokinet Pharmacodyn, 2014

- Disease progression was reduced by 28% (p<0.001) in overall population and by 42% in ApoE4 carriers only (p<0.001) (data not shown)
- Amyloid plaque removal was statistically significant as a predictor of disease slowing (p<0.001)



iADRS = Integrated Alzheimer's Disease Rating Scale; mean and 90% CI
ApoE4 = apolipoprotein E4; CI = Confidence interval; PET = Positron Emission Tomography; PK = pharmacokinetics

Conclusions

- Donanemab induced a rapid and robust decrease in amyloid plaque levels sustained without significant re-accumulation over 1 year off treatment

Amyloid plaque levels at baseline

- ✓ Early amyloid plaque negative level achieved
- ✓ Early dose reduction

- ✓ Greater rate of amyloid plaque decrease

- After 6 months of donanemab treatment:
  - participants with greater plaque clearance showed less tau progression in frontal, parietal, and temporal brain regions
  - greater amyloid plaque changes associated with less cognitive decline

Acknowledgements

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