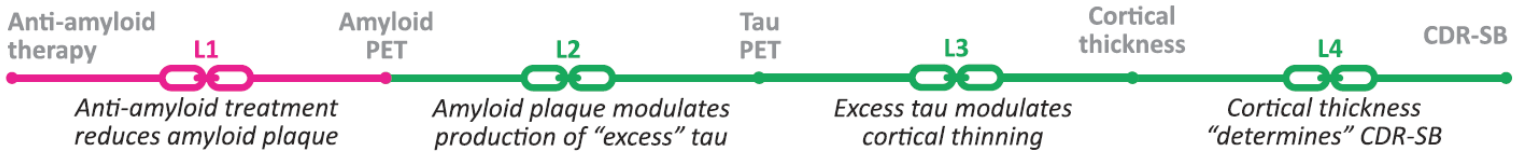
NAM Consulting

The Q-ATN Model of Alzheimer's Disease:

A Work in Progress

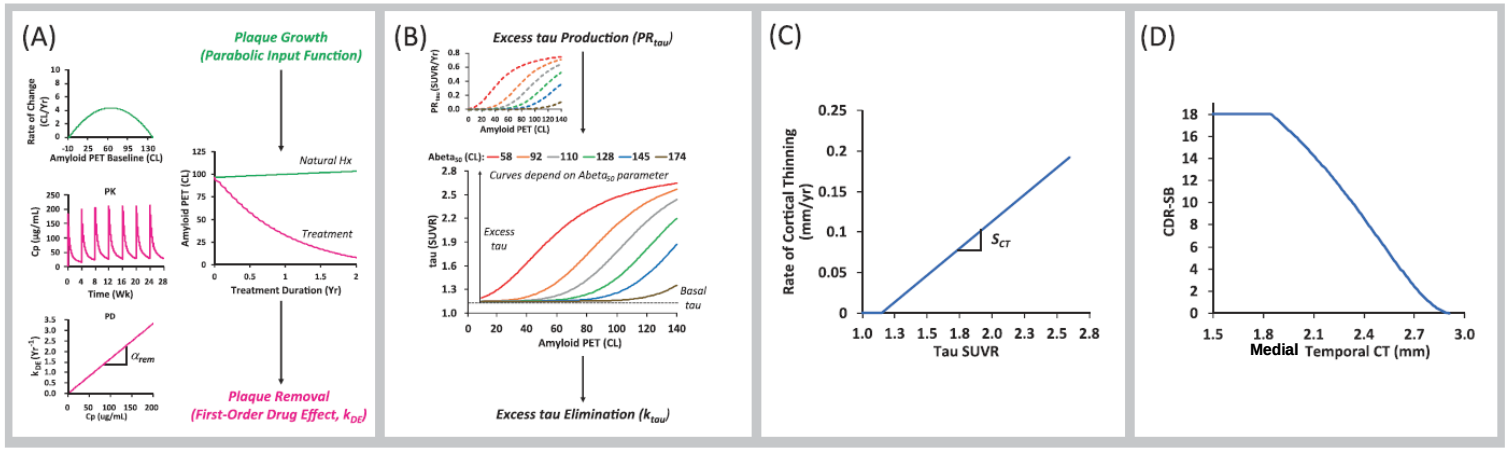


Norman Alan Mazer, M.D., Ph.D.

Disease Modeler *"Emeritus"*

Roche Pharma (2008 – 2023)

Founder, NAM Consulting (2023)



Presented on December 13, 2023 in the world-wide webinar series "Impact of Modeling & Simulation in Drug Development" hosted by Rosa & Co. LLC.

Acknowledgements to my former Roche colleagues and to AD modelers past , present and future…

Roxana Aldea, Monika Baudler-Klein, Frank Boess, Rachelle Doody, Ronald Gieschke, Mar Ferrero, Hans Peter Grimm, Carsten Hofmann, Geoff Kerchner, Greg Klein, Luka Kulic, Dominik Lott, Marzia Scelsi, Janice Smith, Stefan Sturm and Matteo Tonietto (Roche)

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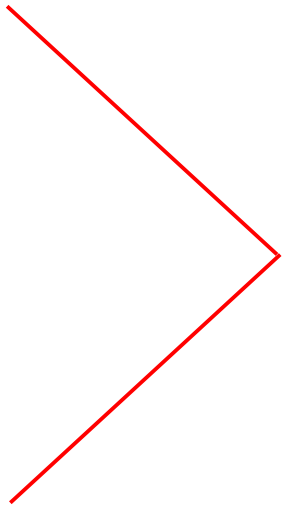
Rebecca Baillie and Christina Friedrich (ROSA and Co.)

Background:
What is Alzheimer’s Disease and Why Do We Need a Model?

What is Alzheimer's Disease?

Dementia, Amyloid Plaques, Tau Tangles and Neurodegeneration

- **Alzheimer's Disease (AD)**
  - Described in 1906 by Alois Alzheimer, a German psychiatrist and neuropathologist
  - Accounts for 60-80% of dementia cases (general term for loss of memory, language and thinking abilities)
  - Majority of patients are age 65 or older (younger-onset associated with rare genetic abnormalities)
  - Typically live 4 to 8 years after diagnosis; some can live as long as 20 years
  - Symptoms progress from mild cognitive impairment to marked interference with daily life and death
- **Amyloid Plaques**
  - Clumps of aggregated b-amyloid protein that form outside of the neurons
  - Thought to be the initial pathological species in AD
- **Tau Tangles**
  - Twisted fibers of aggregated tau protein that accumulate within neurons
  - Spread from medial structures to outer cortical regions of the brain
- **Neurodegeneration**
  - Loss of synapses, death of neurons, thinning of brain cortex



Lead to dementia

Adapted from: https://www.alz.org/alzheimers-dementia/what-is-alzheimers and other sources

How is Dementia Quantified in Clinical Studies?

Clinical Dementia Rating – Sum of Boxes (CDR-SB)

Table 1 - Classification of the categories evaluated by the Clinical Dementia Rating.

	Impairment level	None (0)	Questionable (0.5)	Mild (1)	Moderate (2)	Severe (3)
1	Memory	No memory loss or slight inconsistent forgetfulness	Consistent forgetfulness, partial recollection of events.	Moderate memory loss; more marked for recent events; defect interferes with daily activities.	Severe memory loss; only highly learned material retained.	Severe memory loss; only fragments remain.
2	Orientation	Fully oriented.	Fully oriented except with slight difficulties with time relationships.	Moderate difficulty with time relationships, oriented in familiar areas.	Severe difficulty with time relationships, almost always disoriented to place.	Oriented to person only.
3	Judgement & Problem Solving	Solves everyday problems, such as financial affairs; judgement preserved.	Slight difficulty in solving problems, similarities and differences.	Moderate difficulty on handling problems, similarities and differences, social judgement maintained.	Severely impaired in handling problems, similarities and differences; social judgment impaired.	Unable to make judgements or solve problems.
4	Community Affairs	Independent function in job, shopping, social groups.	Slight impairment in these activities.	Is not independent in these activities, appears normal to casual inspection.	Is not independent outside home, appears well enough to be taken to events outside the home.	Is not independent outside the home, appears to be too ill to be taken to events outside the home.
5	Home and Hobbies	Daily life at home, hobbies and intellectual interests well maintained.	Daily life at home, hobbies and intellectual interests slightly impaired.	Slight impairment of tasks at home, more difficult chores, hobbies and interests are abandoned.	Only simple chores are maintained, restricted interests, poorly maintained.	No significant function at home.
6	Personal Care	Fully capable of self-care.	Fully capable of self-care.	Needs assistance.	Requires assistance in dressing and hygiene.	Requires much help with personal care; frequent incontinence.

Fonte: Bertolucci et al[2]

CDR-SB = sum of the scores of the 6 categories (based on an interview with the subject and caregiver)

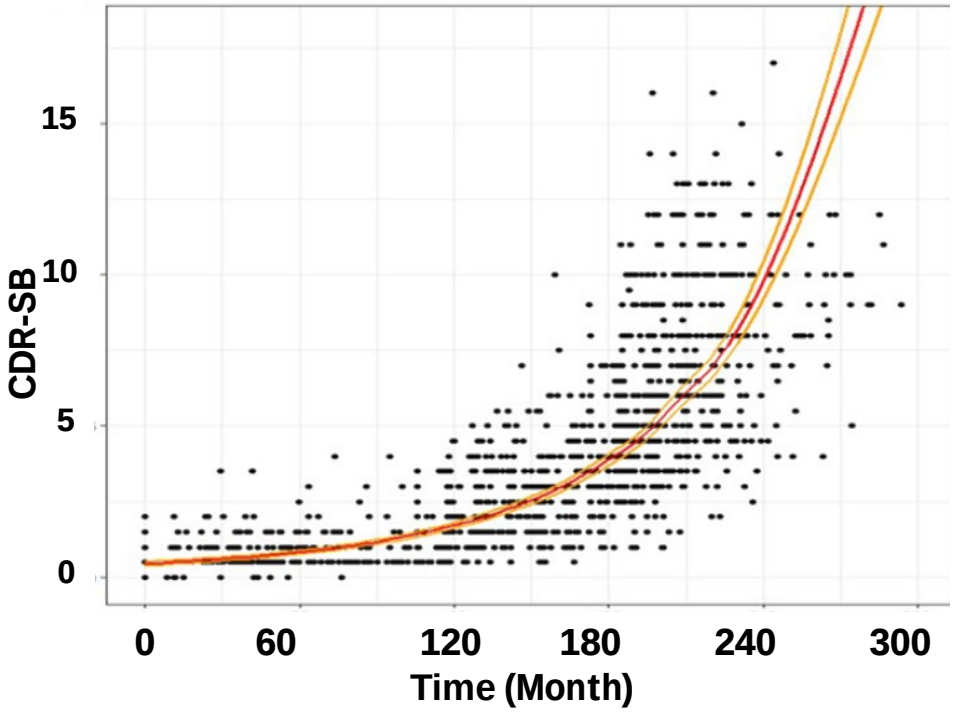
Scores can range from 0 to 18

https://www.scielo.br/j/rsp/a/K3TRXLdkq7T7C3chjHTPV6S/?lang=en#

Why Do We Need a Model of Alzheimer's Disease?

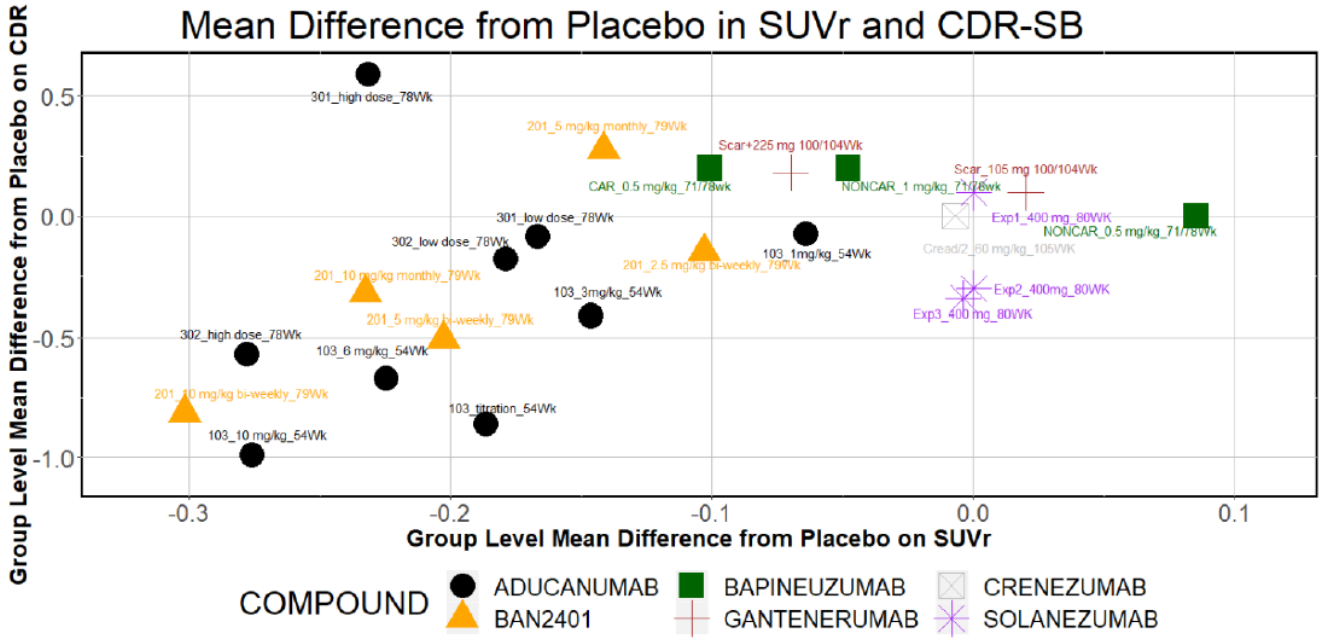
To understand and predict disease progression and the short-/long- term effects of anti-amyloid treatment on clinical outcome

Time-course of CDR-SB over 300 months (25 years)



From: Kim KW et al. Scientific Reports. 2020 Oct 8;10(1):16808

Correlation between extent of amyloid removal and CDR-SB (over 18 – 24 mo.)

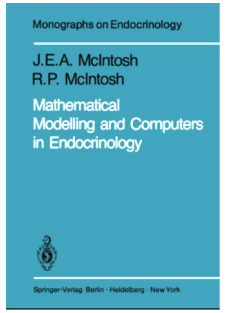


CDER: Application No. 761178Orig1s000 (Aduhelm)
Clinical Pharmacology and Biopharmaceutics Review(s)

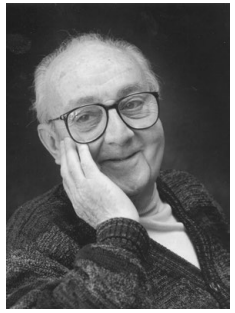
A Few Thoughts on Models and Modeling?

What are Models?

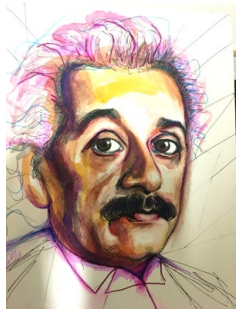
From different perspectives



- **A <u>model</u> may define, behave like or "explain" the workings of a system … mathematics offers rigorous methods for testing hypotheses by comparing models with experimental data**
  - James E. A. McIntosh and Rosalind P. McIntosh (Endocrine Physiologists)



- **All <u>models</u> are wrong, but some are useful…**
  - George E. P. Box (Statistician)



- **A theory (<u>model</u>) should be as simple as possible, but not simpler…**
  - Albert Einstein (Physicist)

Drawing by Laila Sarah Mazer (2017)

What is Modeling?

A cyclic process that ultimately leads to the "refinement" of the model and ideas about the system

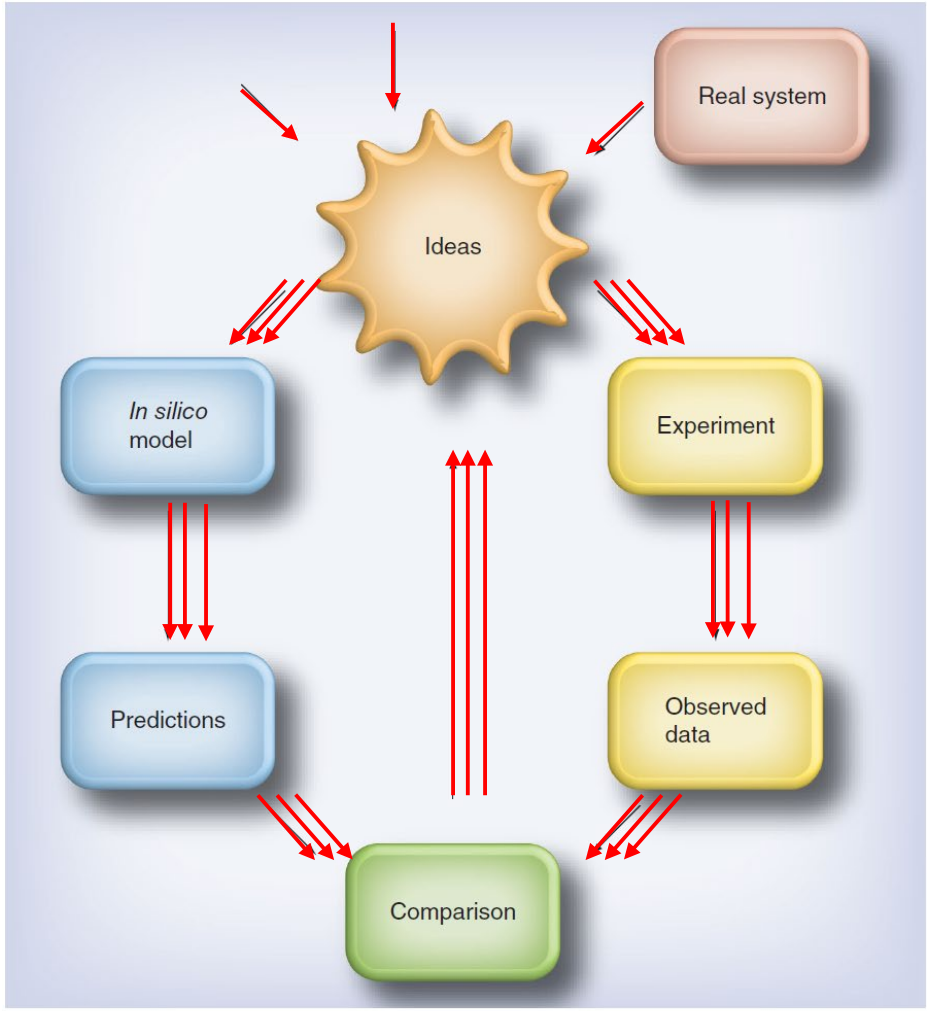


Figure 1. Both modeling and experiments are usually derived from ideas about how a real system may behave.

...In this paradigm, modeling and experimentation are linked together in a cyclic process that ultimately leads to the refinement of the model and the ideas (assumptions) about the system on which the model has been built.

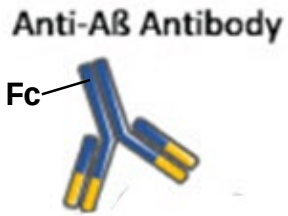
From:
Mathematical Models of lipoprotein metabolism and kinetics: current status and future perspective.
James Lu, Norman A. Mazer & Katrin Hübner
Clinical Lipidology, 2013

Based on: McIntosh JEA & McIntosh RP, "Mathematical Modeling and Computers in Endocrinology", Springer 1980

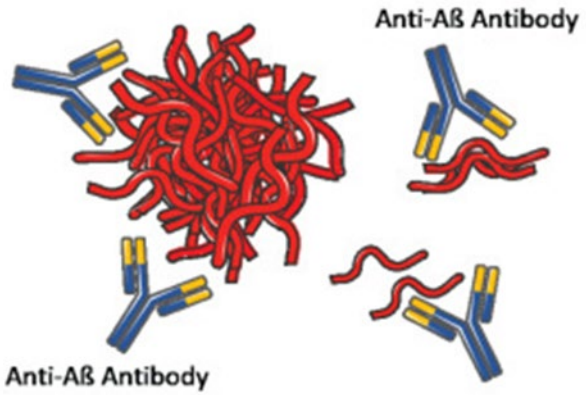
Gantenerumab, an Anti-Amyloid Therapeutic Antibody and GRADUATE I & II Studies in Subjects with Early Symptomatic AD

Interactions Between Gantenerumab, Amyloid Plaque and Microglia

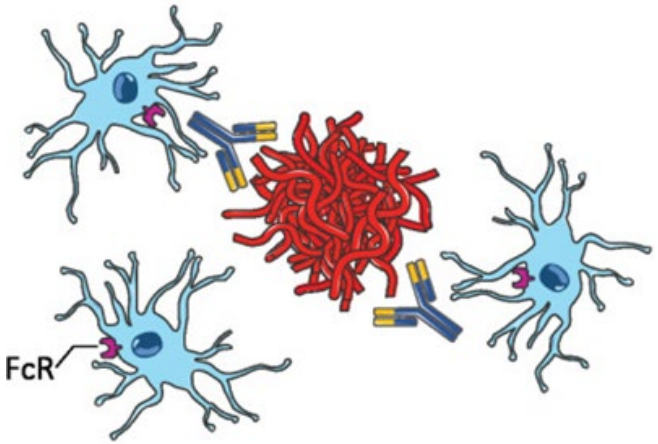
"Cartoon" model of the presumed mechanism of action



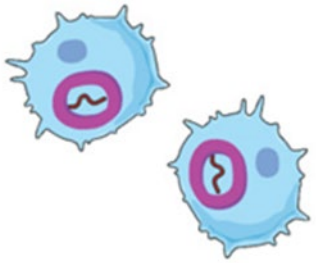
Gantenerumab (IgG)



Gantenerumab binds to amyloid Plaque



Microglia cells bind to gantenerumab (Fc)

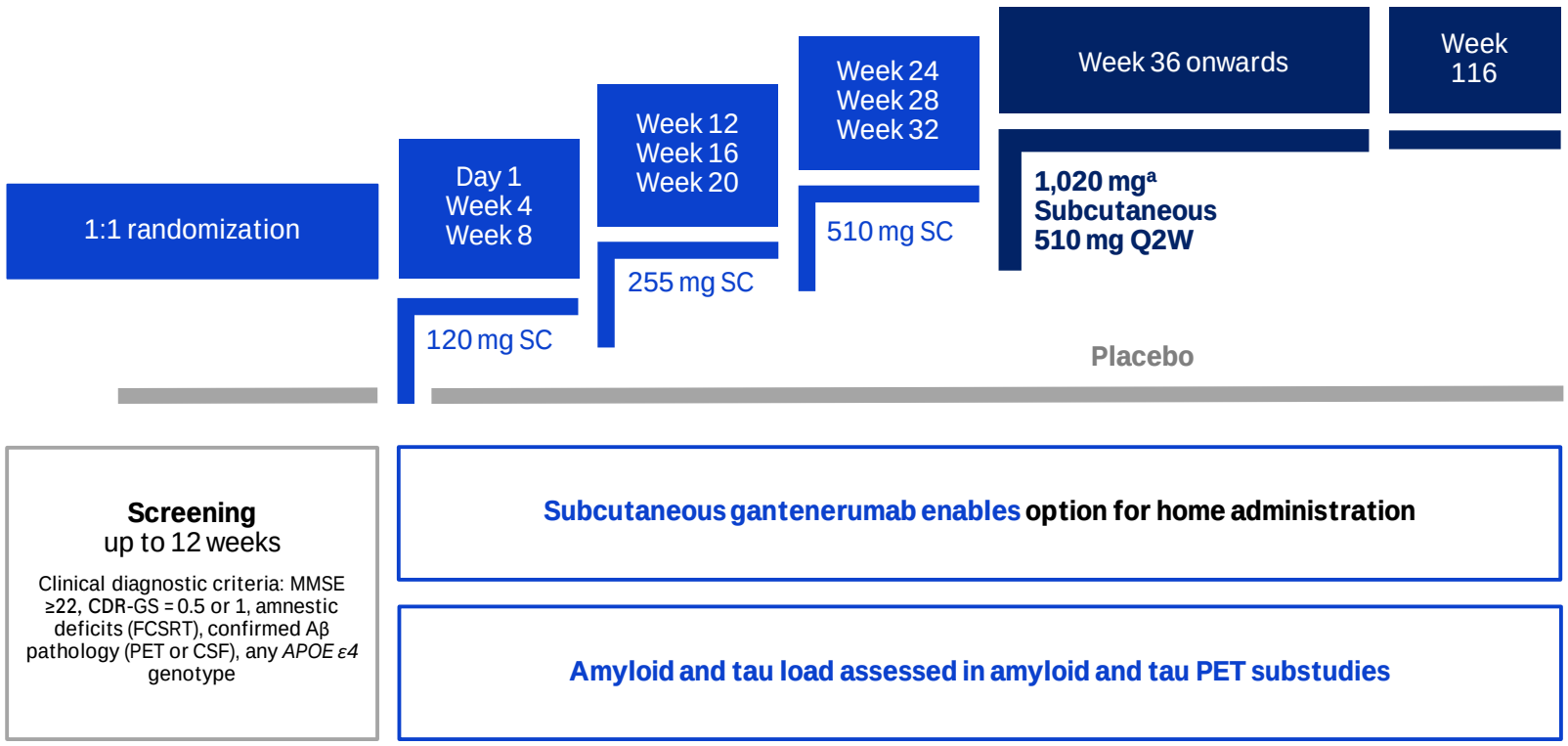


Microglia ingests plaque

Adapted from: https://www.ncbi.nlm.nih.gov/books/NBK566116/figure/Ch2-f0002/

GRADUATE Studies I & II in patients with early symptomatic AD

Efficacy and safety of gantenerumab assessed in approximately 1000 people per study



Primary Endpoint: Clinical Dementia Rating – "Sum of Boxes" (CDR-SB) at Week 116 (27-months)

Adapted from: Bateman R et al. Presentation at CTAD, November 31, 2022

The Q-ATN Model (Version 1.0): Linking Amyloid and Its Removal to Clinical Outcome

Received: 29 July 2022 | Revised: 27 September 2022 | Accepted: 21 October 2022

DOI: 10.1002/alz.12877

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THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

FEATURED ARTICLE

Development of a quantitative semi-mechanistic model of Alzheimer's disease based on the amyloid/tau/neurodegeneration framework (the Q-ATN model)

Norman A. Mazer[1] | Carsten Hofmann[1] | Dominik Lott[1] | Ronald Gieschke[1] | Gregory Klein[1] | Frank Boess[2] | Hans Peter Grimm[1] | Geoffrey A. Kerchner[1] | Monika Baudler-Klein[2] | Janice Smith[3] | Rachelle S. Doody[2,4] | for the Alzheimer's Disease Neuroimaging Initiative

https://alz-journals.onlinelibrary.wiley.com/doi/full/10.1002/alz.12877

Amyloid/Tau/Neurodegeneration Biomarker Research Framework

Based on the phenomenological descriptions of Clifford Jack Jr. and colleagues

ELSEVIER

CrossMark

Alzheimer's & Dementia 14 (2018) 535-562

Alzheimer's & Dementia

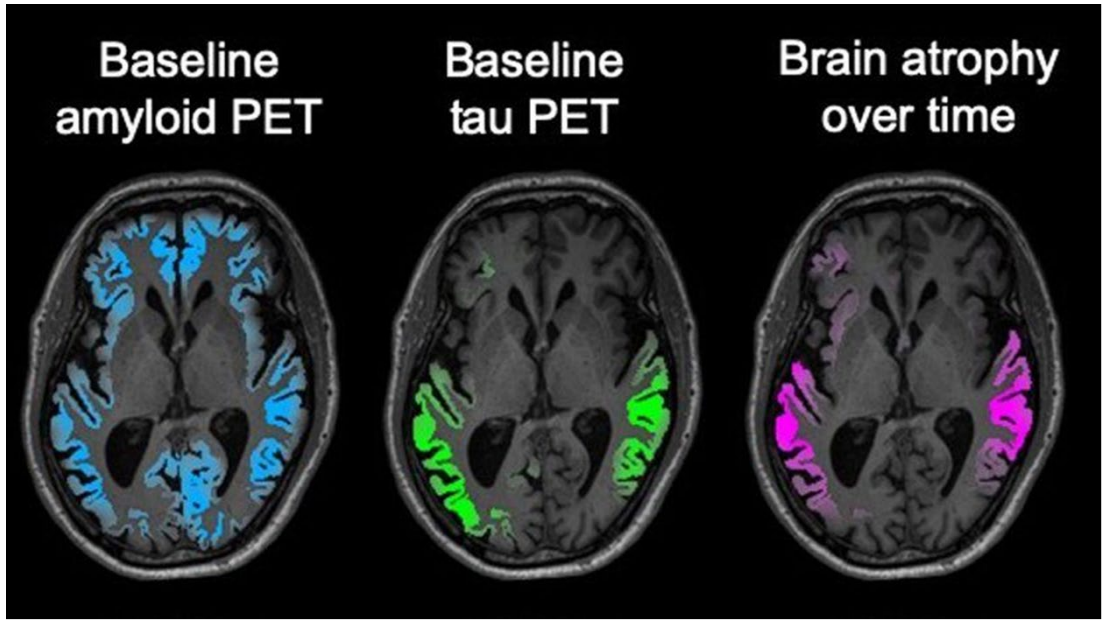
2018 National Institute on Aging—Alzheimer's Association (NIA-AA) Research Framework

NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease

Clifford R. Jack, Jr.,[a,*], David A. Bennett[b], Kaj Blennow[c], Maria C. Carrillo[d], Billy Dunn[e], Samantha Budd Haeberlein[f], David M. Holtzman[g], William Jagust[h], Frank Jessen[i], Jason Karlawish[j], Enchi Liu[k], Jose Luis Molinuevo[l], Thomas Montine[m], Creighton Phelps[n], Katherine P. Rankin[o], Christopher C. Rowe[p], Philip Scheltens[q], Eric Siemers[r], Heather M. Snyder[d], Reisa Sperling[s]

Contributors[†]**:** Cerise Elliott, Eliezer Masliah, Laurie Ryan, and Nina Silverberg

A **T** **N**

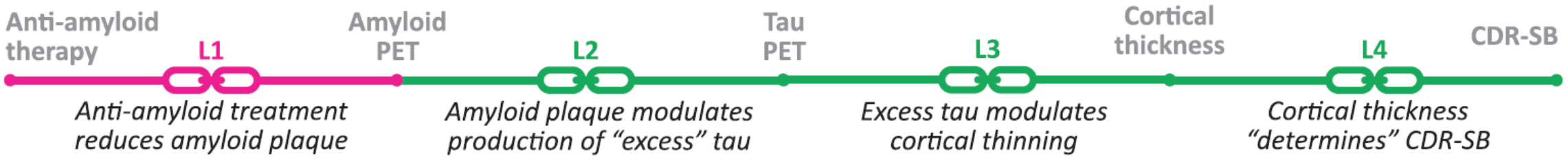


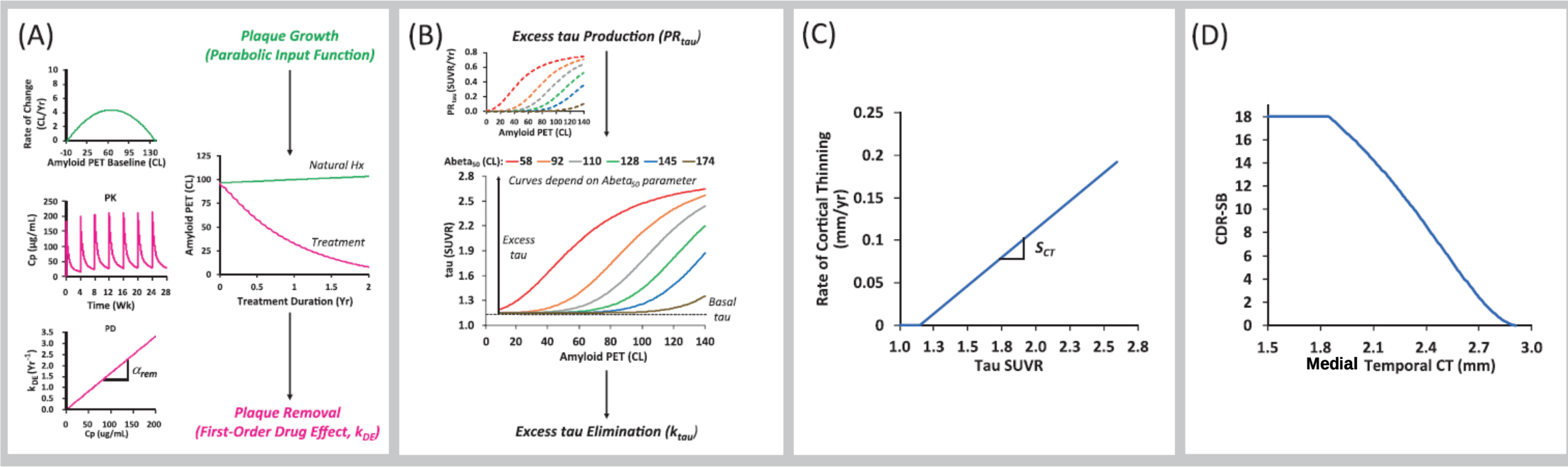
Rabinovici Lab
UCSF Research 2020

Amyloid Cascade **A** → **T** → **N** → **Cognitive Impairment**

High Level View of the Q-ATN Model (Version 1.0)

Four linkages (L1 to L4) quantify the biological mechanisms between anti-amyloid therapy and CDR-SB



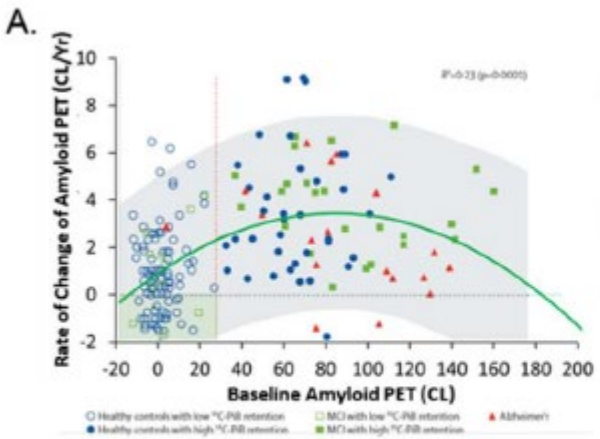


From: Mazer N.A. et al. Alzheimer's & Dementia 01 December 2022; https://doi.org/10.1002/alz.12877

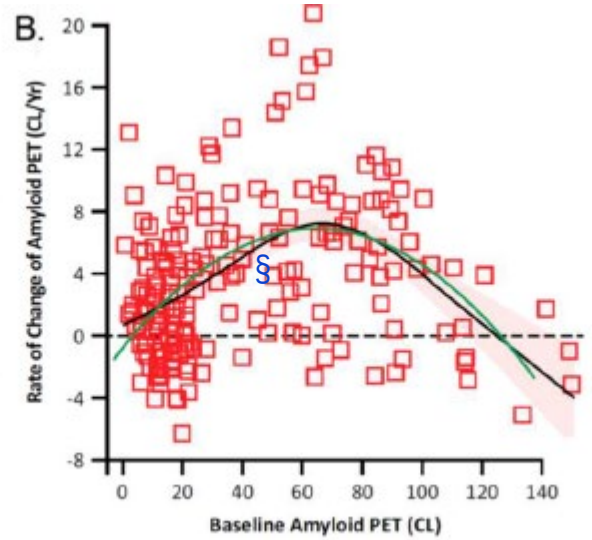
Calibration of Linkage 1: *Amyloid Input Function (Inverted Parabola)*

Determines the accumulation of amyloid plaque over time in centiloids (CL)

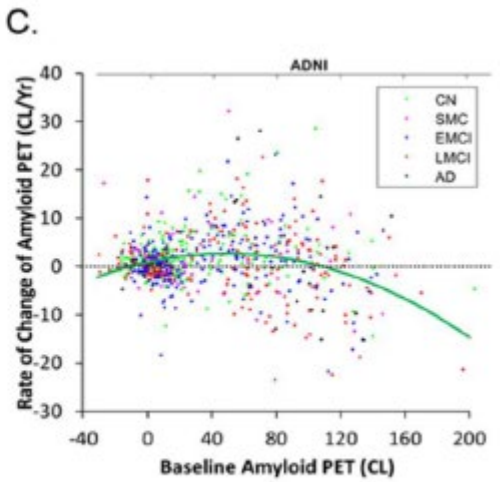
Villemagne et al. 2013



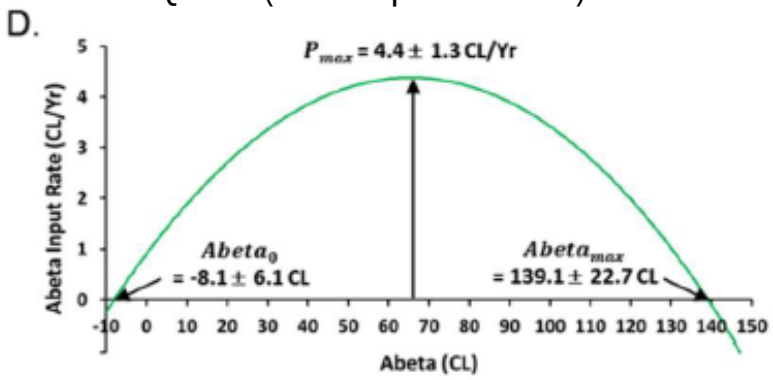
Jack et al. 2013



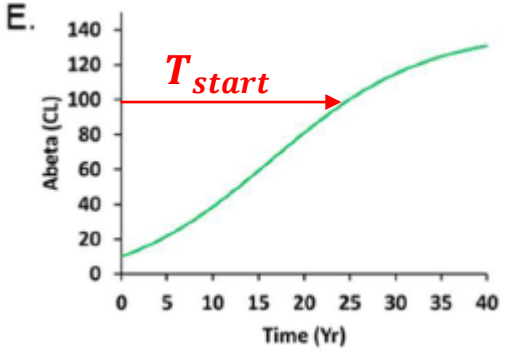
ADNI (Gieschke 2019; unpublished)



Q-ATN (mean input function)



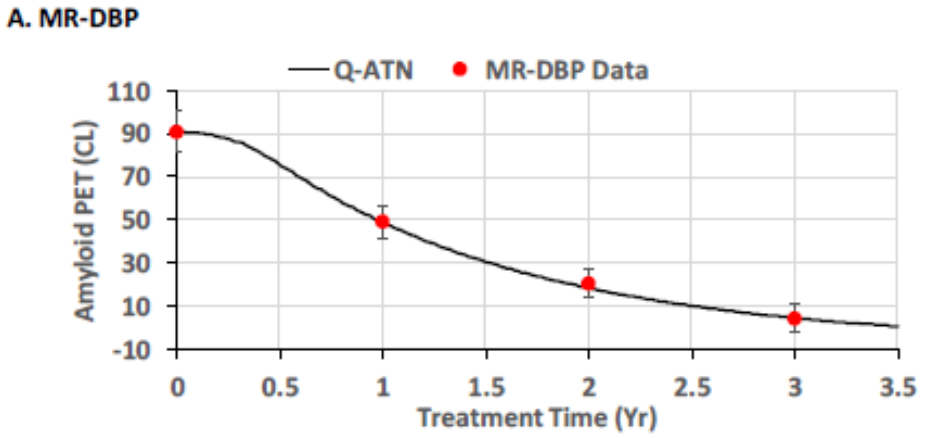
Integrated input function

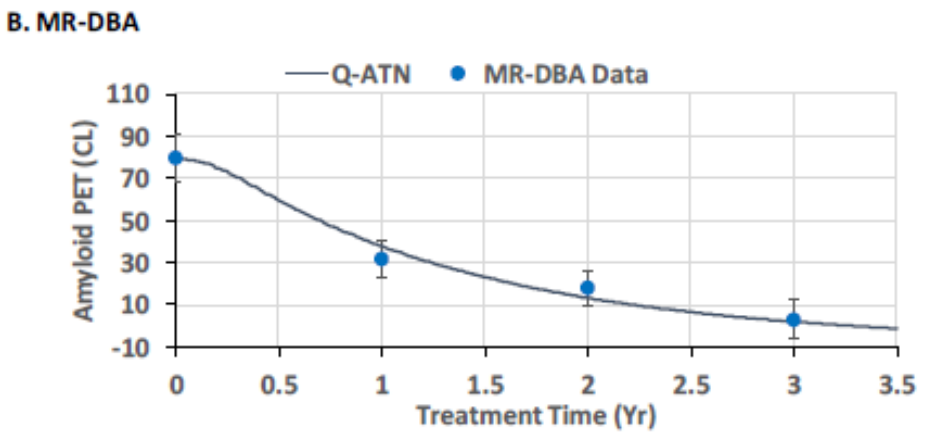


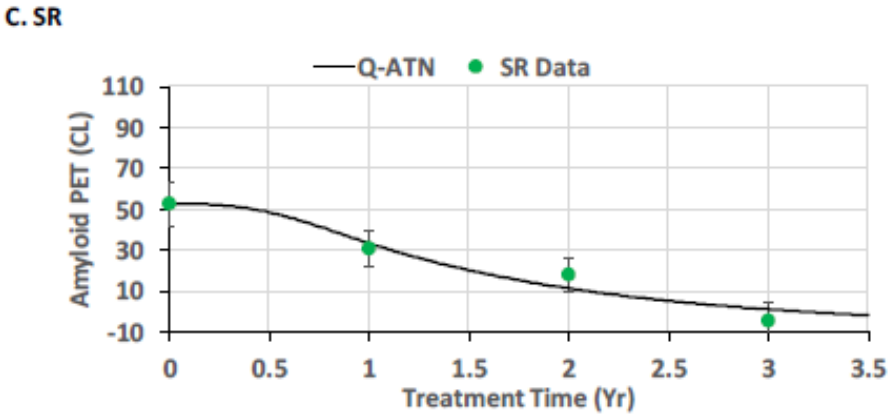
From: Mazer N.A. et al. Alzheimer's & Dementia 01 December 2022; https://doi.org/10.1002/alz.12877

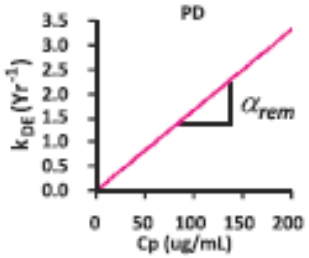
Calibration of Linkage 1: *Kinetics of Plaque Removal*

Effect of gantenerumab in open-label extension of the SR and MR studies (Klein G. et al. 2019)









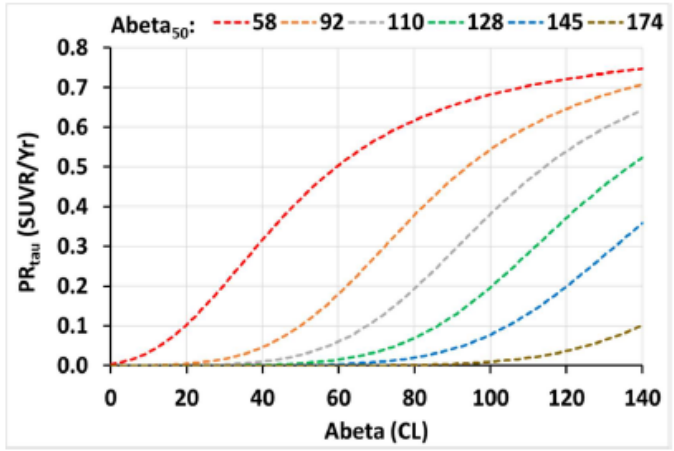
$a_{rem} = 0.0137\ Yr^{-1}/(ng/mL)$

From: Mazer N.A. et al. Alzheimer's & Dementia 01 December 2022; https://doi.org/10.1002/alz.12877

Calibration of Linkage 2: *Dynamics of tau PET*

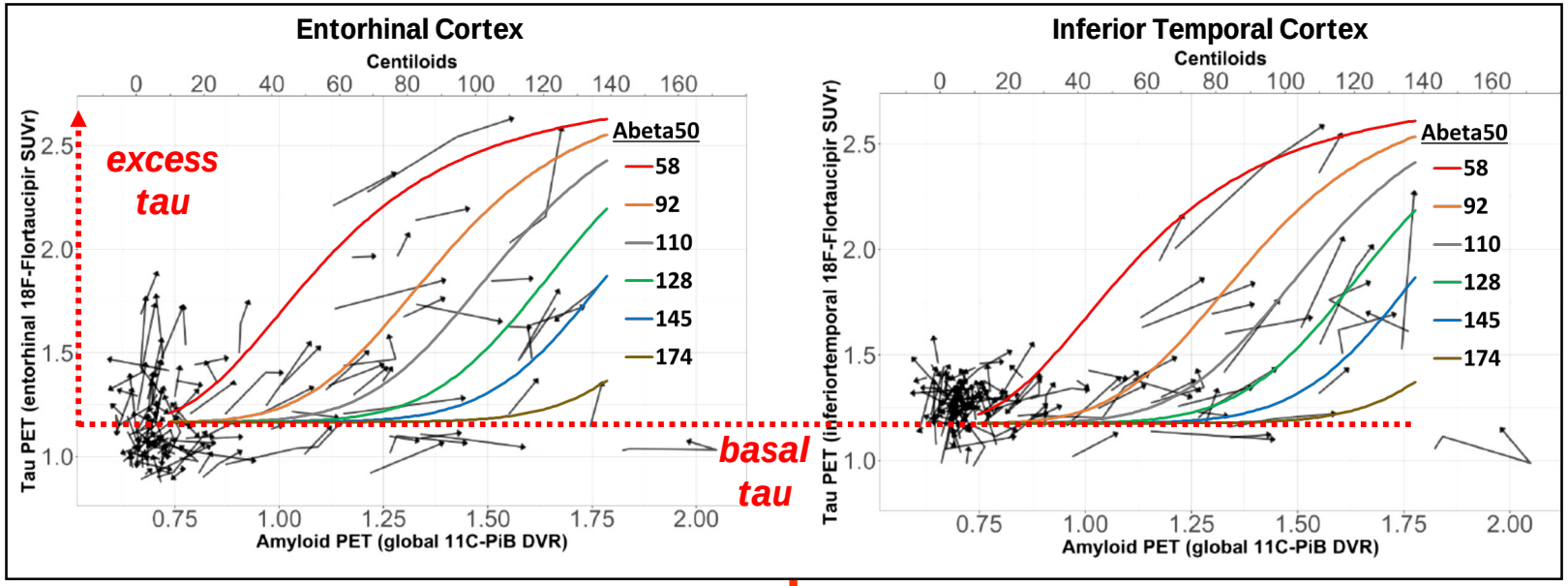
Longitudinal tau PET * vs. amyloid PET from Harvard Aging Brain Study (Johnson K and Sperling R 2020)

Estimated Tau PET Production Rate



Abeta$_{50}$ values:
Shift tau production curves to the right (determines the "ca-tau-strophe" points)

"Ca-Tau-Strophe" Plots



* Flortaucipir tracer; white matter reference

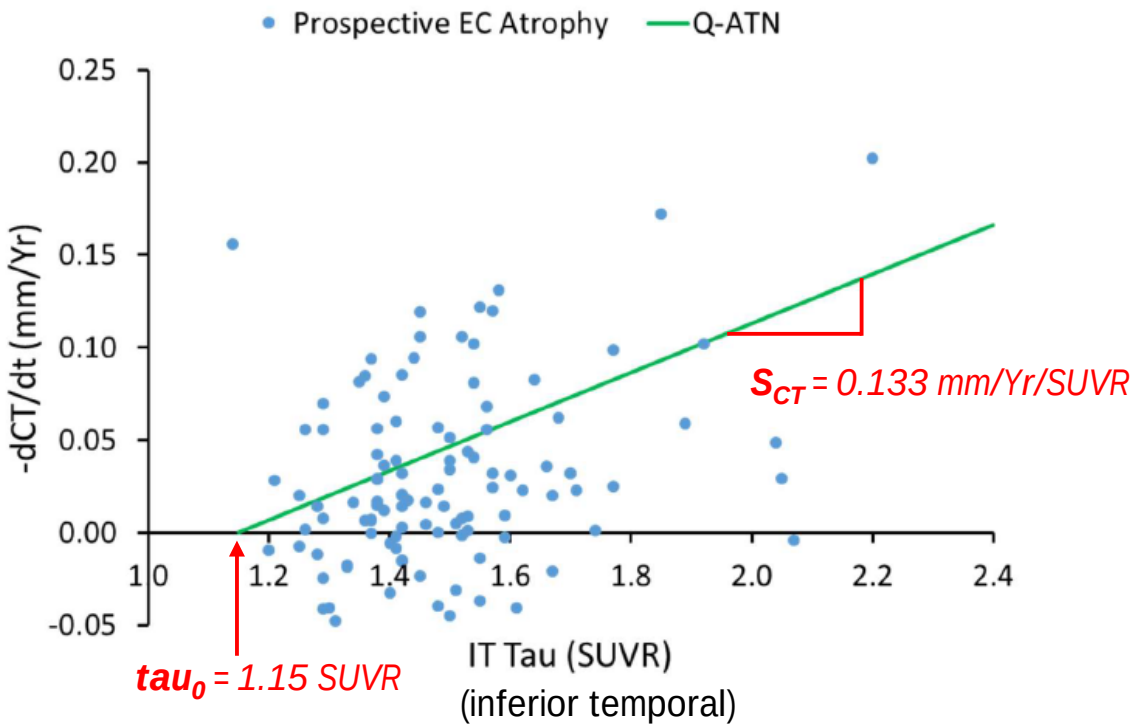
tau elimination rate constant (k_{tau}):
Nominal value taken to be 0.5 Yr^{-1} based on limited pre-clinical data

From: Mazer N.A. et al. Alzheimer's & Dementia 01 December 2022; https://doi.org/10.1002/alz.12877

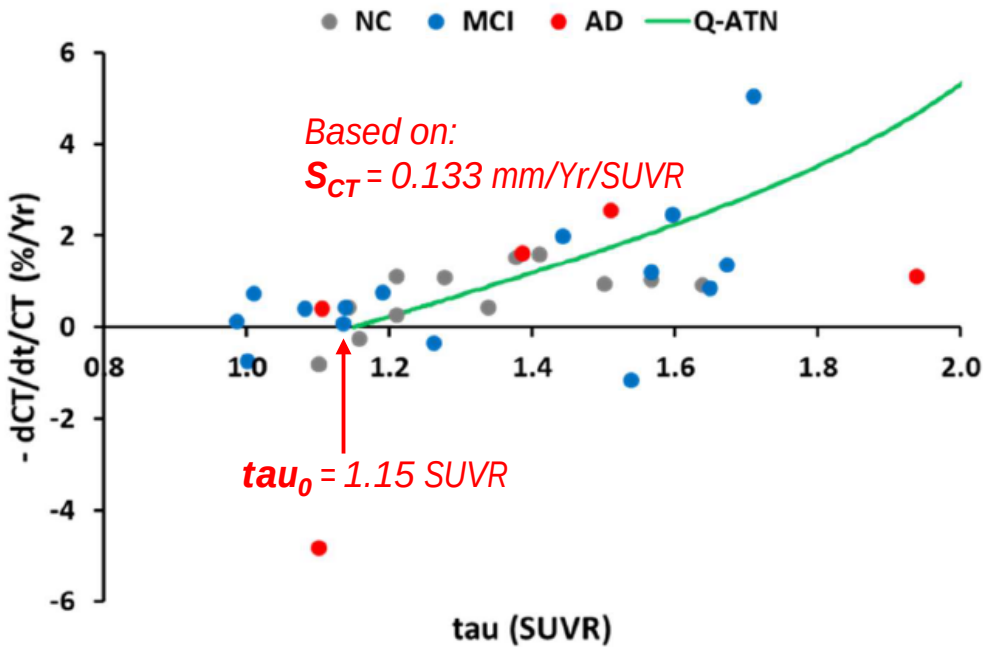
Calibration of Linkage 3: Natural History Studies of Cortical Thinning

Simulated dependence of -dCT/dt on tau PET

Data from Scott et al. 2020 (entorhinal cortex)



Data from Xie et al. 2018 (medial temporal cortex)

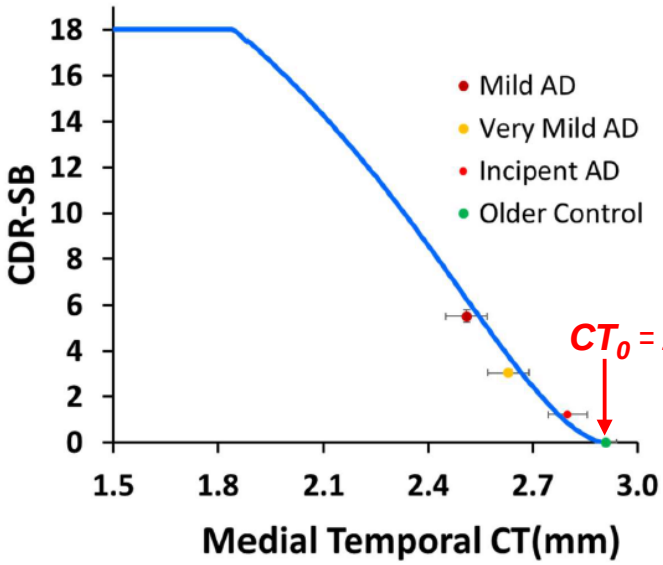


From: Mazer N.A. et al. Alzheimer's & Dementia 01 December 2022; https://doi.org/10.1002/alz.12877

Calibration of Linkage 4: Natural History Studies of CDR-SB

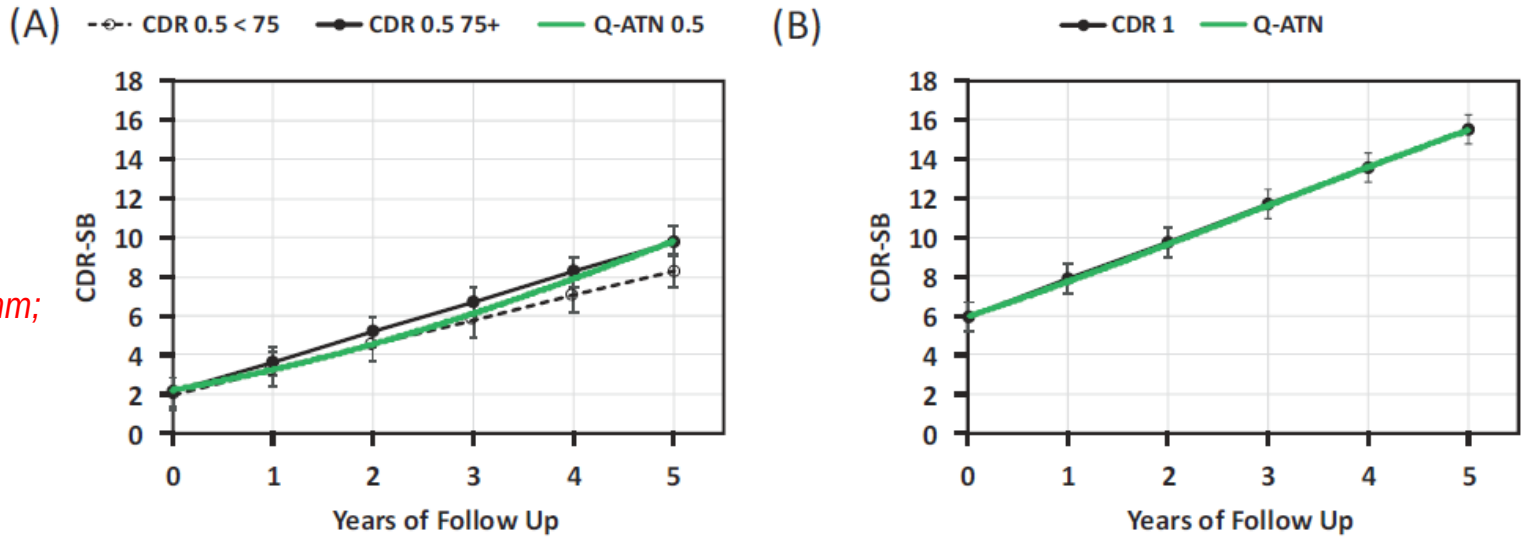
Simulated dependence of CDR-SB on CT and time-course of CDR-SB

CDR-SB vs Medial Temporal CT: Dickerson et al. 2008



CT_0 = 2.91 mm;

Longitudinal studies of CDR-SB in MCI and early AD: Williams et al 2009



$$CDR - SB = Minimum\ \langle\ E_{max} \times \left(\frac{CT_0 - CT}{CAT_{50}}\right)^{n_{CDR}} / [1 + \left(\frac{CT_0 - C}{CAT_{50}}\right)^{n_{CDR}}]\ ,\ 18\ \rangle$$

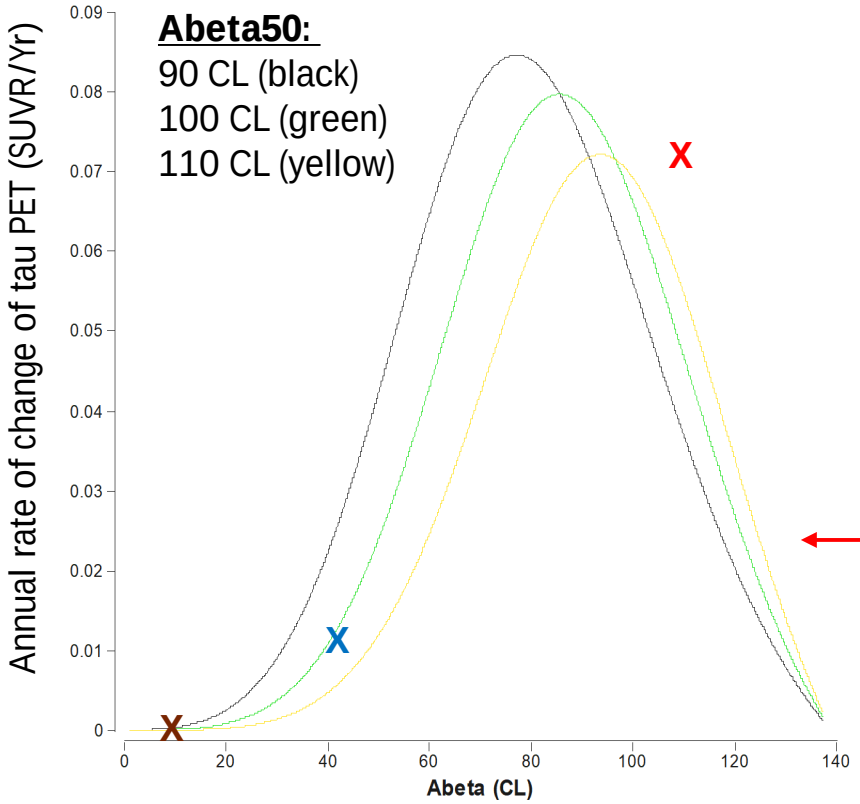
Emax= 32.76; $\mathbf{CAT_{50}}$ = 0.946 mm; $\mathbf{n_{CDR}}$ = 1.674

From: Mazer N.A. et al. Alzheimer's & Dementia 01 December 2022; https://doi.org/10.1002/alz.12877

Validation of Q-ATN Model: Longitudinal Studies of tau PET

Simulation of the rate of change of tau PET SUVR: Comparison to data of Jack Jr. et al

Q-ATN Simulation:



Mean tau PET data from Jack Jr. CR et al (Brain 2018):
Flortaucipir tracer; temporal composite; cerebellar crus gray ref.

X = Cognitively Impaired (CI) / Amyloid Positive (A +)
X = Cognitively Unimpaired (CU) / Amyloid Postive (A +)
X = Cognitively Unimpaired (CU) / Amyloid Negative (A -)

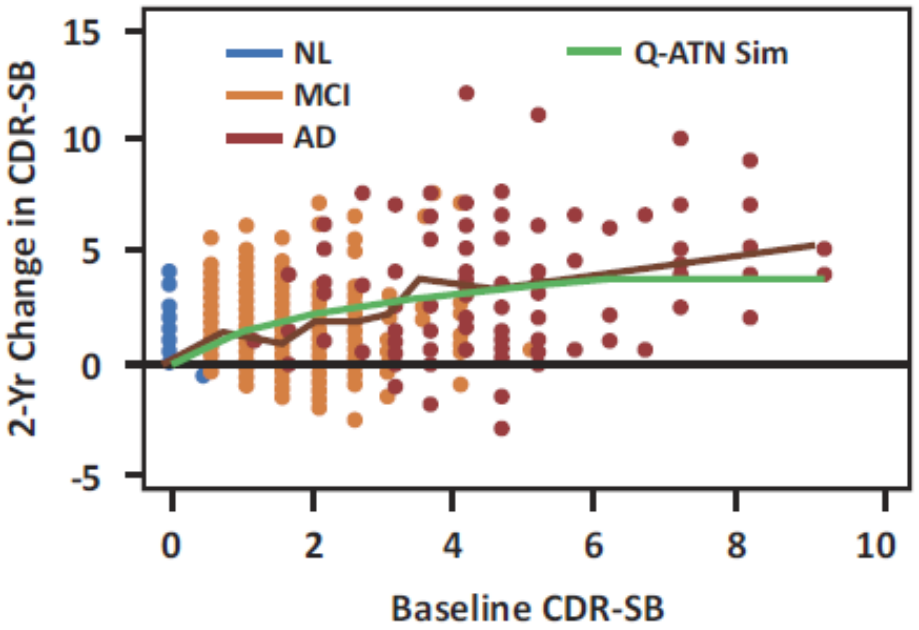
Data at high amyloid plaque levels are needed to verify the predicted decline in tau accumulation rate

From: Mazer N.A. et al. Alzheimer's & Dementia 01 December 2022; https://doi.org/10.1002/alz.12877

Validation of Q-ATN Model: Natural History Studies of CDR-SB

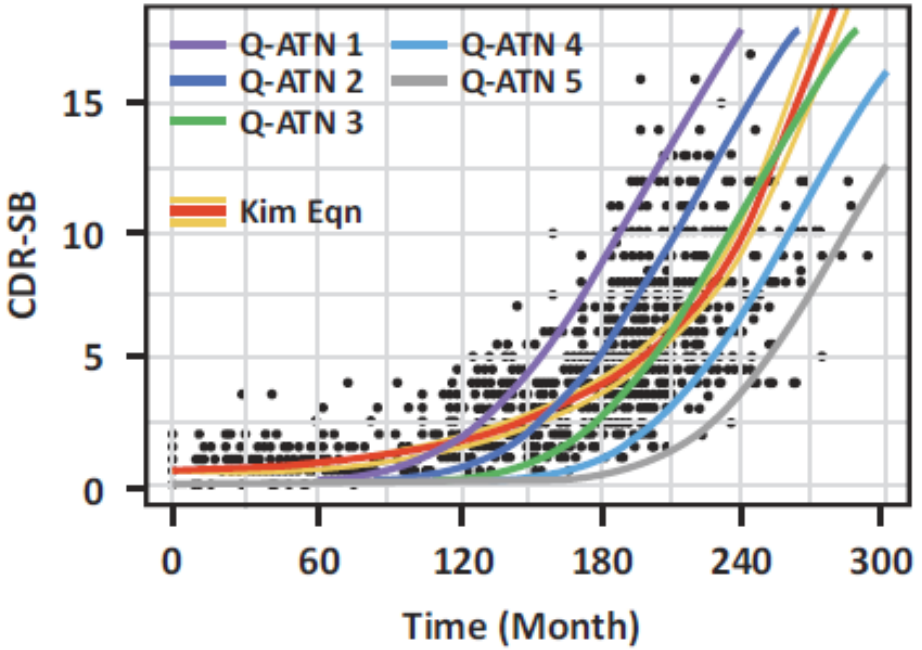
Simulated dynamics of CDR-SB

ADNI Data (from Delor I et al. 2013)



Rate of change varies with baseline level

Simulated time-course over 300 months (Kim KW et al 2020)

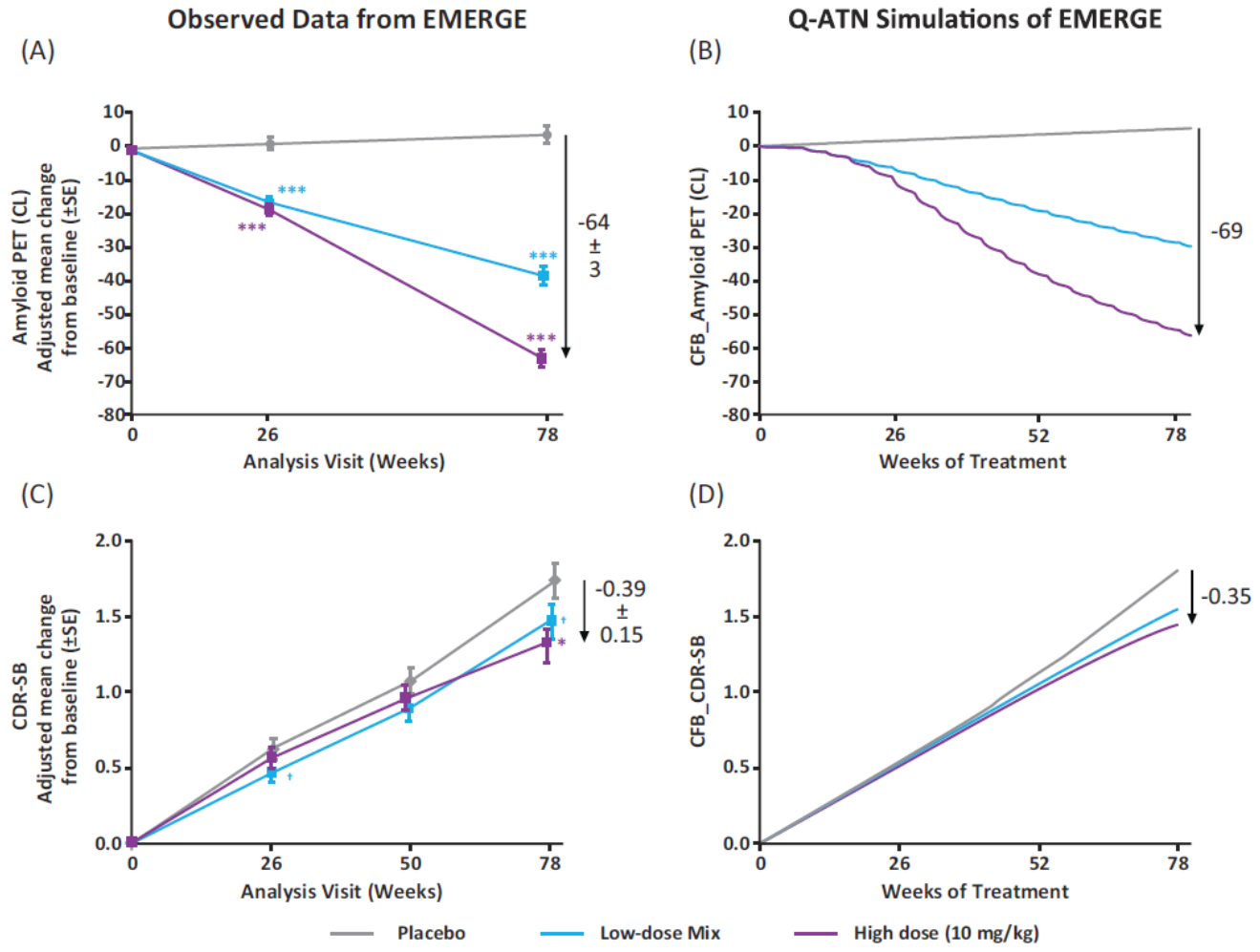


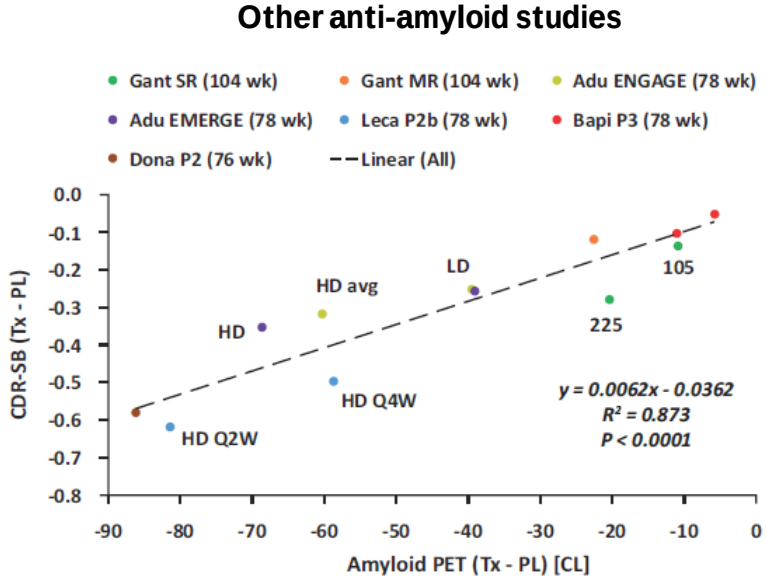
Individual Q-ATN curves have different initial amyloid plaque levels:
1 (42.4 CL), 2 (34.8 CL), 3 (27.9 CL), 4 (21.8 CL)** and **5 (16.5 CL)

From: Mazer N.A. et al. Alzheimer's & Dementia 01 December 2022; https://doi.org/10.1002/alz.12877

Validation of Q-ATN Model: Anti-Amyloid Studies

Simulations of Aducanumab EMERGE study (Budd Haeberlein S et al 2022) and other clinical trials



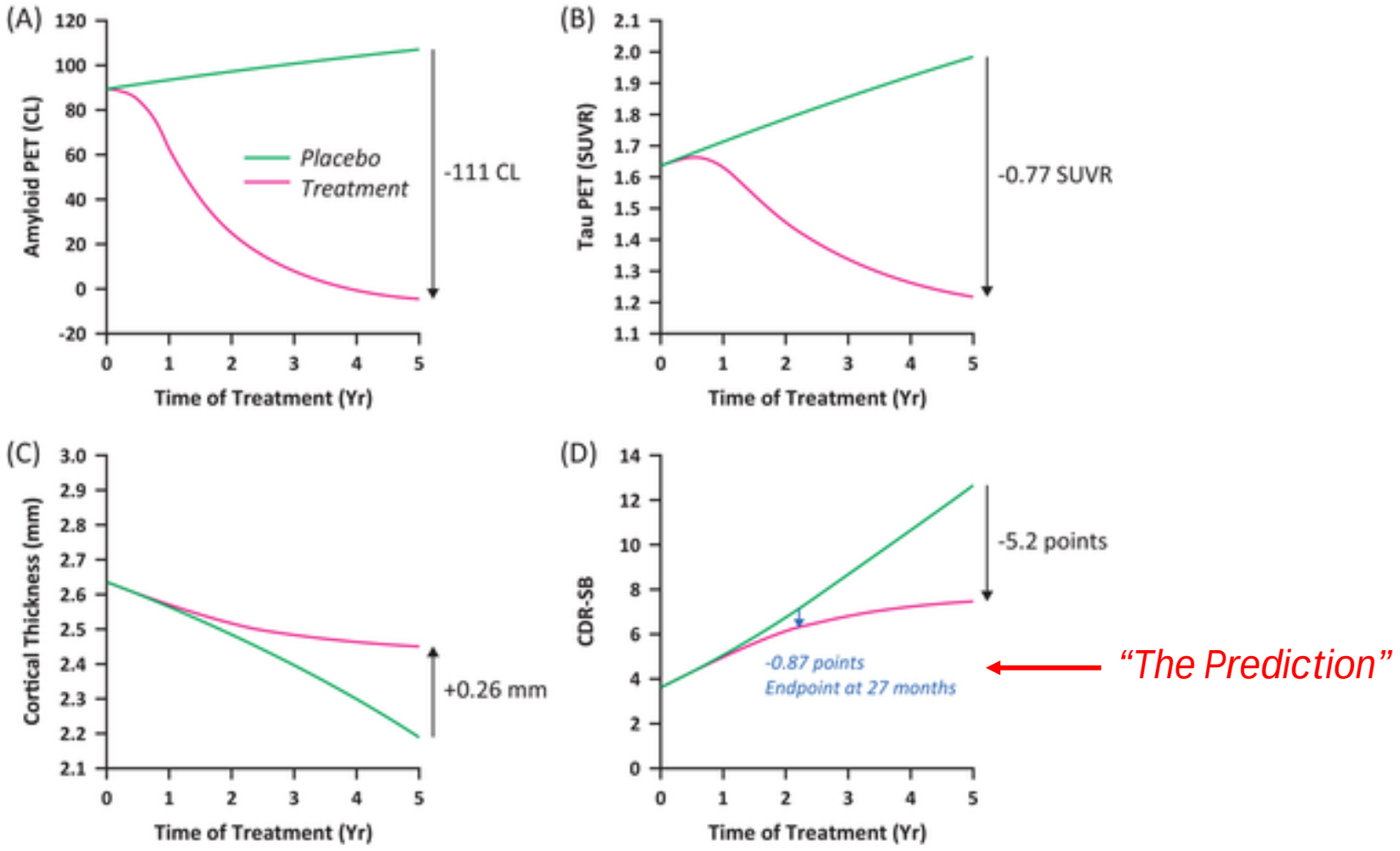


Similar to the FDA's plot …

From: Mazer N.A. et al. Alzheimer's & Dementia 01 December 2022; https://doi.org/10.1002/alz.12877

Q-ATN Simulations for a Hypothetical 5-Year Study of Gantenerumab

Treatment regimen used in the GRADUATE studies (maintaining the target dose after 27-months)



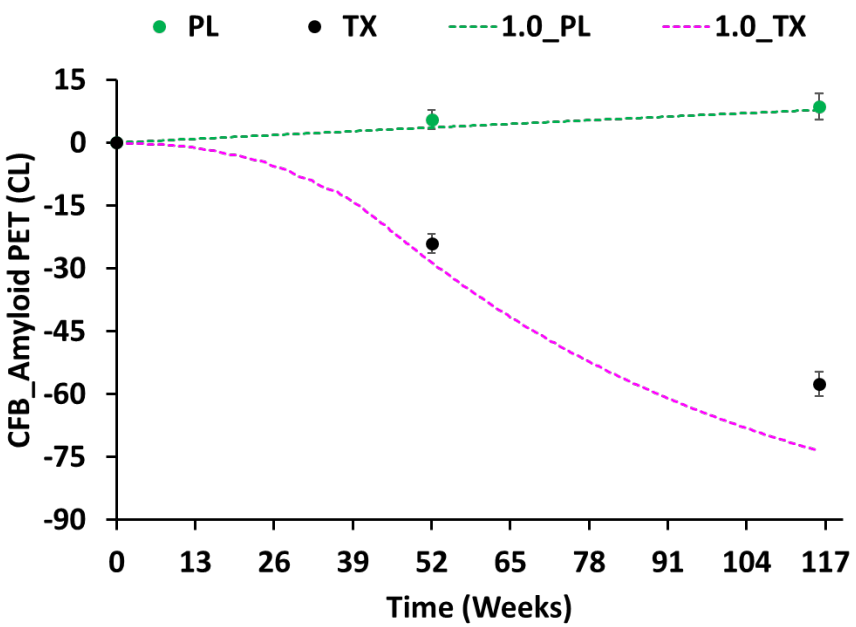
From: Mazer N.A. et al. Alzheimer's & Dementia 01 December 2022; https://doi.org/10.1002/alz.12877

Comparing the Q-ATN Prediction to the GRADUATE I & II Outcomes

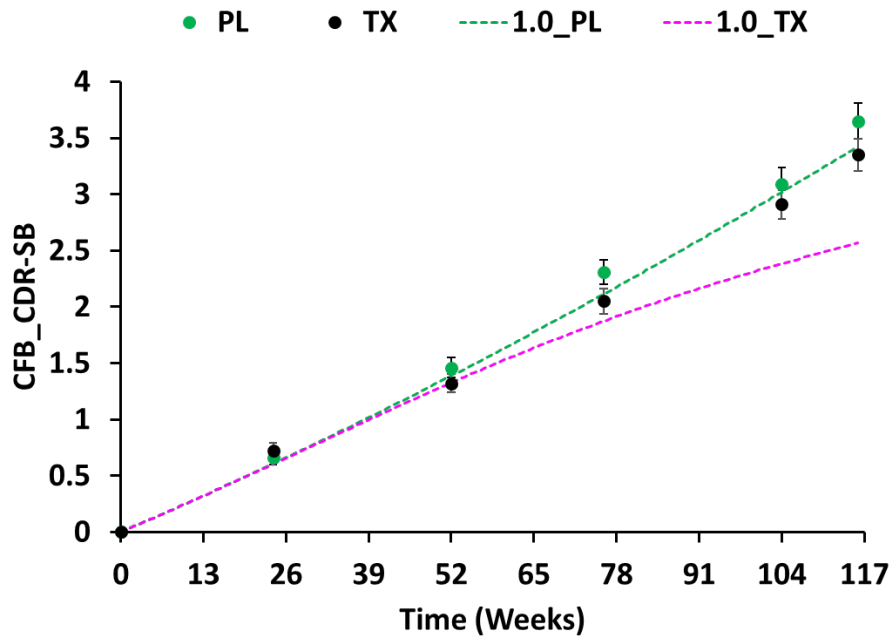
Comparison of Q-ATN Prediction with GRADUATE I Results

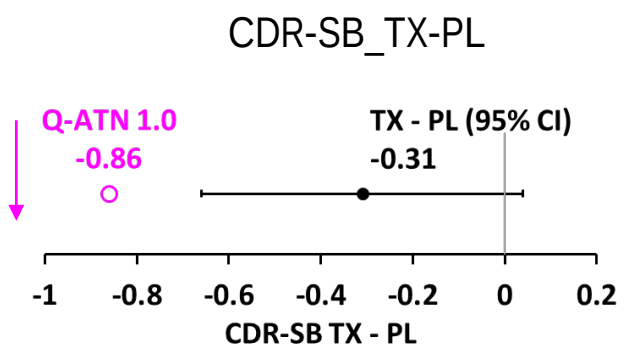
Prediction based on combined baseline values of amyloid PET and CDR-SB from both studies

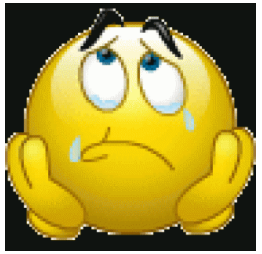
Amyloid PET (Change from Mean Baseline; 95.7 CL)



CDR-SB (Change from Mean Baseline; 3.71)





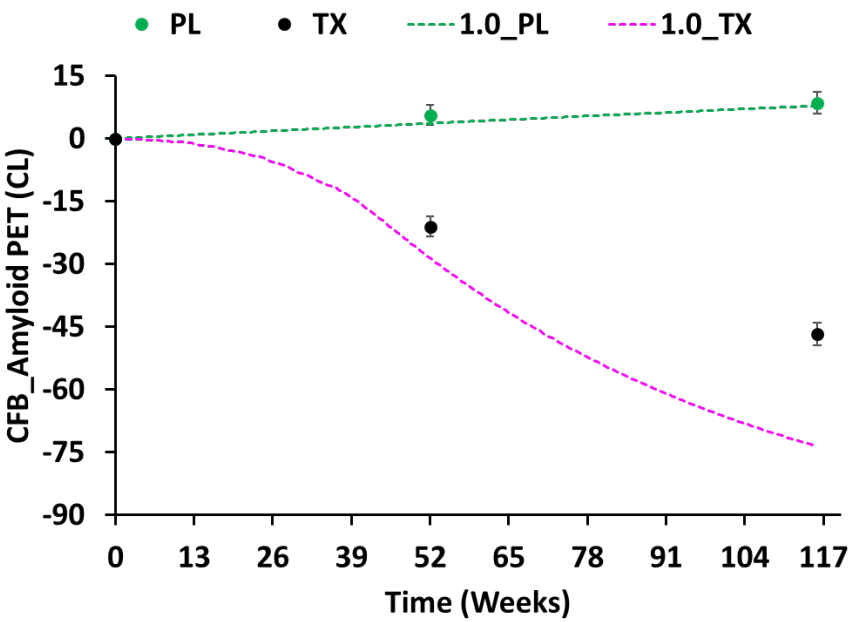


Data from Bateman RJ et al. (CTAD 2022)

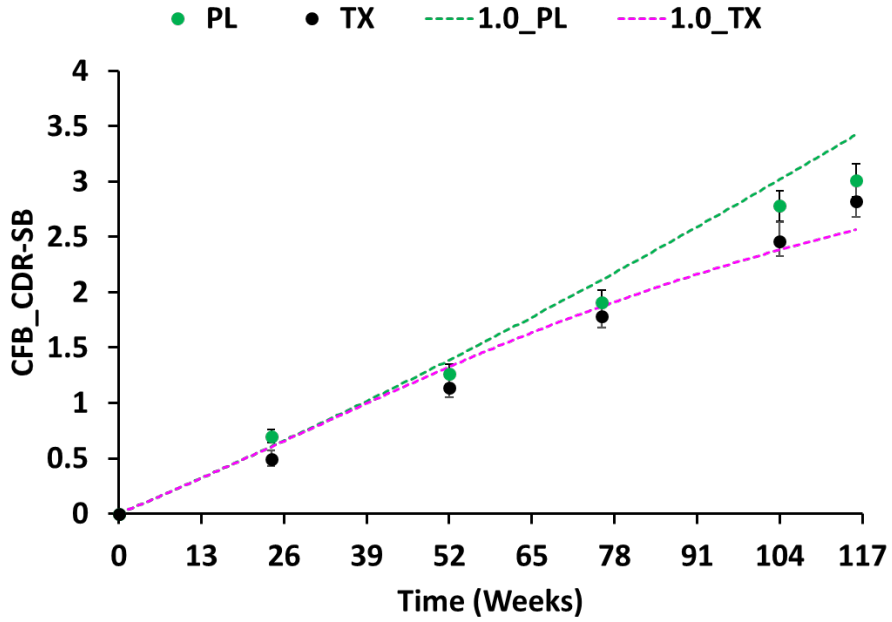
Comparison of Q-ATN Prediction with GRADUATE II Results

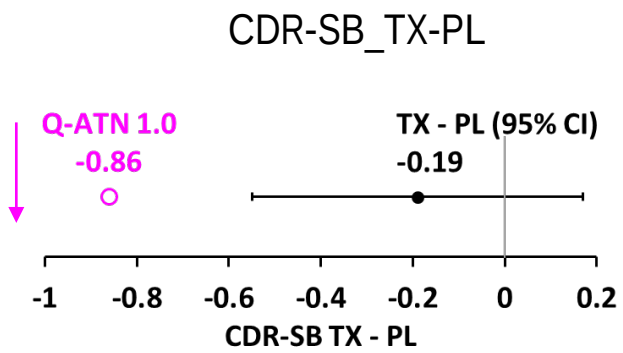
Prediction based on combined baseline values of amyloid PET and CDR-SB from both studies

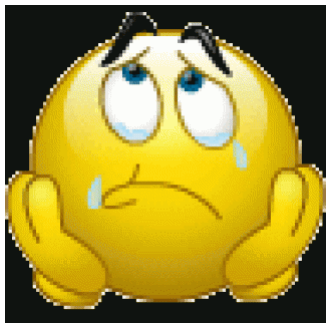
Amyloid PET (Change from Mean Baseline; 93.1 CL)



CDR-SB (Change from Mean Baseline; 3.60)



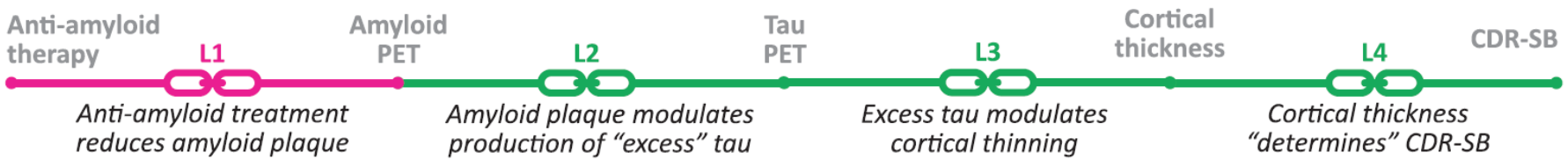


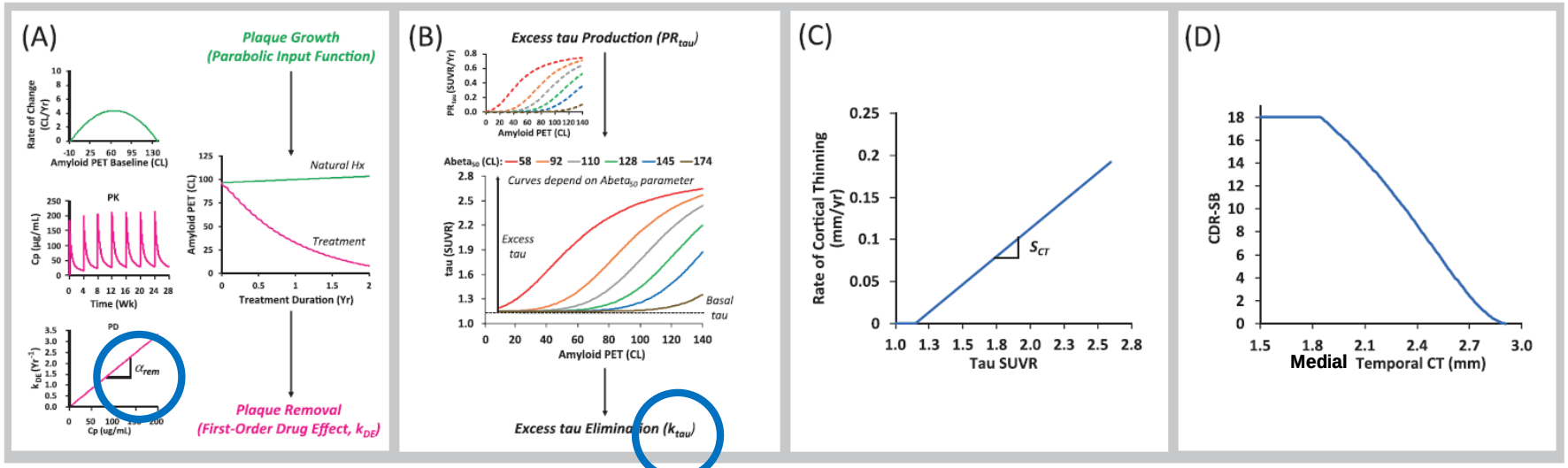


Data from Bateman RJ et al. (CTAD 2022)

Updating the Q-ATN Model (Version 1.1)

Re-estimating the amyloid removal parameter (a_{rem}) in L1 linkage and the pathological tau turnover rate constant (k_{tau}) in L2 linkage





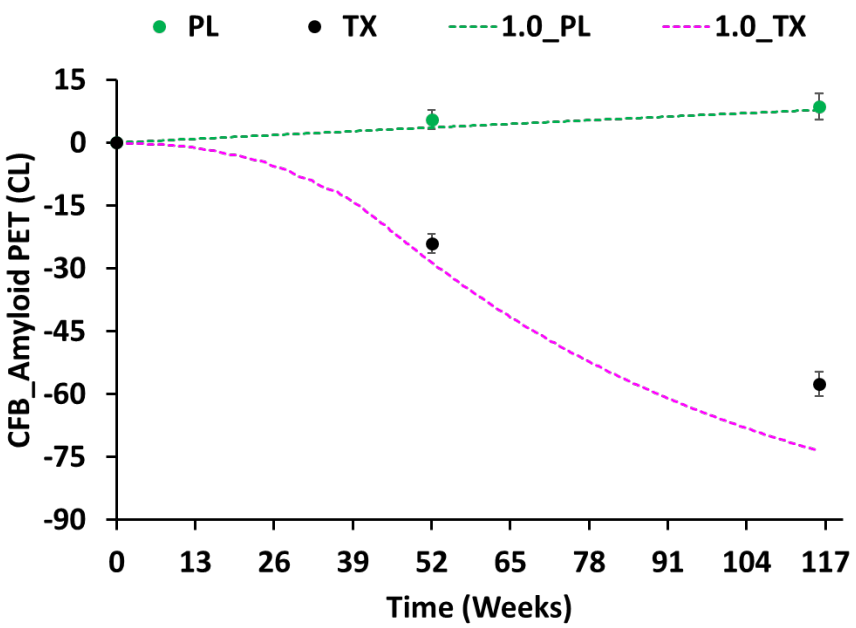
a_{rem} is drug-specific; estimated for each anti-amyloid antibody

k_{tau} is a property of aggregated tau; estimated from sensitivity analysis of multiple treatment arms

Updated Q-ATN Model (Version 1.1) vs. GRADUATE I Results

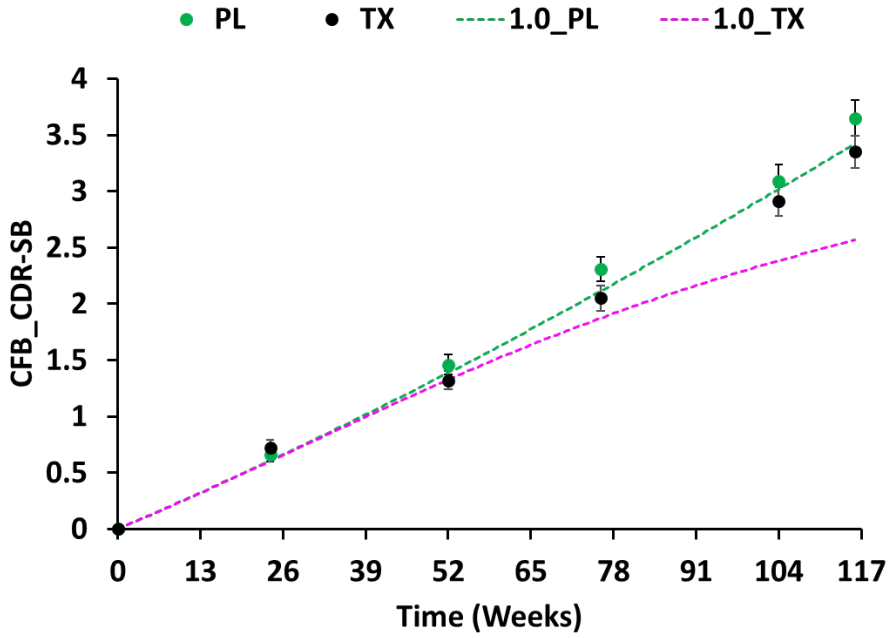
Re-estimated amyloid removal parameter (a_{rem}) and pathological tau turnover rate (k_{tau})

Amyloid PET (Change from Mean Baseline; 95.7 CL)

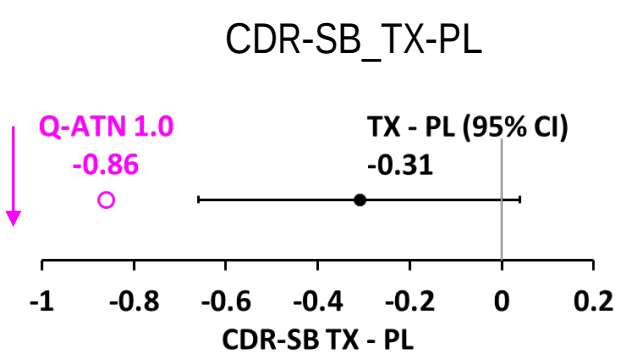


a_{rem} = 0.0137 Yr-1/(µg/mL)

CDR-SB (Change from Mean Baseline; 3.71)



k_{tau} = 0.5 Yr-1

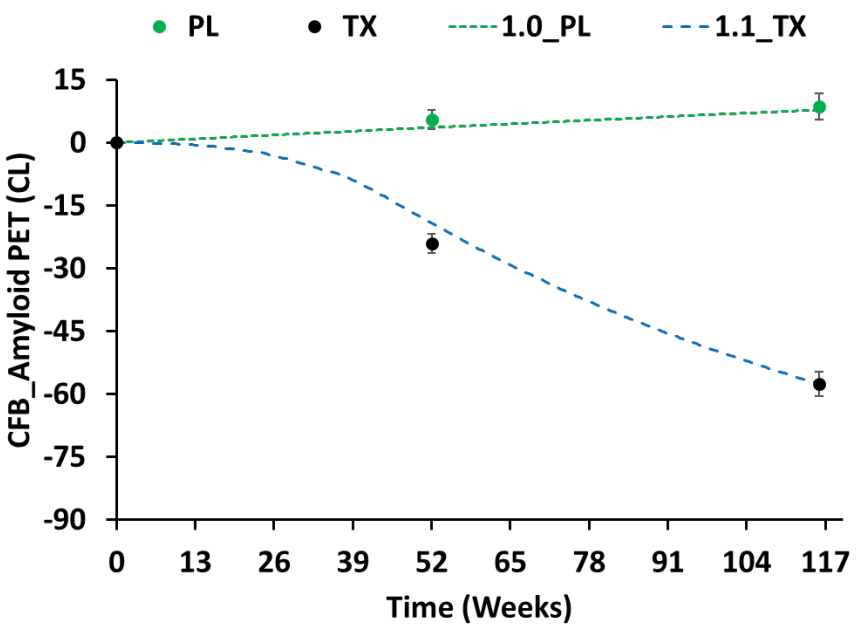


Data from Bateman RJ et al. (CTAD 2022); Simulations from Boess F et al.; AAIC 2023

Updated Q-ATN Model (Version 1.1) vs. GRADUATE I Results

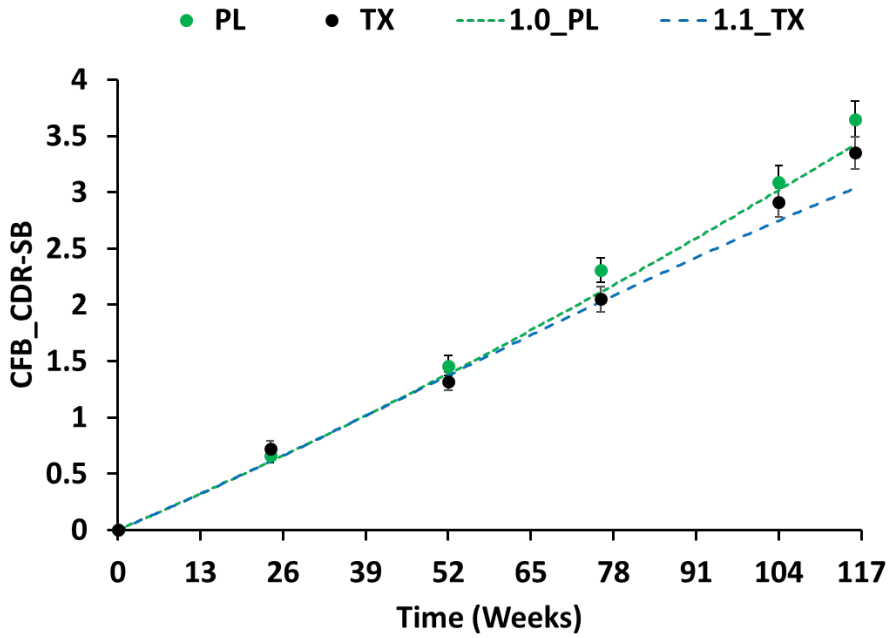
Re-estimated amyloid removal parameter (a_{rem}) and pathological tau turnover rate (k_{tau})

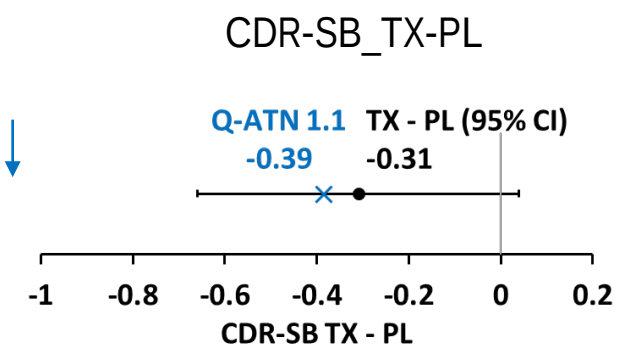
Amyloid PET (Change from Mean Baseline; 95.7 CL)



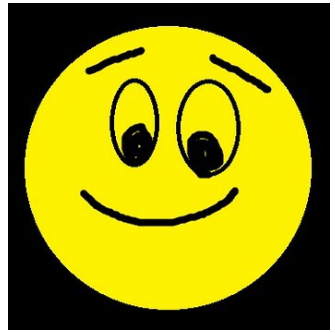
a_{rem} = 0.0091 Yr-1/(µg/mL) ; - *34%*

CDR-SB (Change from Mean Baseline; 3.71)





k_{tau} = 0.2 Yr-1; - *60%*

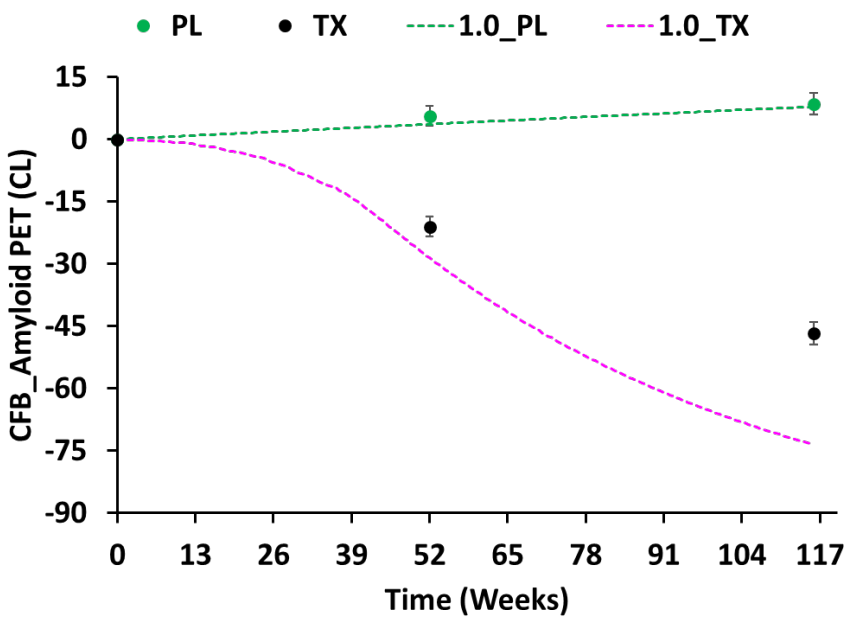


Data from Bateman RJ et al. (CTAD 2022); Simulations from Boess F et al.; AAIC 2023

Updated Q-ATN Model (Version 1.1) vs. GRADUATE II Results

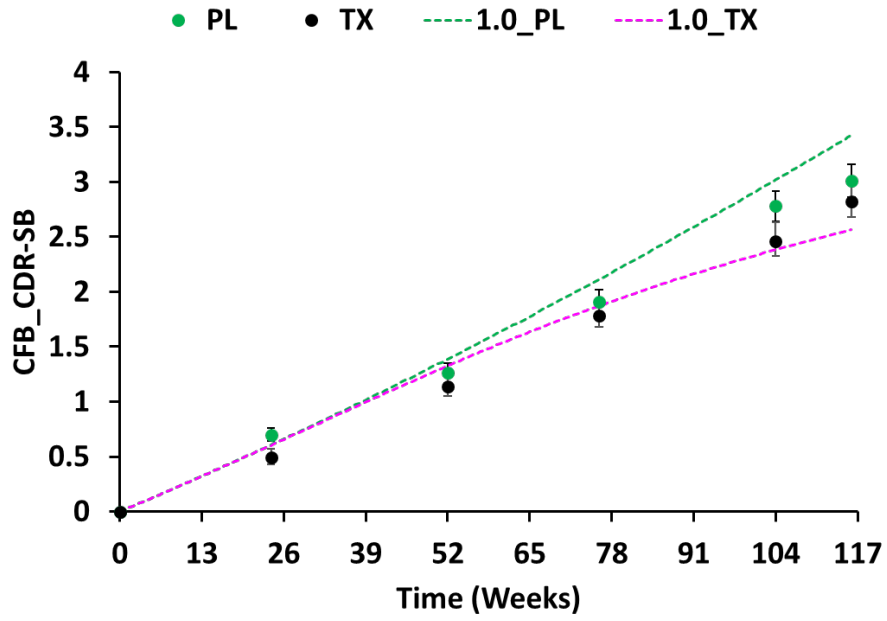
Re-estimated amyloid removal parameter (a_{rem}) and pathological tau turnover rate (k_{tau})

Amyloid PET (Change from Mean Baseline; 93.1 CL)

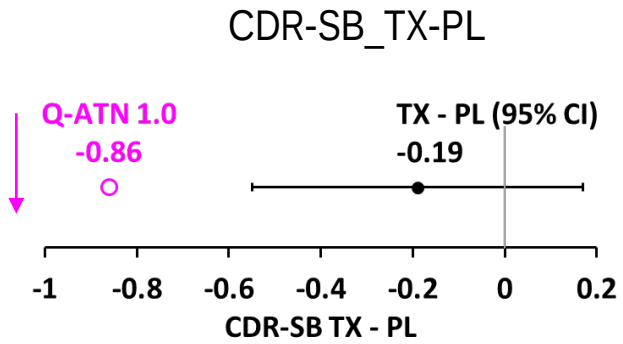


a_{rem} = 0.0137 Yr-1/(µg/mL)

CDR-SB (Change from Mean Baseline; 3.60)



k_{tau} = 0.5 Yr-1

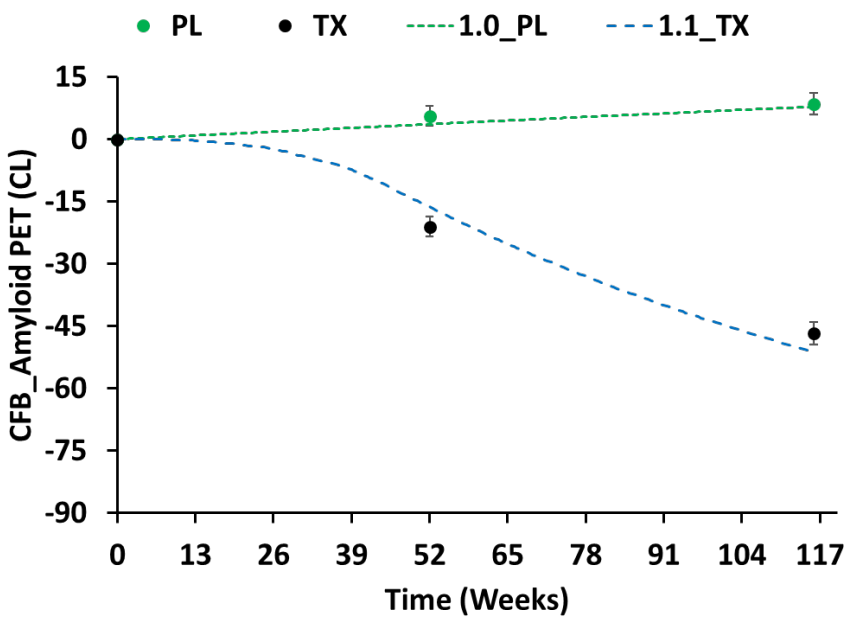


Data from Bateman RJ et al. (CTAD 2022); Simulations from Boess F et al.; AAIC 2023

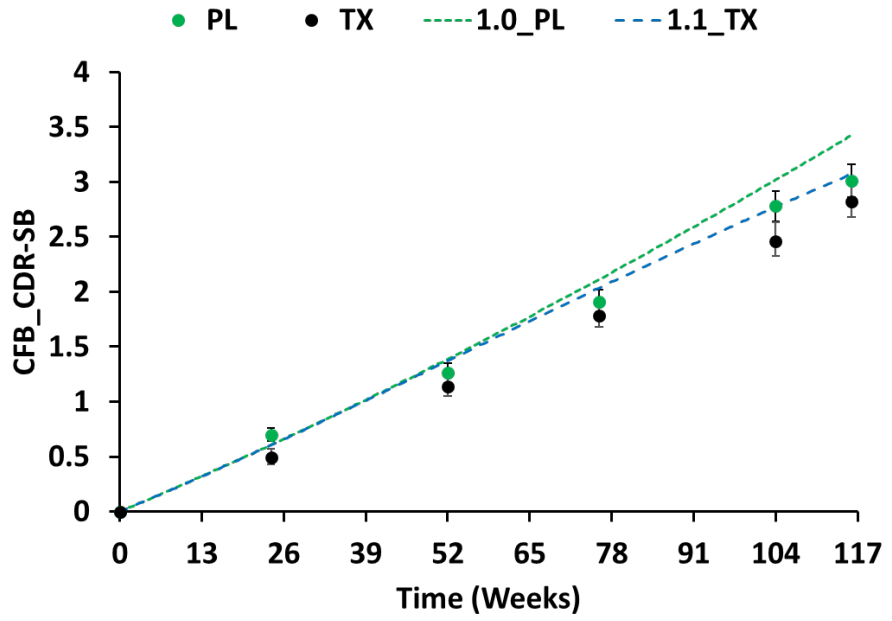
Updated Q-ATN Model (Version 1.1) vs. GRADUATE II Results

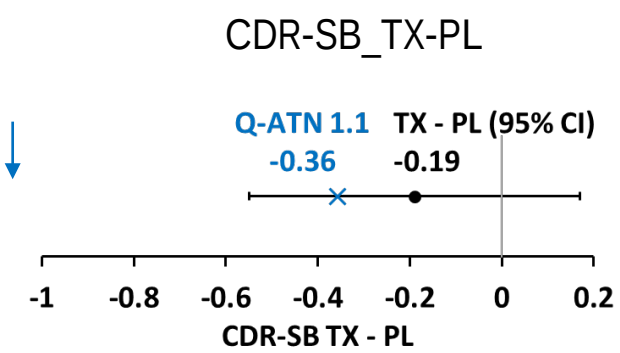
Re-estimated amyloid removal parameter (a_{rem}) and pathological tau turnover rate (k_{tau})

Amyloid PET (Change from Mean Baseline; 93.1 CL)



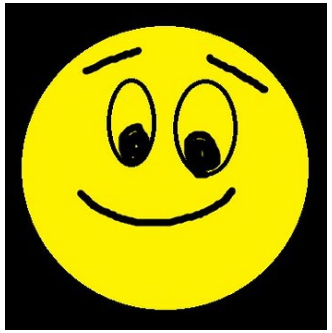
CDR-SB (Change from Mean Baseline; 3.60)





a_{rem} = 0.0081 Yr-1/(µg/mL) ; - *41%*

k_{tau} = 0.2 Yr-1; - *60%*



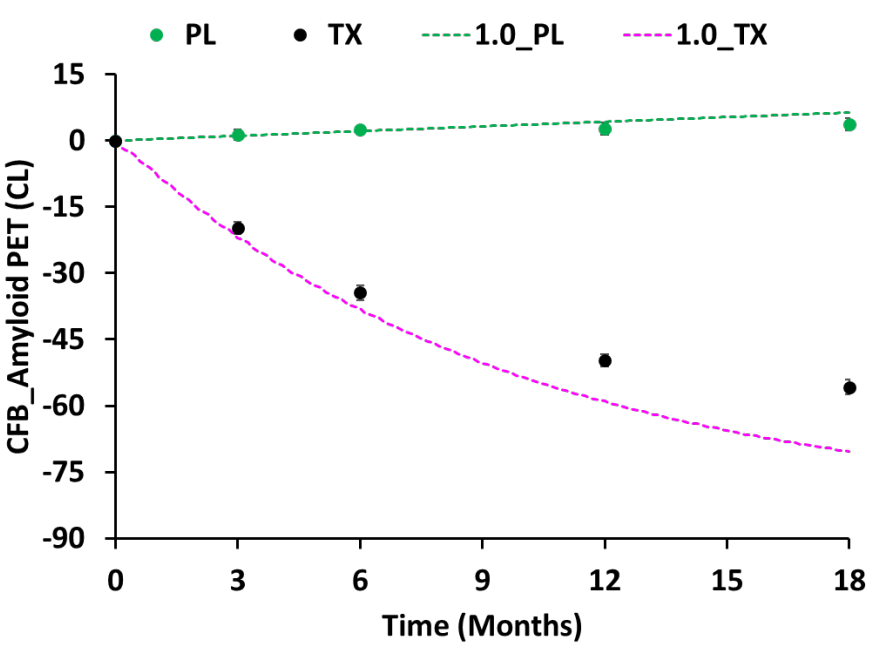
Data from Bateman RJ et al. (CTAD 2022); Simulations from Boess F et al.; AAIC 2023

Updated Q-ATN Model of CLARITY and Other Studies

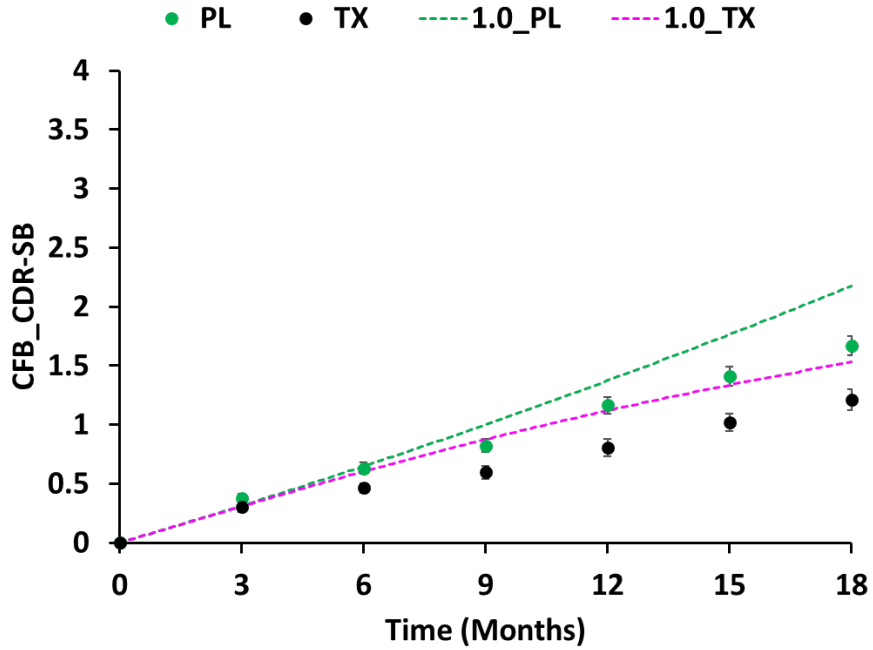
Updated Q-ATN Model (Version 1.1) vs. CLARITY Results (18-months)

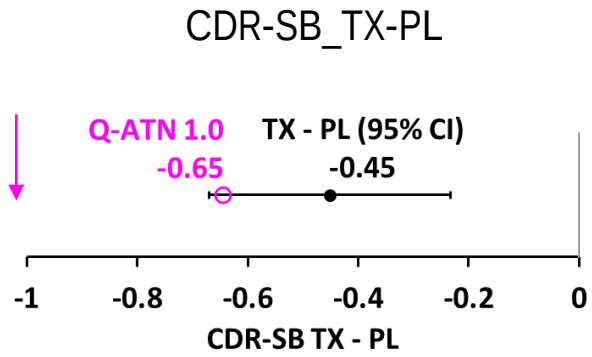
Re-estimated amyloid removal parameter (a_{rem}) and pathological tau turnover rate (k_{tau})

Amyloid PET (Change from Mean Baseline; 76.0 CL)



CDR-SB (Change from Mean Baseline; 3.21)





a_{rem} = 0.0109 Yr-1/(µg/mL)

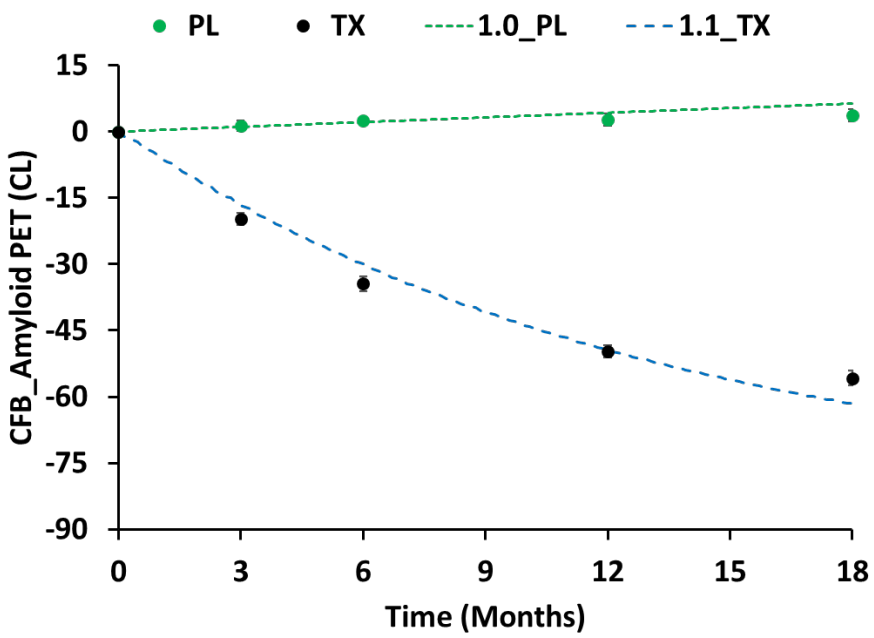
k_{tau} = 0.5 Yr-1

Data from Bateman RJ et al. (CTAD 2022); Simulations from Boess F et al. (AAIC 2023)

Updated Q-ATN Model (Version 1.1) vs. CLARITY Results (18-months)

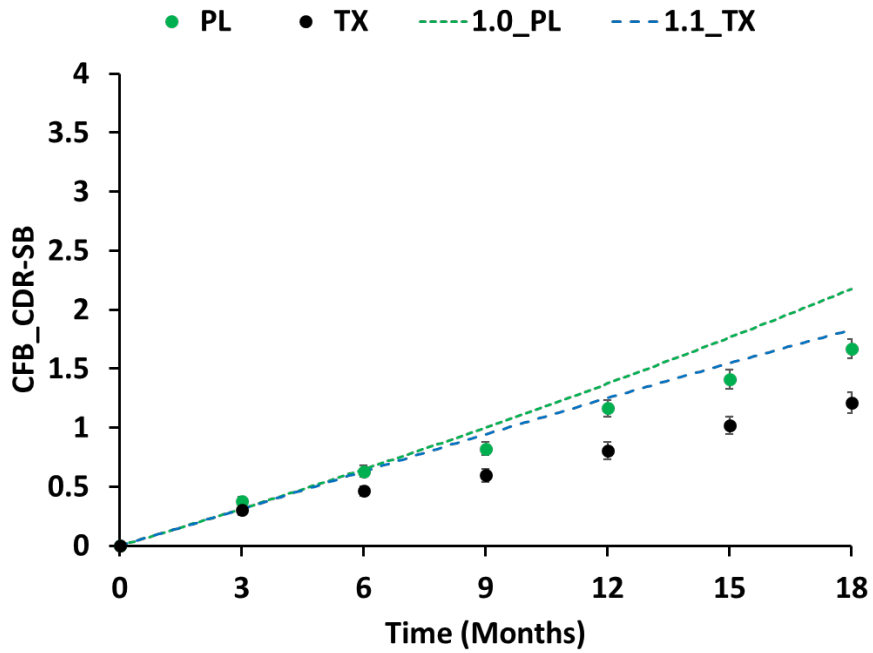
Re-estimated amyloid removal parameter (a_{rem}) and pathological tau turnover rate (k_{tau})

Amyloid PET (Change from Mean Baseline; 76.0 CL)

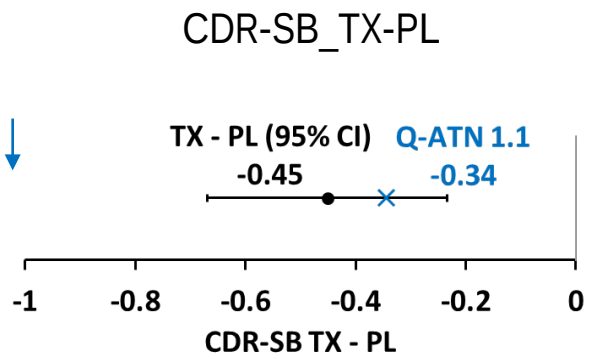


a_{rem} = 0.0081 Yr-1/(µg/mL) ; - *26%*

CDR-SB (Change from Mean Baseline; 3.21)



k_{tau} = 0.2 Yr-1; - *60%*

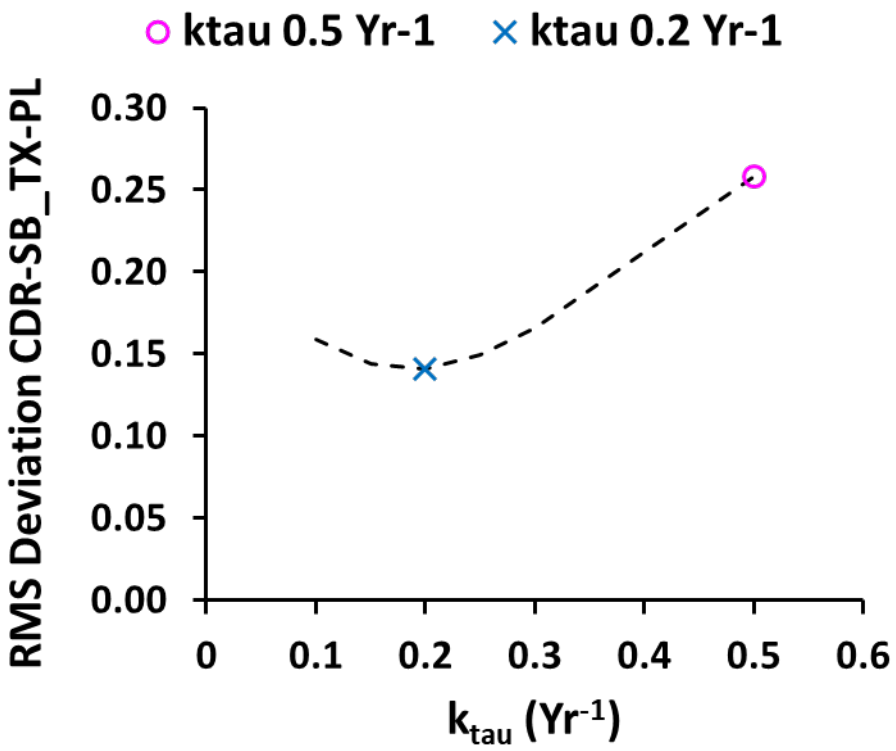


Data from Bateman RJ et al. (CTAD 2022); Simulations from Boess F et al. (AAIC 2023)

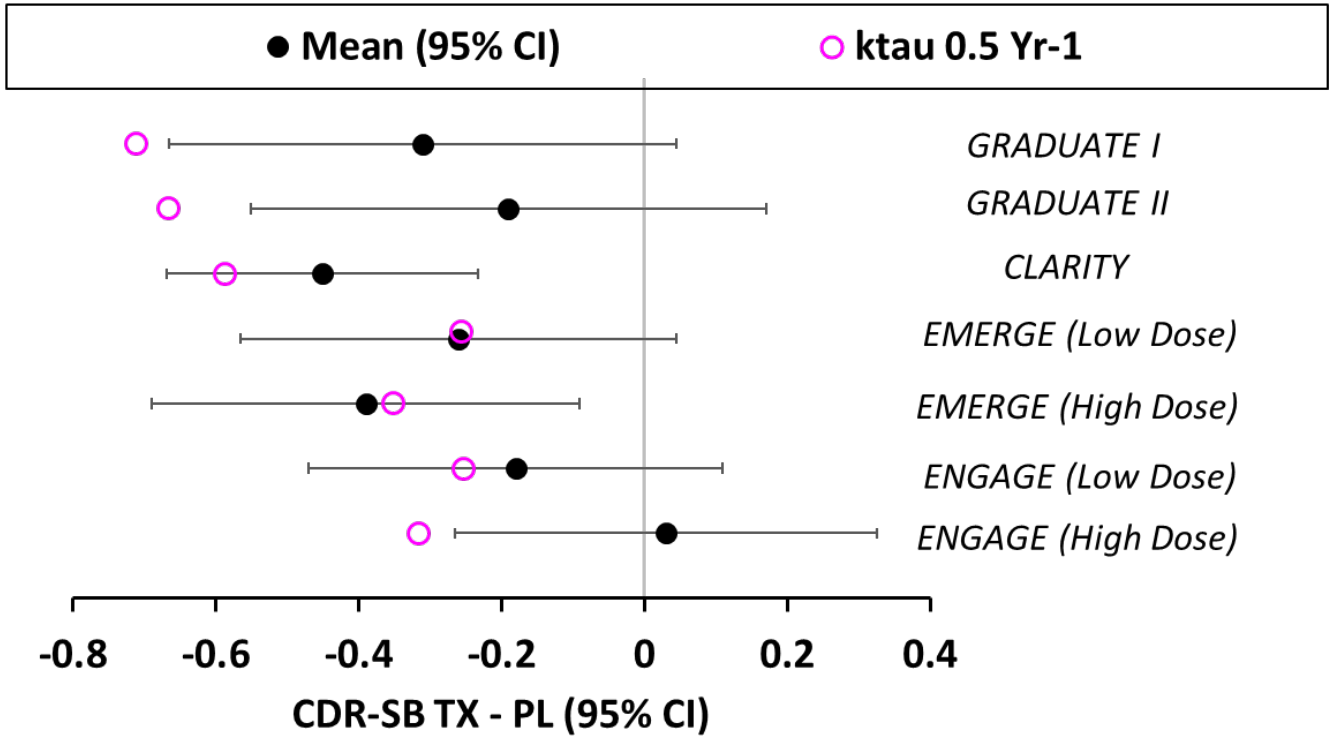
Re-estimate of Pathological Tau Elimination Rate Constant (k_{tau})

Based on sensitivity analysis of treatment effects from gantenerumab, lecanemab and aducanemab studies

Sensitivity analysis of k_{tau} on CDR-SB_TX-PL



Original vs updated treatment effects in 7 treatment arms



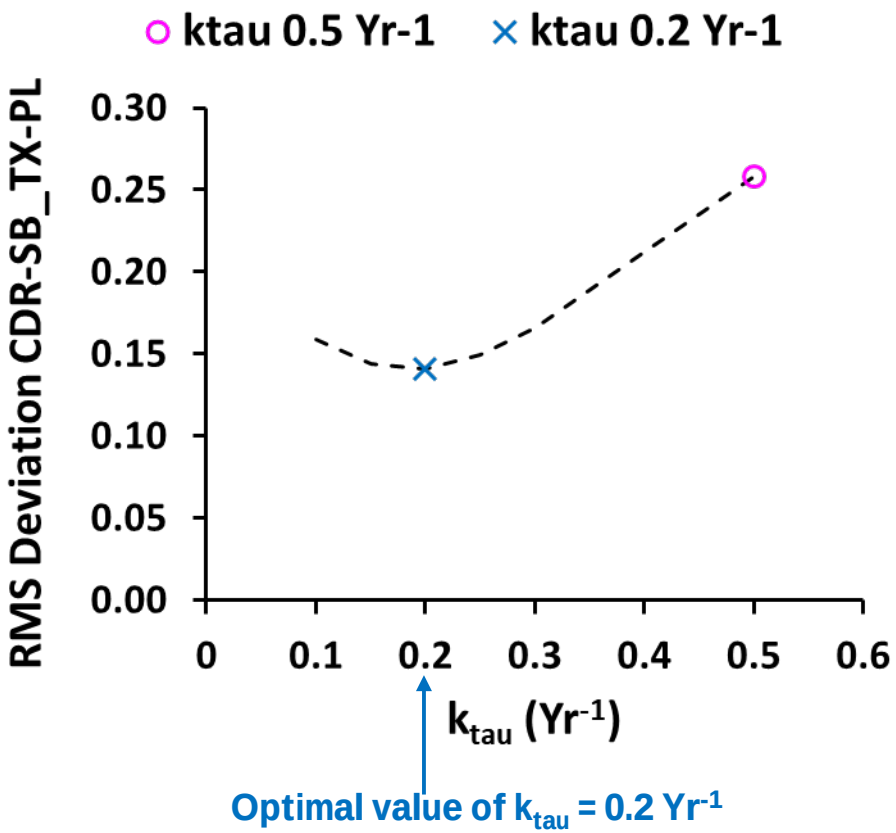
Original treatment effects fall outside the 95% CI in 3 cases

Simulations from Boess F et al. (AAIC 2023)

Re-estimate of Pathological Tau Elimination Rate Constant (k_{tau})

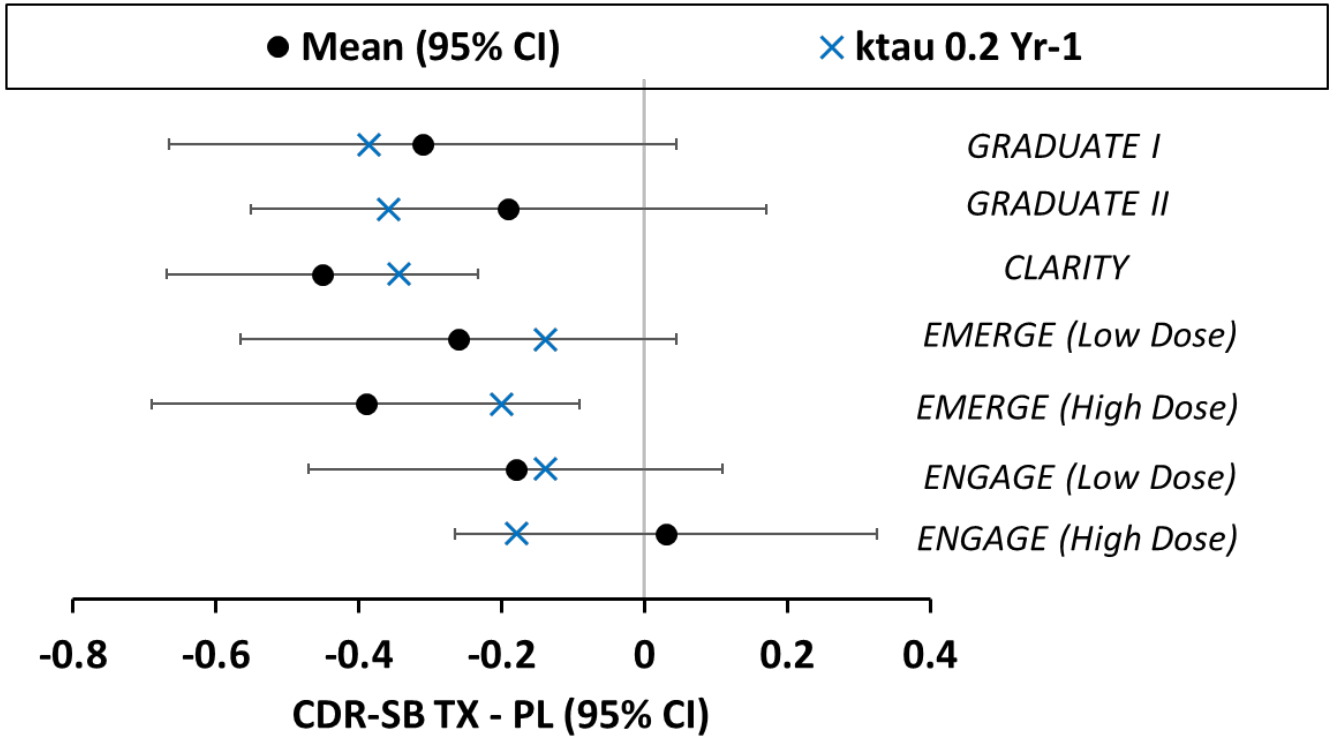
Based on sensitivity analysis of treatment effects from gantenerumab, lecanemab and aducanemab studies

Sensitivity analysis of k_{tau} on CDR-SB_TX-PL



Optimal value of k_{tau} = 0.2 Yr^{-1}

Original vs updated treatment effects in 7 treatment arms



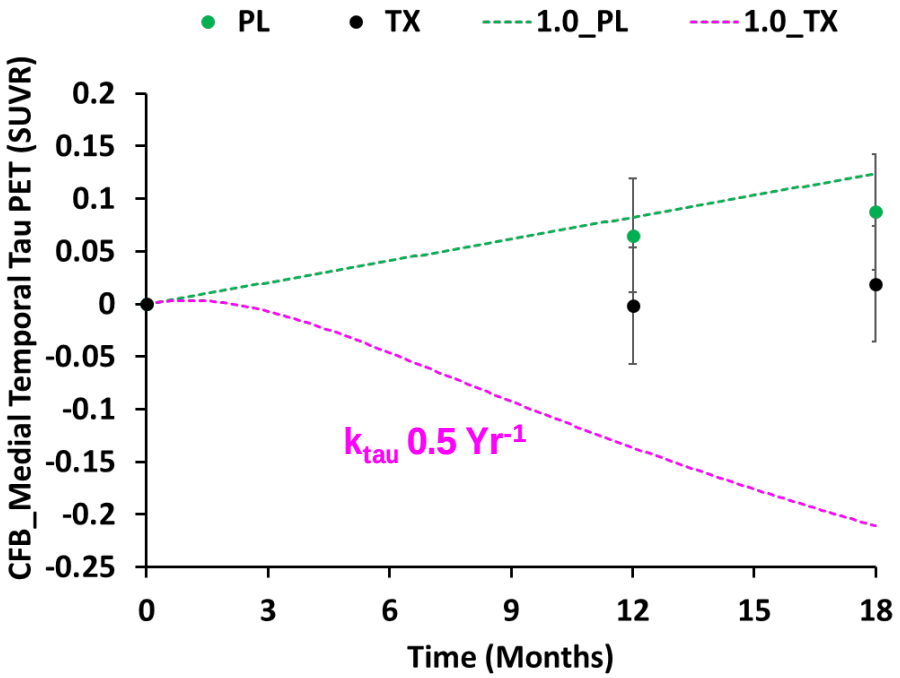
Updated treatment effects fall within the 95% CI in all 7 cases

Simulations from Boess F et al. (AAIC 2023)

Updated Q-ATN Model (Version 1.1) and Tau PET Results (Leca and Adu)

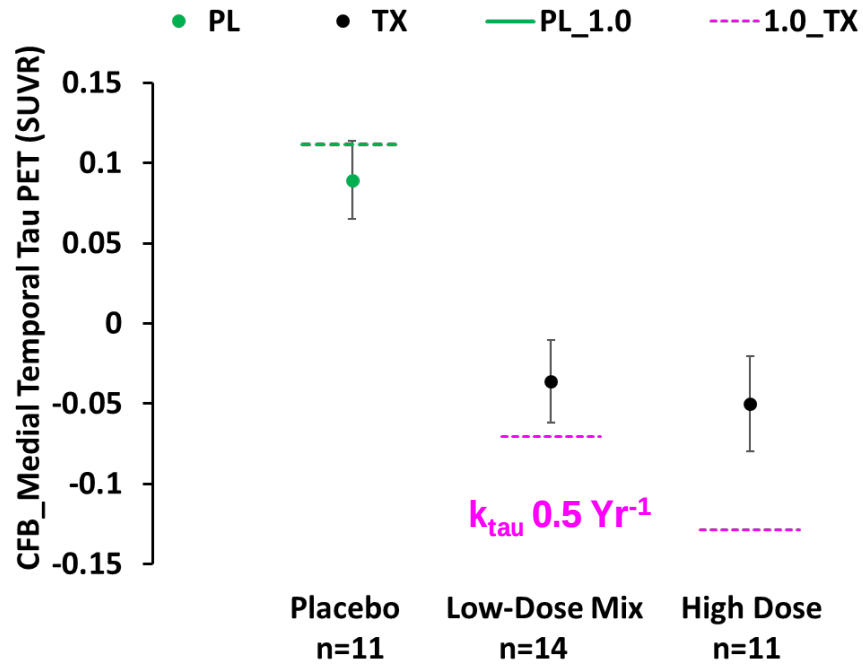
Measurements in medial temporal ROI

Lecanemab: CLARITY Tau PET STUDY* (N = 210)



PET tracer MK-6240; ventral cerebellum reference
Data from Bateman RJ et al. (CTAD 2022)
Simulations from Boess F (AAIC 2023)

Aducanumab: EMERGE/ENGAGE Tau PET* STUDY (N = 36)

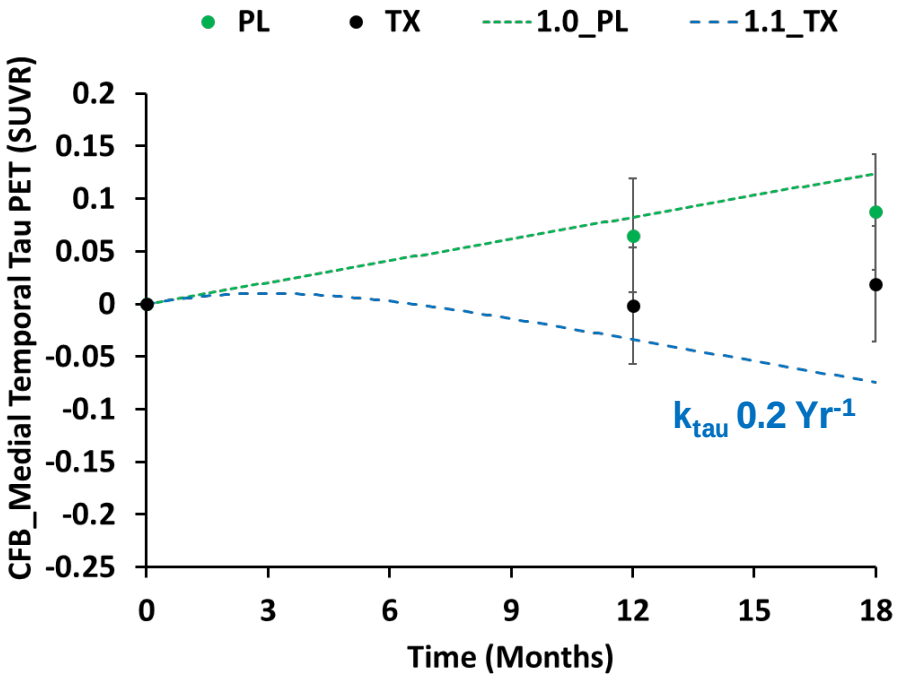


PET tracer; cerebellar gray reference
Data from Budd Haeberlein S et al. (J Prev Alz Dis 2022)
Simulations from Boess F (AAIC 2023)

Updated Q-ATN Model (Version 1.1) and Tau PET Results (Leca and Adu)

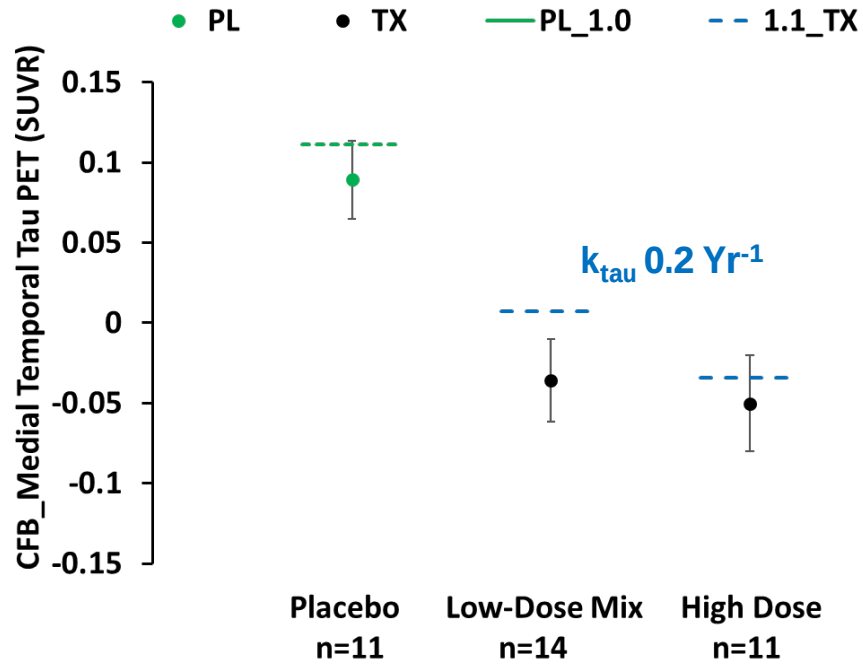
Measurements in medial temporal ROI

Lecanemab: CLARITY Tau PET STUDY* (N = 210)



PET tracer MK-6240; ventral cerebellum reference
Data from Bateman RJ et al. (CTAD 2022)
Simulations from Boess F (AAIC 2023)

Aducanumab: EMERGE/ENGAGE Tau PET* STUDY (N = 36)

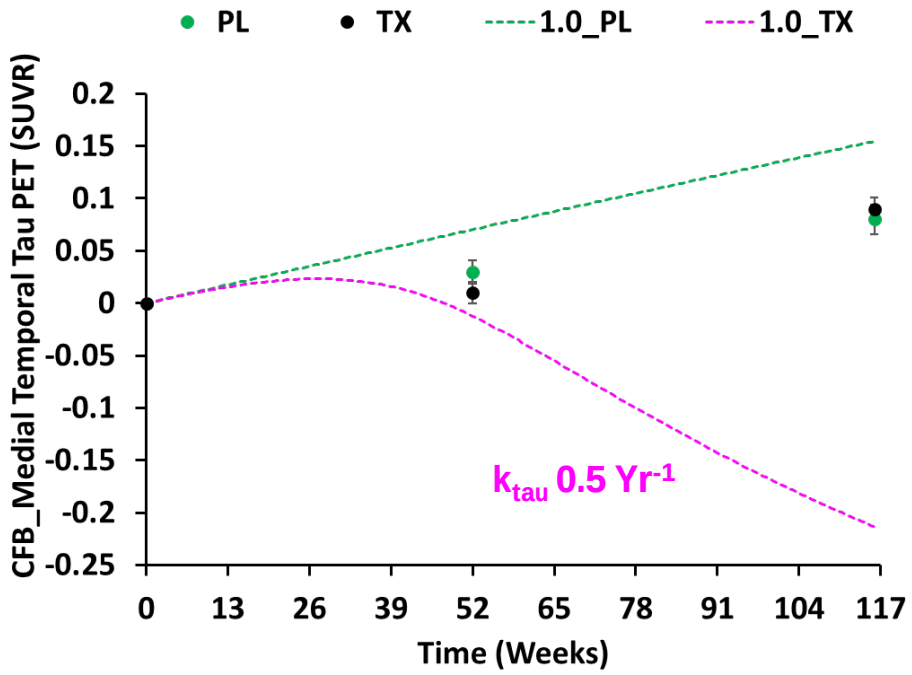


PET tracer; cerebellar gray reference
Data from Budd Haeberlein S et al. (J Prev Alz Dis 2022)
Simulations from Boess F (AAIC 2023)

Updated Q-ATN Model (Version 1.1) and Tau PET Results (Gant)

Measurements in medial temporal ROI

Gantenerumab Tau PET Sub-Study: Pooled Results from GRADUATE I and II



PET tracer GTP1; inferior cerebellum reference
Data from Barkhoff F et al. (ADPD 2023)
Simulations from Boess F (AAIC 2023)

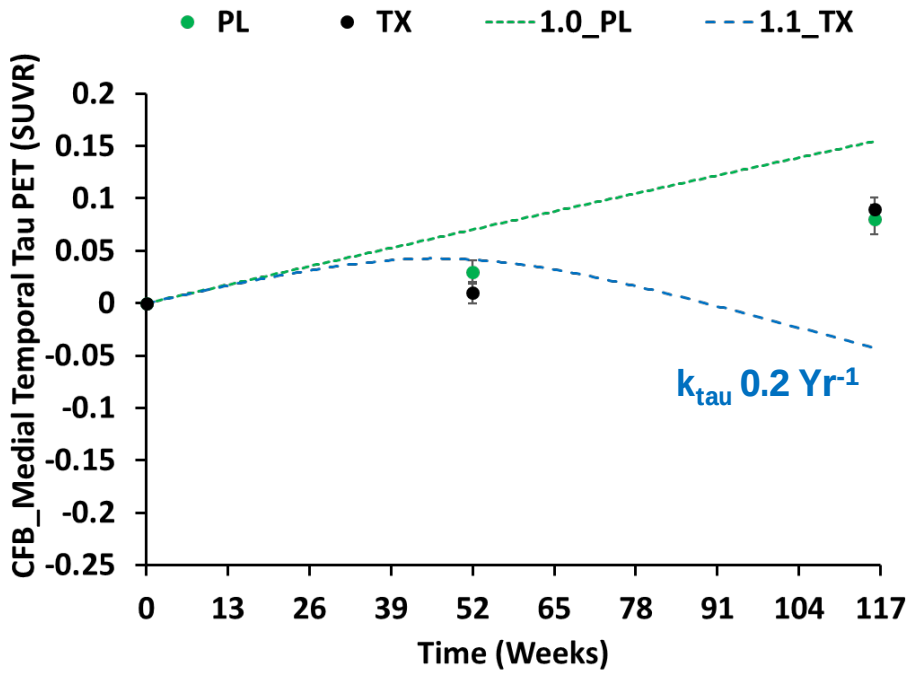
Many Discontinuations from sub-study

Number of Subjects		
Weeks	Placebo	Treatment
0	93	109
52	53	70
116	29	48

Updated Q-ATN Model (Version 1.1) and Tau PET Results (Gant)

Measurements in medial temporal ROI

Gantenerumab Tau PET Sub-Study: Pooled Results from GRADUATE I and II



PET tracer GTP1; inferior cerebellum reference
Data from Barkhoff F et al. (ADPD 2023)
Simulations from Boess F (AAIC 2023)

Many Discontinuations from sub-study

Number of Subjects		
Weeks	Placebo	Treatment
0	93	109
52	53	70
116	29	48

No significant differences between PL and TX in tau PET data (or CDR-SB)

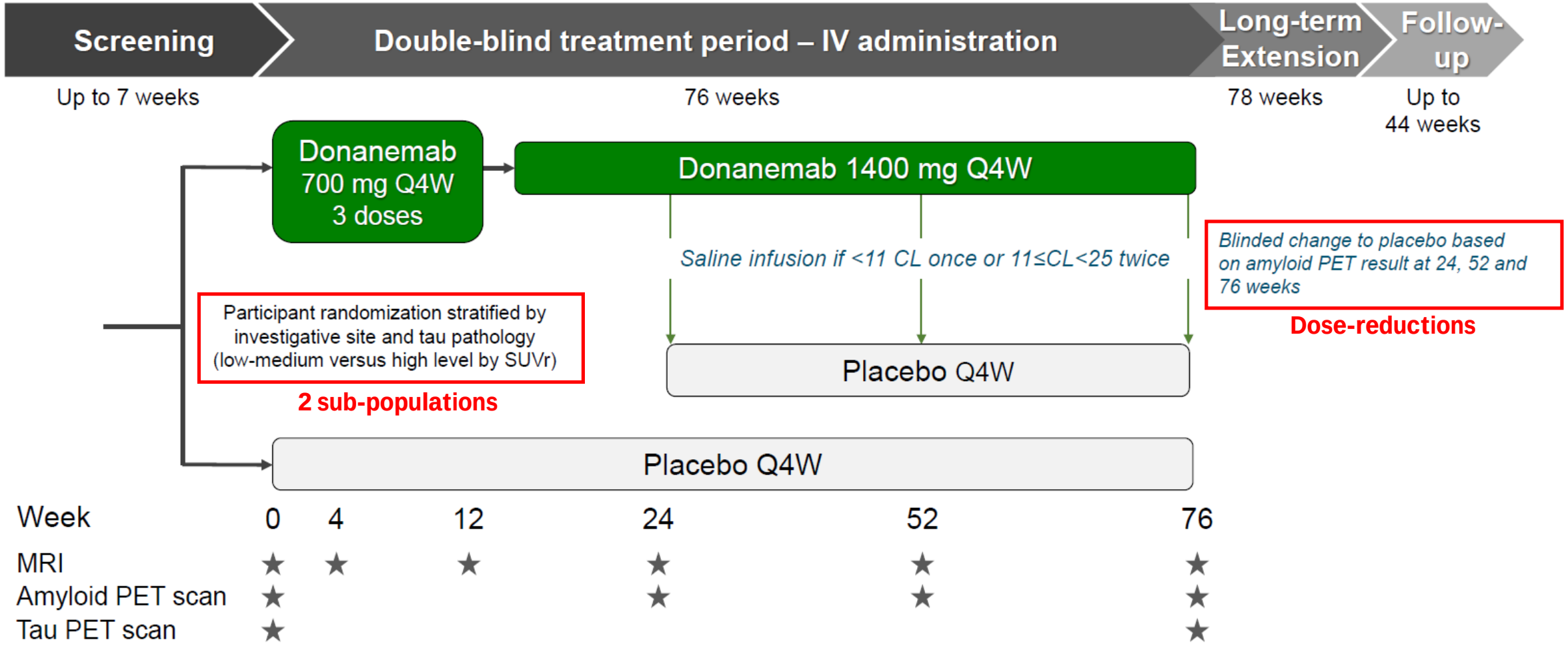
Disparity between data and simulations may have resulted from tau PET tracer GTP1.

Latest “Unpublished” Analyses Using the Q-ATN Model (version 1.2):

1. Donanemab Phase 3 Study (TRAILBLAZER-ALZ 2)
2. Tau-Targeted Anti-Sense Oligonucleotide BIIB080 (MAD Study)

Donanemab Phase 3 Study: TRAILBLAZER-ALZ 2

Trial Design Features



From Shcherbinin S et al. (CTAD 2023)

Donanemab Phase 3 Study: TRAILBLAZER-ALZ 2

Baseline Data in low/medium tau and high tau groups

Baseline tau PET in neocortical composite ([1] medial temporal cortex)

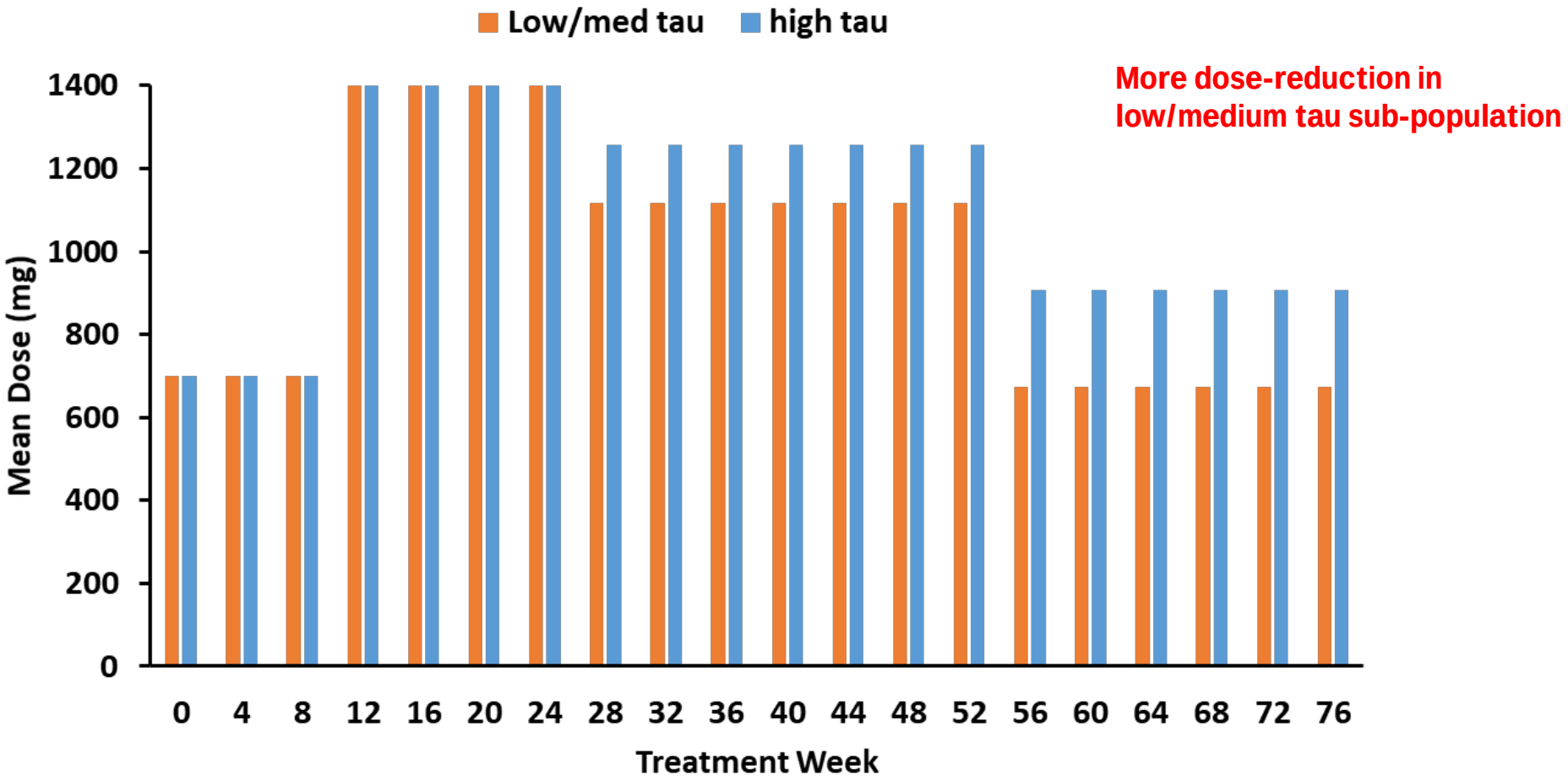
1.1 to 1.46 **> 1.46**

	Low/Medium tau SUVR		High tau SUVR	
Characteristic	Donanemab	Placebo	Donanemab	Placebo
N	588	594	271	281
Women (%)	55.3	54	61.6	64.4
Men (%)	44.7	46	38.4	35.6
Age, Mean (SD)	74.3 (5.7)	74.3 (5.8)	70.1 (6.2)	70.5 (6.3)
APOE e4 carrier (%)	71.7	72.3	65.4	68.9
Acetylcholinesterase inhibitor/memantine use (%)	56.5	57.4	69.4	70.1
CDR-SB, Mean (SD)	3.7 (2.1)	3.7 (2.0)	4.4 (2.0)	4.4 (2.0)
Amyloid PET in Centiloids, mean (SD)	102.4 (34.7)	100.9 (35.1)	106.0 (33.8)	103.1 (33.1)
tau PET neocortical composite in SUVR, mean (SD)	1.21 (0.12)	1.21 (0.13)	1.68 (0.17)	1.70 (0.20)

Data from Sims JR et al. (JAMA 2023)

Donanemab Phase 3 Study: TRAILBLAZER-ALZ 2

Mean dosing of donanemab treatment low/medium and high tau sub-populations



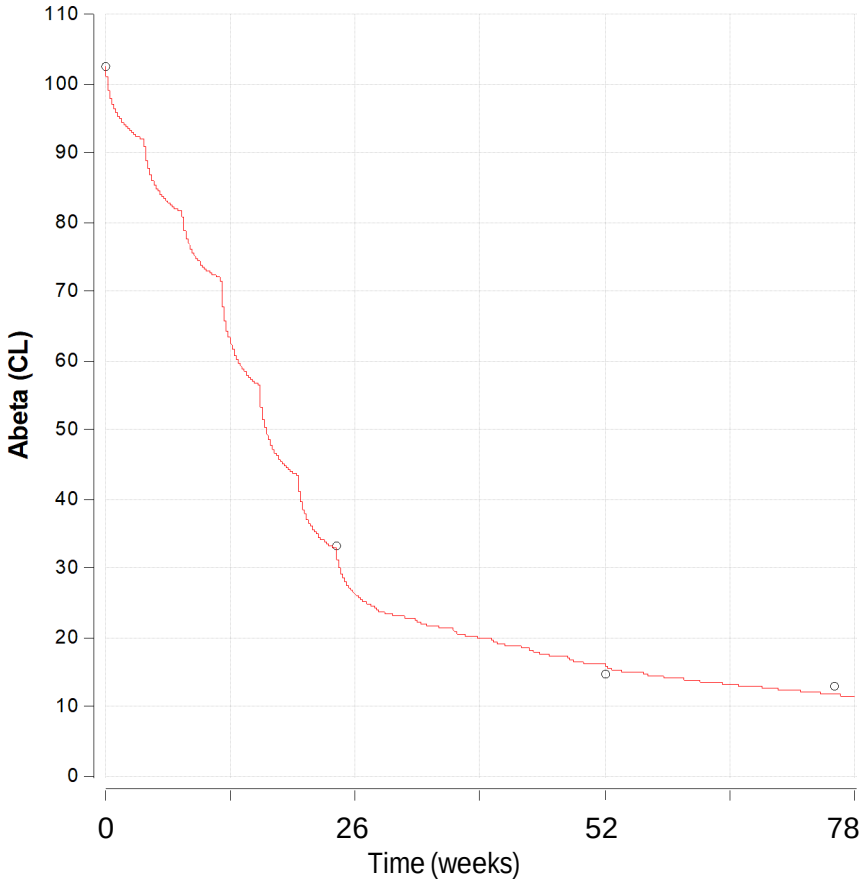
More dose-reduction in low/medium tau sub-population

Derived from data in Sims JR et al. (JAMA 2023)

Simulation of Phase 3 Study TRAILBLAZER-ALZ 2: Amyloid PET

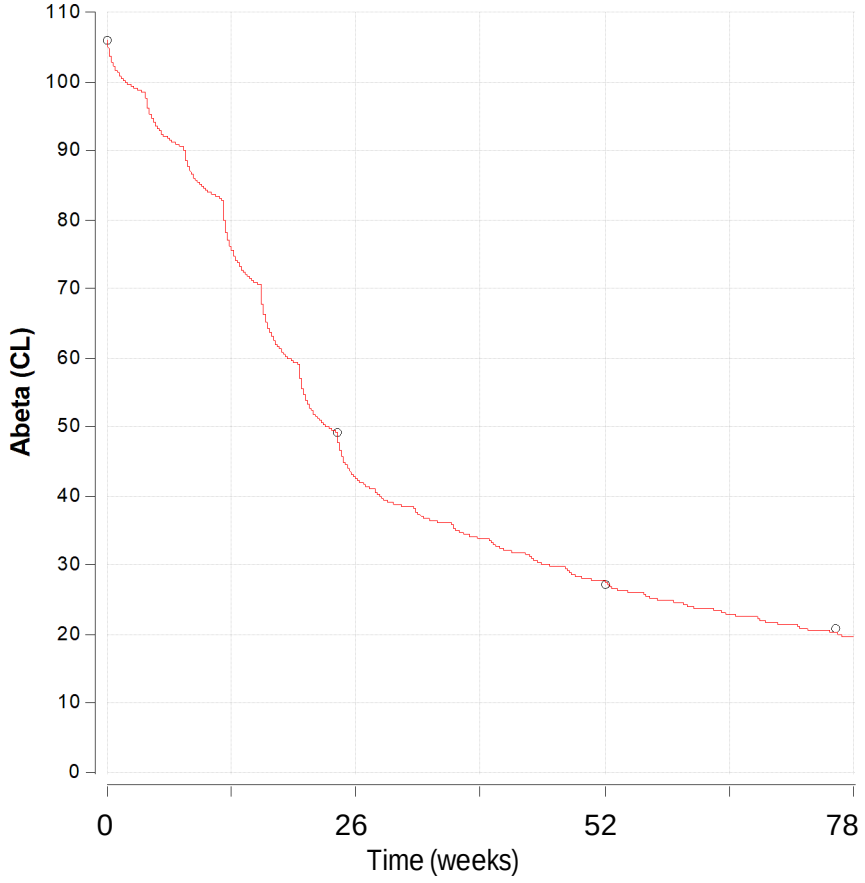
Estimates of a_{rem} for low/medium and high tau sub-populations

Low/medium tau: Amyloid PET (CL)



a_{rem} = 0.0345 Yr-1/(µg/mL) ; *f = 0.33*

High tau: Amyloid PET (CL)



a_{rem} = 0.0247 Yr-1/(µg/mL) ; *f = 0.40*

Larger a_{rem} in low/medium tau group may reflect older mean age (74.3 yr vs 70.1 yr)

f parameter accounts for slower kinetics after dose-reduction (see Alz & Dement 2022)

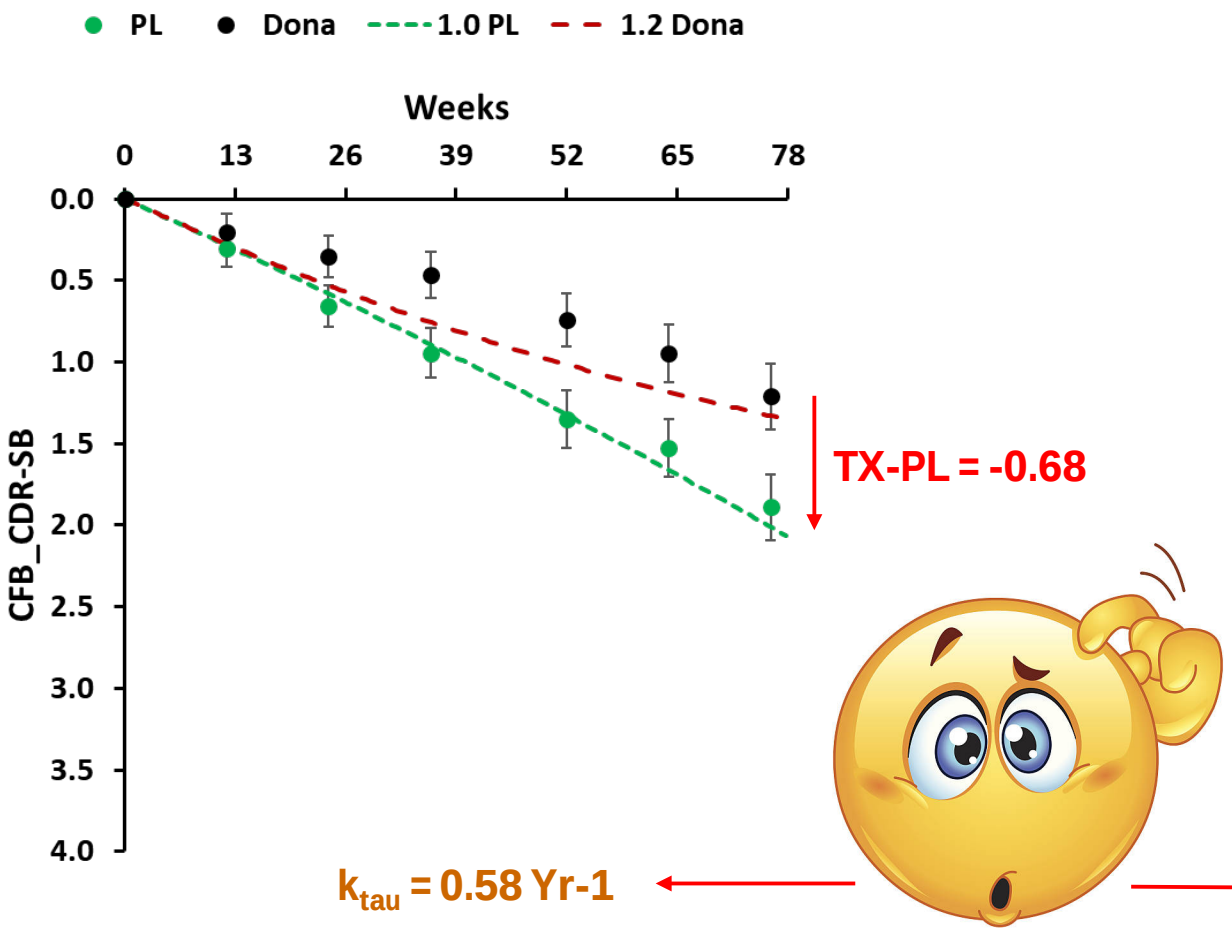
Comparable values to phase 2 estimate (mean age 75.0 yr).

Similar effects of age on plaque removal seen with Adu and Leca

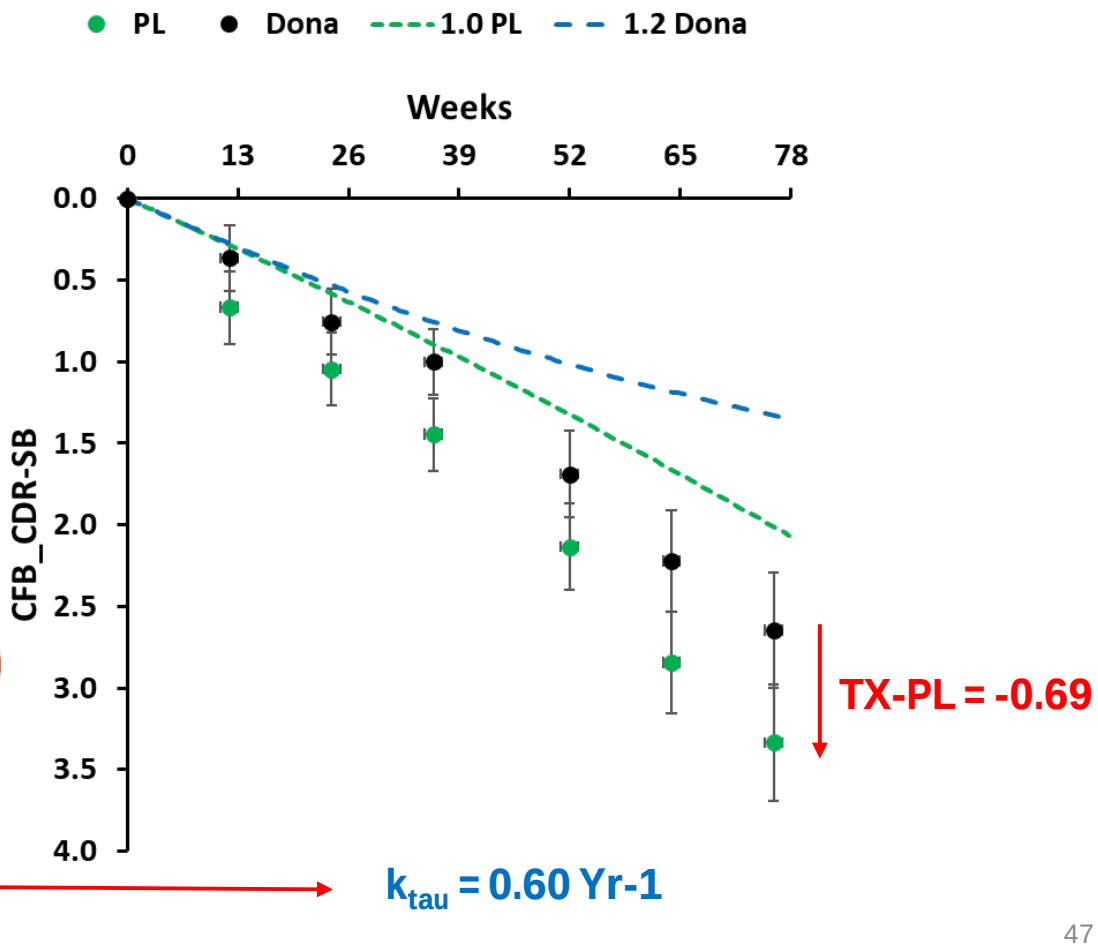
Simulation of Phase 3 Study TRAILBLAZER-ALZ 2 (Version 1.2): CDR-SB

Estimates of k_{tau} for low/medium and high tau sub-populations (to match treatment effects)

Low/medium tau : CDR-SB (Change from mean BL; 3.70)



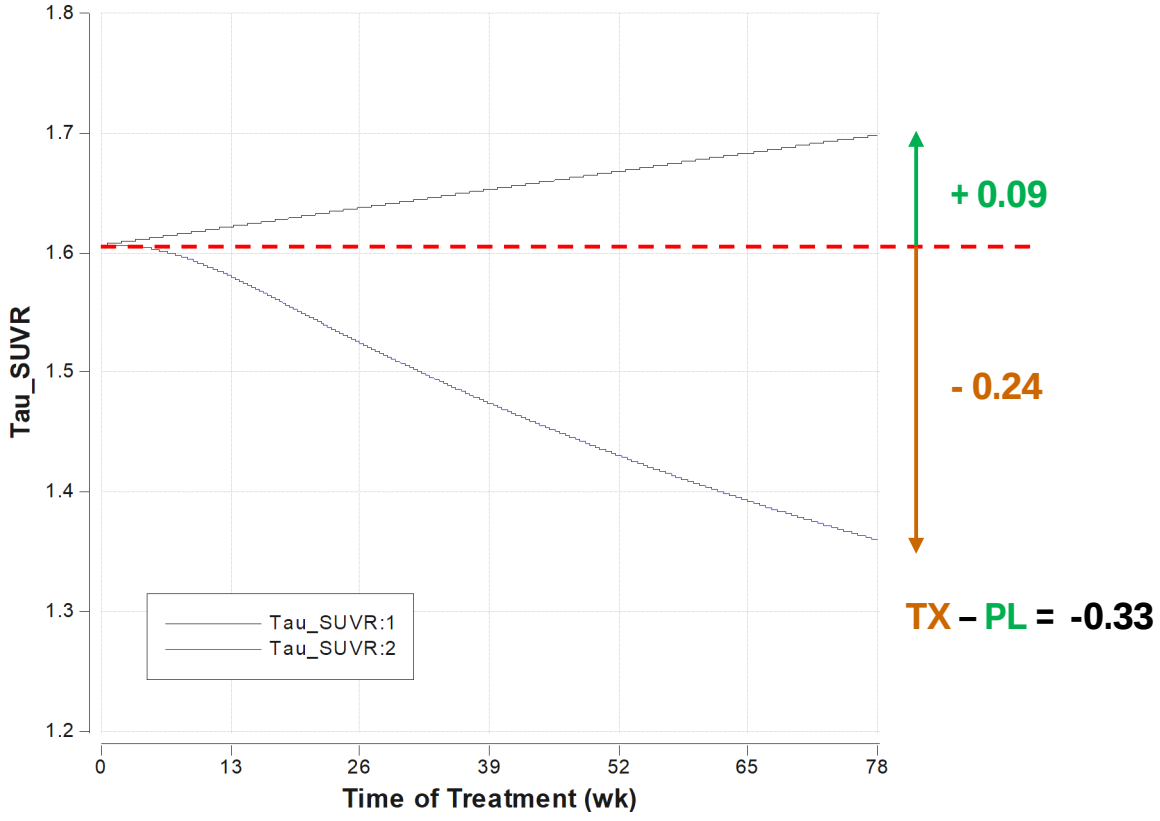
High tau: CDR-SB (Change from mean BL; 4.40)



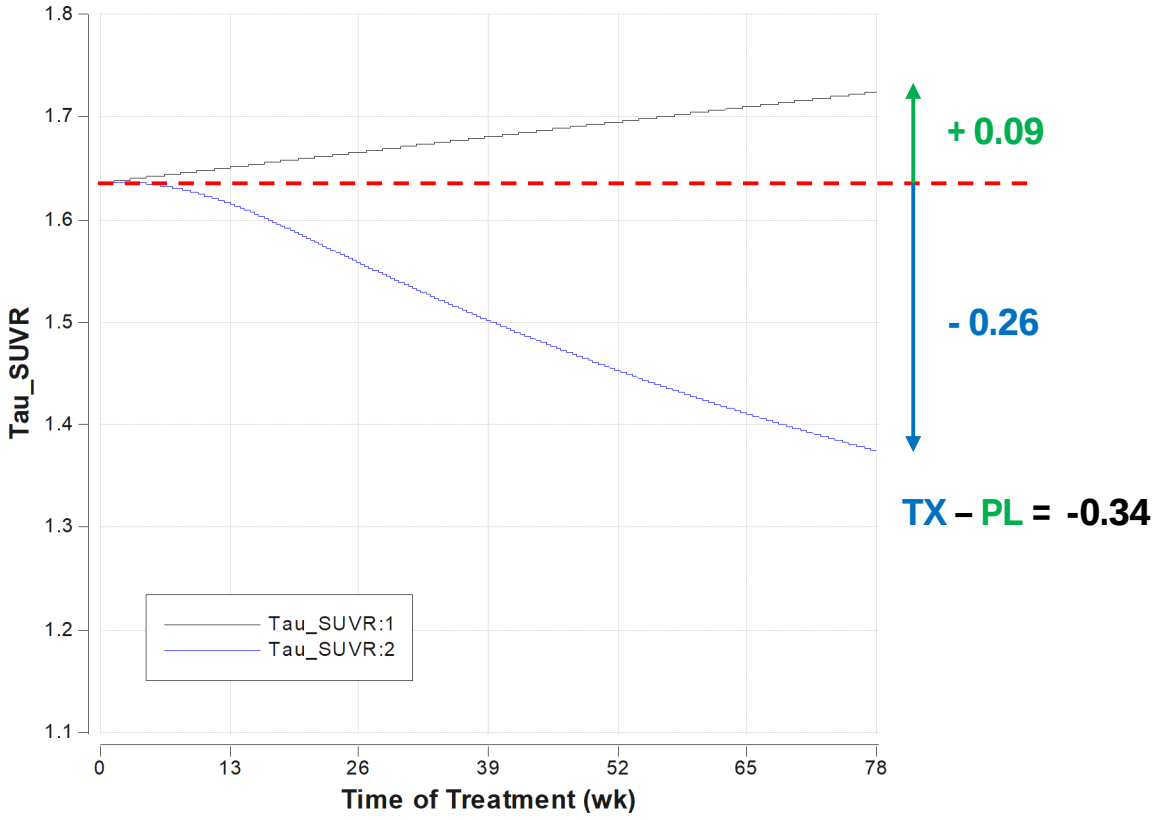
Simulation of TRAILBLAZER-ALZ 2 (Version 1.2): Tau PET

Calibrated to flortaucipir tracer in entorhinal and inferior temporal cortex (from Johnson and Sperling data 2020)

Low/medium tau : tau PET SUVR

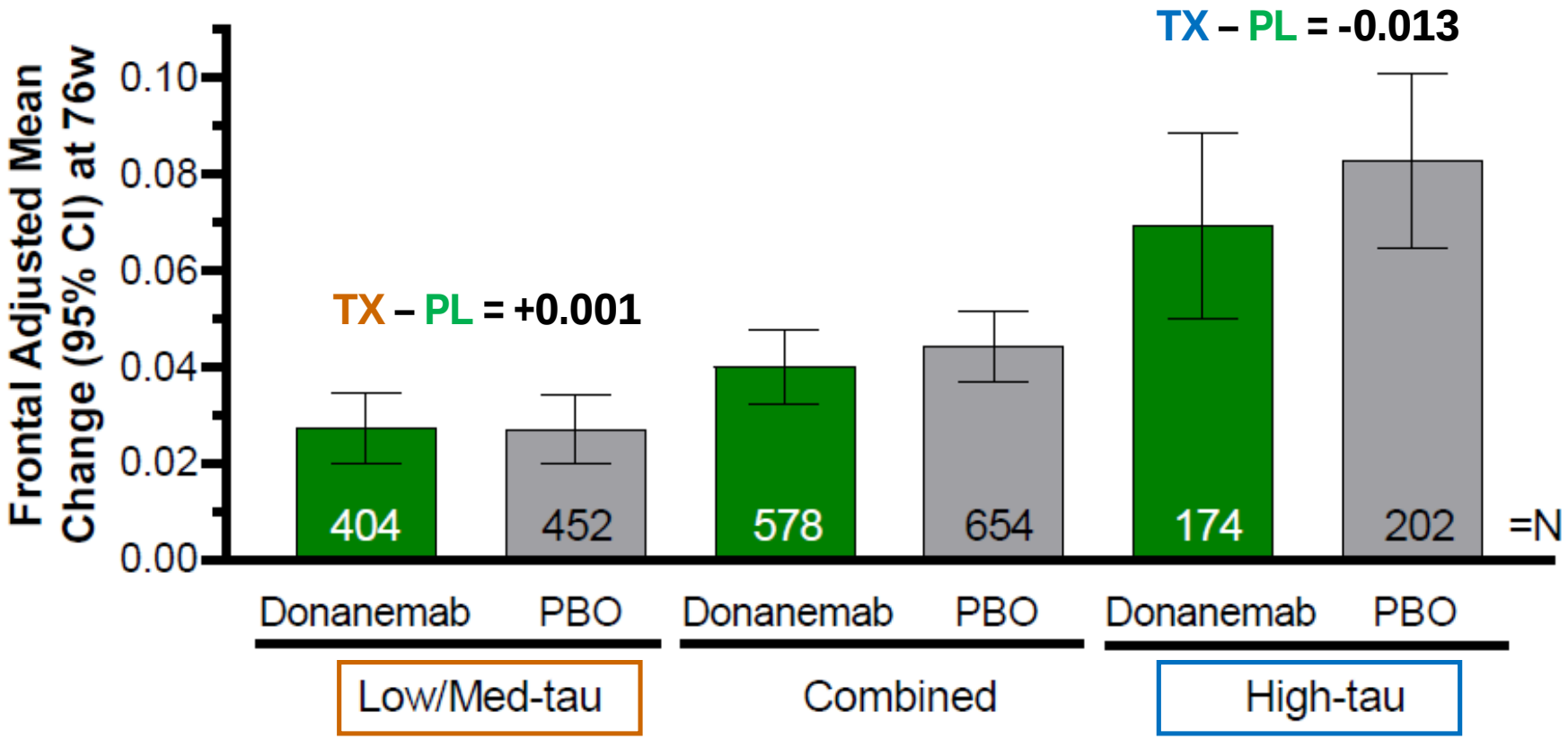


High tau: tau PET SUVR



Observed tau PET results in TRAILBLAZER-ALZ 2

Tau PET measured with flortaucipir tracer, neocortical composite ([1] medial temporal cortex)



Discrepancies between the simulated and observed tau PET data could be due to a number of factors:

1. ***Differences between the medial temporal cortex (MTC) and the neocortical composite region used in the donanemab study.***
2. ***Insensitivity of the flortaucipir tracer.***
3. ***Deficiencies of the Q-ATN model.***

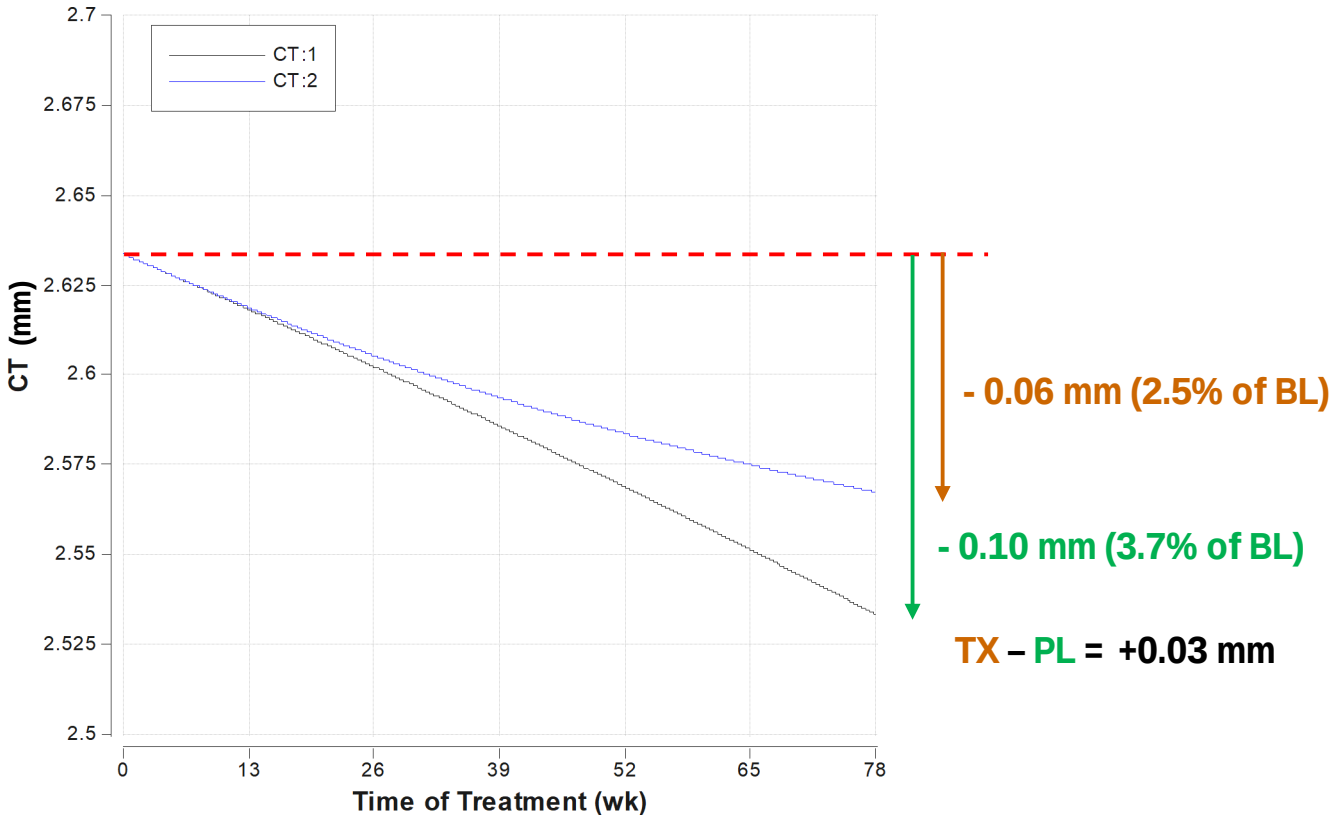
tau PET study data from the MTC would be most helpful to resolve this matter….

From Sims JR et al. (JAMA 2023)

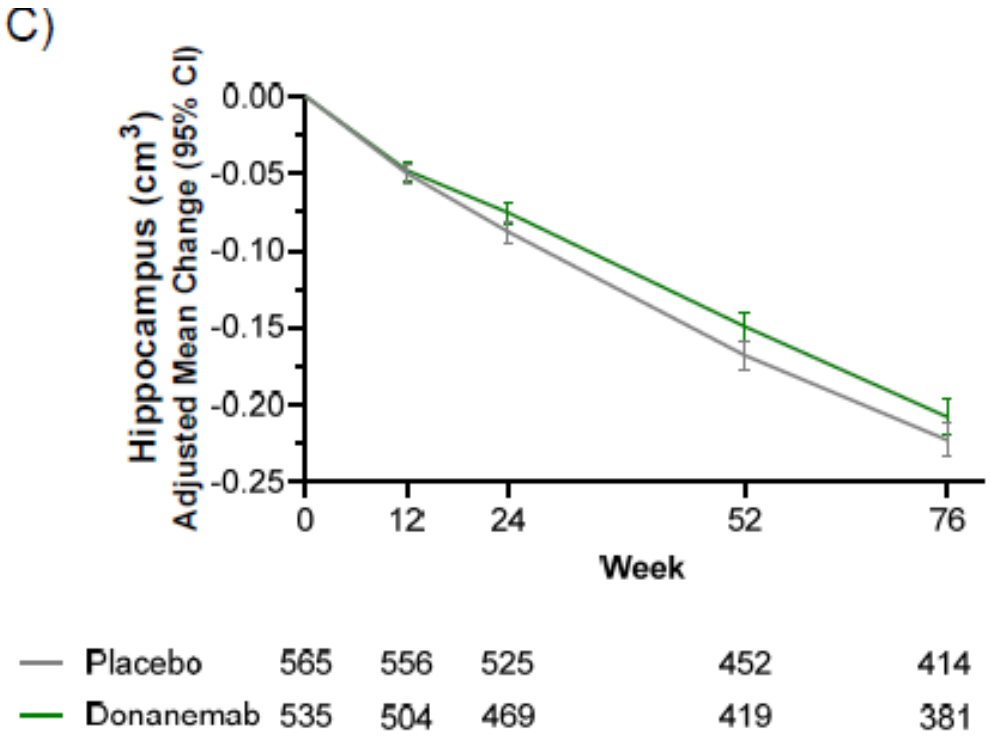
Simulation of TRAILBLAZER-ALZ 2 (Version 1.2): Cortical Thickness (MTC)

Comparison to hippocampus volume changes

Low/medium tau : Medial Temporal Cortical Thickness



Low/medium tau : CFB_hippocampus volume (mm^3)



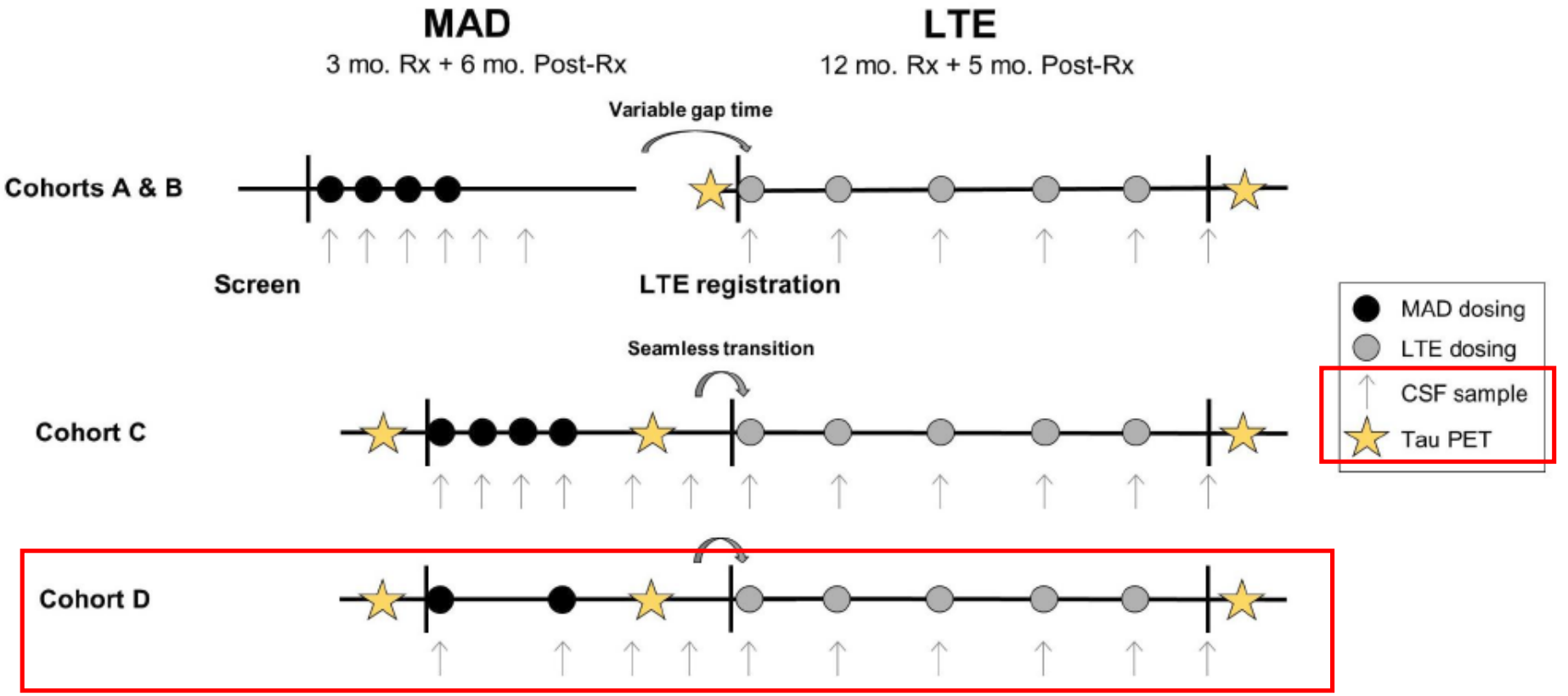
From Sims JR et al. (JAMA 2023)

TX – PL = 0.014 cm^3 (14 mL)

Baseline volumes needed to compute % changes from BL

Tau-Targeted Anti-Sense Oligonucleotide BIIB080: MAD Study

Trial Design Features



p-tau 181 in CSF

MK-6240 tracer in Medial temporal composite

Analyzed Cohort (MAD + LTE) 115 mg IT q 12 wk

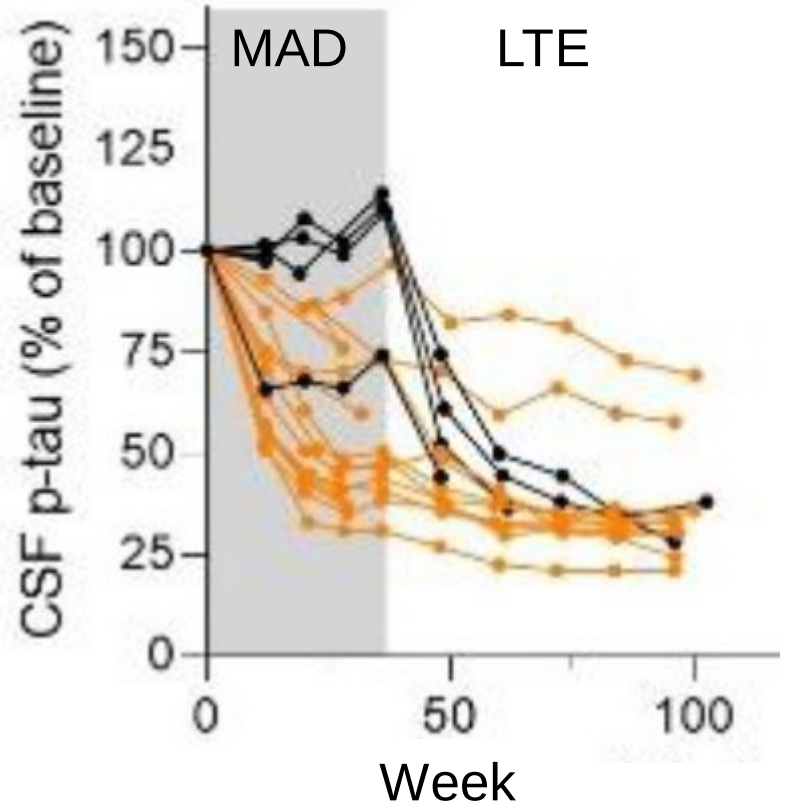
From Edwards AL et al. (JAMA 2023)

Tau-Targeted Anti-Sense Oligonucleotide BIIB080: MAD Study

Cohort D: Baseline characteristics and CSF p-tau

Characteristic	Cohort D
N	8
Women (%)	37.5
Men (%)	62.5
Age, Mean (SD)	67.4 (7.7)
APOE ε4 carrier (%)	75
Acetylcholinesterase inhibitor/memantine use (%)	100
CDR-SB, Mean (SD)	3.5 (1.2)
Amyloid PET in Centiloids, mean (SD)	NA
tau PET medial temporal composite in SUVR, mean (SD)	2.39 (0.53)

CSF p-tau 181



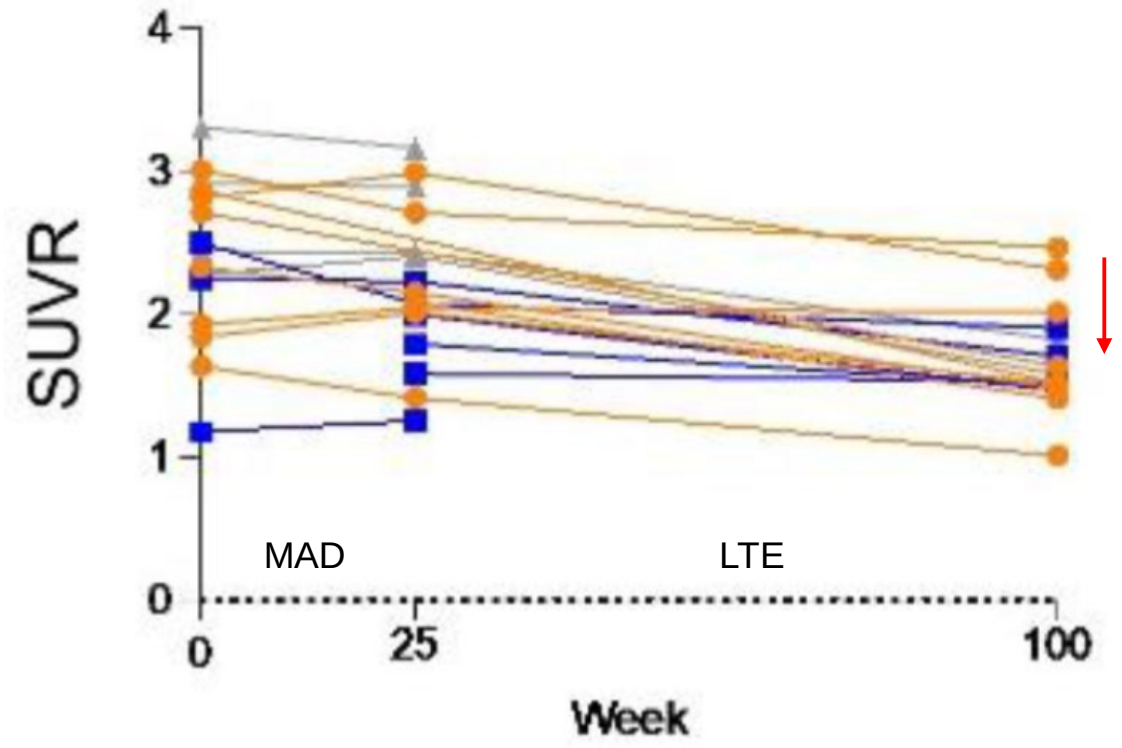
Rapid suppression of CSF p-tau

Adapted from Edwards AL et al. (JAMA 2023)

Tau-Targeted Anti-Sense Oligonucleotide BIIB080: MAD Study

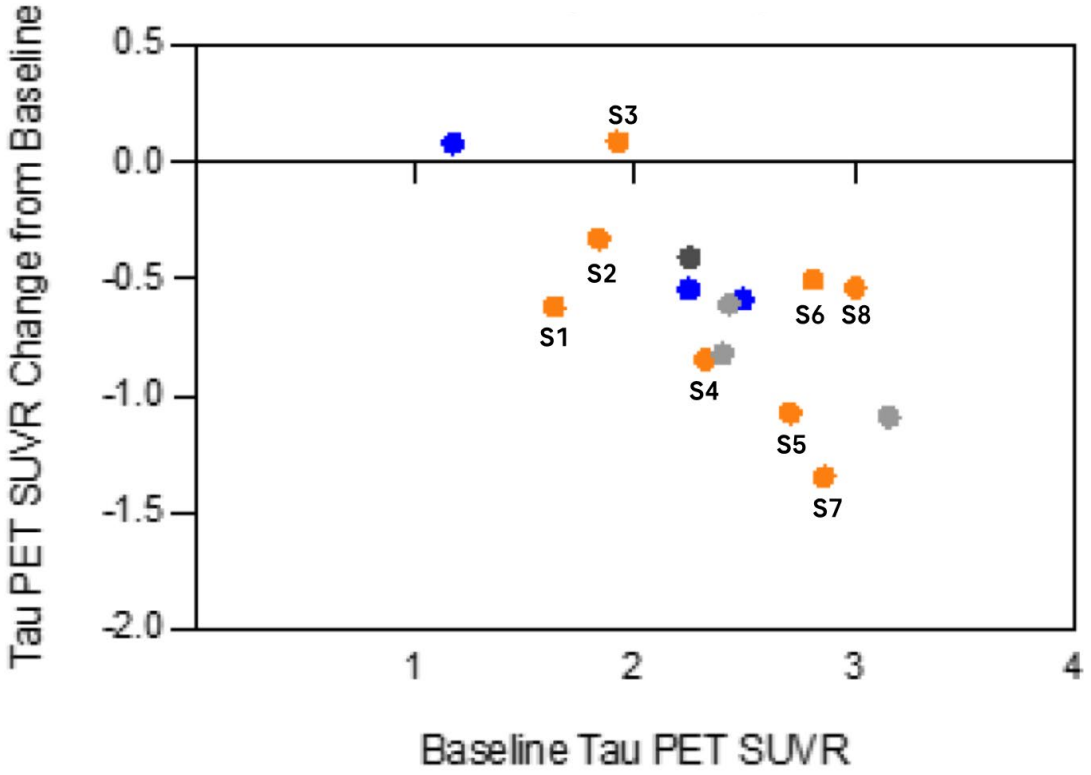
Cohort D: tau PET in Medial Temporal Composite)

tau PET in MAD and LTE (cohort D)



Mean (SD) change from baseline = -0.647 (0.444)

CFB vs BL (cohort D)



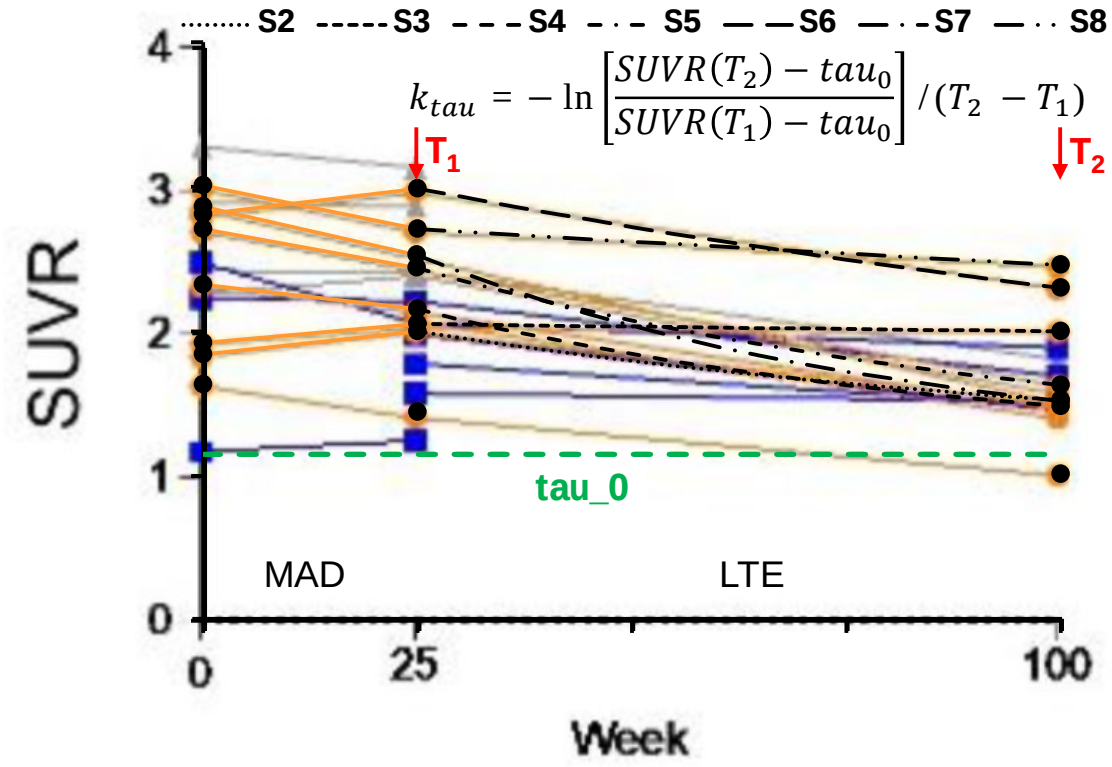
CFB correlates with baseline value

Adapted from Edwards AL et al. (JAMA 2023)

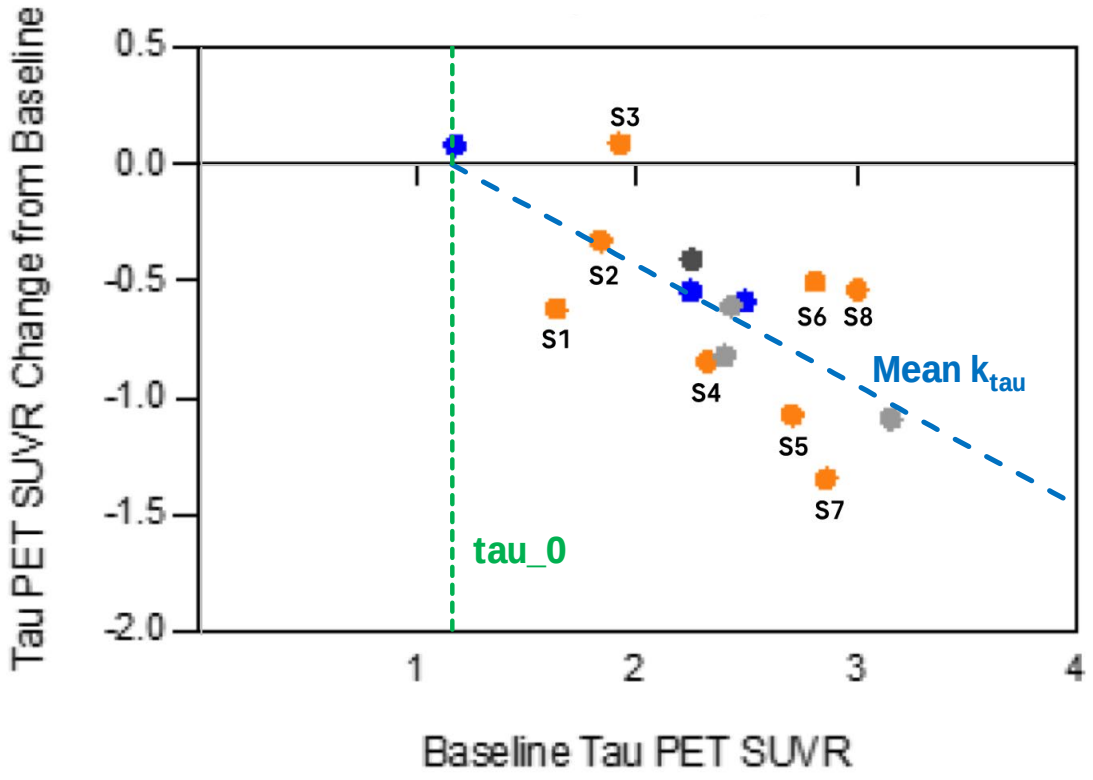
Tau-Targeted Anti-Sense Oligonucleotide BIIB080: MAD Study

Cohort D: individual estimates of k_{tau} based on the change in tau SUVR – tau_0 from week 25 to week 100

tau PET in MAD and LTE (cohort D)



CFB vs BL (cohort D)



Mean (SD) k_{tau} = 0.489 (0.333) Yr^{-1}... *Close to Donanemab values!*

First-order elimination in Q-ATN model "explains" correlation

Adapted from Edwards AL et al. (JAMA 2023)

Is the Q-ATN Model Too Simple?

Probably Yes: More Data are Needed, Particularly Tau PET

Future Improvements to consider

- L1 linkage: Differentiate clearance of amyloid monomers, fibrils and plaque
- L2 linkage: Represent space-time evolution of tau PET signals (beyond medial temporal region); represent mechanisms linking p-tau and tau PET; resolve why k_{tau} values differ (do they depend on the rate of amyloid removal?)
- L3 linkage: Include inflammatory mechanisms that lead to neurodegeneration (independent of tau?)
- L4 linkage: Map specific regions of neurodegeneration (and loss of synapses) to components of CDR-SB; medial cortical thickness or hippocampal volume?
- Population Model (Version 2.0 and Higher): Use individual subject data to estimate model parameter distributions; explore covariates across studies; potential to splice together analyses of natural history and on-treatment datasets

Is the Q-ATN Model Useful?

Ultimately, the Modelers in the AD Field Will Decide

What has the Q-ATN model provided to date?

- A semi-mechanistic framework for integrating and analyzing data in the AD field and “explaining” how amyloid removal can lead to clinical benefit
- A quantitative framework for simulating the short-term and long-term effects of anti-amyloid treatment on biomarkers and clinical outcome
- An evolving tool for supporting the design and development of future anti-amyloid molecules and clinical trials
- A conceptual framework that could guide future research into the molecular and cellular processes involved in Alzheimer’s Disease …
- A reference model for comparison with empirical approaches (including AI) to simulate natural history and anti-amyloid treatment studies

Overall assessment of the Q-ATN model:

At the moment, the pieces of the model don't all fit together with the available data...

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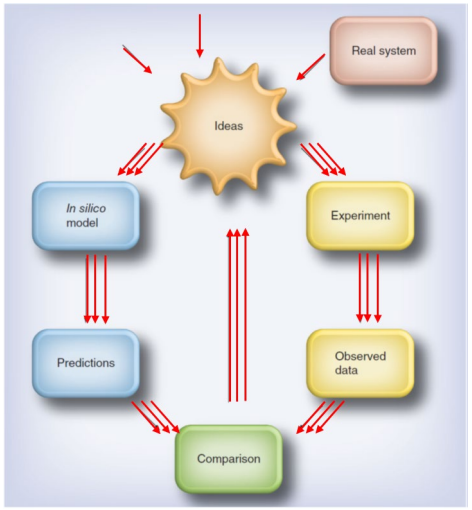

It's a work in progress...

Time for Q&A...