

# Joint Exposure-Response Analysis of PET Amyloid Plaque Data from the BACE1 Inhibitor Verubecestat and Amyloid mAbs Trials Enhances the Understanding of Drug Effects

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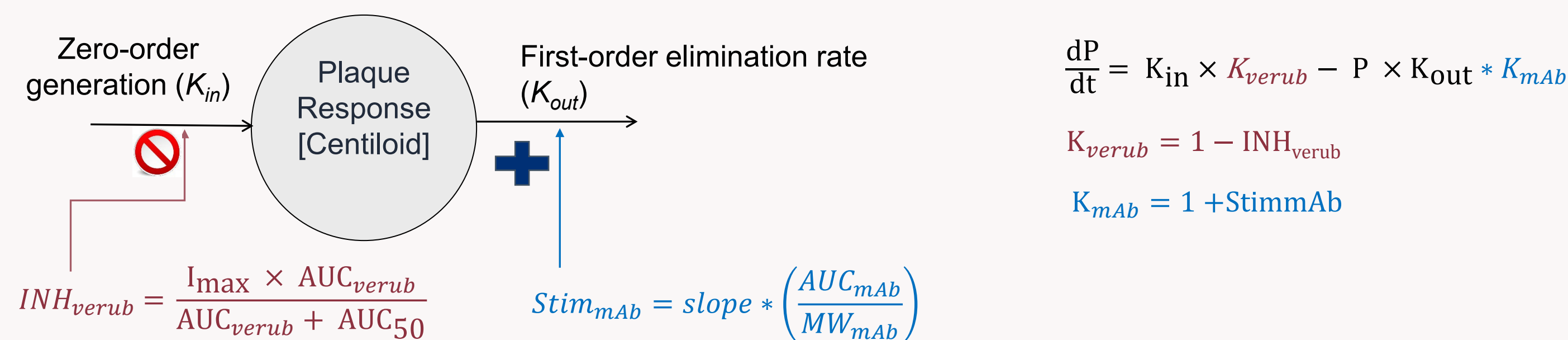
## Background and Objectives

- PET with amyloid radiotracers enables quantification of pathological amyloid deposition in brain tissues
- The objectives of this work were:
  - Quantify amyloid plaque turnover rates
  - Quantify drug effects for amyloid PET of  $\beta$ -secretase-1 (BACE1) inhibitor verubecestat and four amyloid mAbs in patients with Alzheimer's disease (AD), to set benchmarks for anti-amyloid therapy
  - Support prediction of outcomes for untested treatment regimens of amyloid mAbs or verubecestat

## Methods

- Data Sources:
  - Individual-level data from the Phase 3 APECS trial (n=188; 65 placebo, 123 verubecestat) [1]
  - Summary-level data and serum exposures from literature for four anti-amyloid mAbs in AD patients: Aducanumab [2–5], Donanemab [5–8], Gantenerumab [9–13], Lecanemab [14–18]
- Data Processing:
  - Amyloid plaque levels reported in SUVR were converted to Centiloid units [19]
- Modeling Approach:
  - Simultaneous analysis of individual and aggregate data using a joint turnover model (Figure 1)
  - Developed via nonlinear mixed-effects modeling (using NONMEM)
  - Amount of plaque in brain assumed proportional to amyloid PET measured in Centiloids
  - Drug effect was driven by plasma/serum AUCs
  - Effect of verubecestat was modeled as inhibition of the zero-order generation constant ( $K_{in}$ ), with an  $I_{max}$  AUC function
  - Effect of amyloid mAbs was modeled as stimulation of the first-order elimination rate constant of plaque ( $K_{out}$ ), with a linear AUC effect, and a different slope for each mAb
  - Observed "individual" baseline PET data was used as starting condition
- External Validation:
  - Applied to ADNI's natural progression dataset (n=521 amyloid-positive individuals) [20]
- Simulations:
  - Explored the effects of mAb dose titration on amyloid plaque dynamics

Figure 1: Schematic of Amyloid Turnover model



## Results

- The joint model captured plaque dynamics (Figure 2) across natural progression (control arms), BACE1 inhibitor (verubecestat) and anti-amyloid mAb treatment arms
- Plaque turnover rate constant estimated at 0.00029/day (Table 1), corresponding to a half-life of ~6.4 years
- Verubecestat  $\text{AUC}_{50}$  estimated at 0.402  $\mu\text{M}\cdot\text{h}$ , resulting in 91.8% inhibition of plaque formation at a typical 40 mg AUC
- Model-estimated slopes for the linear effect of the mAbs ranks potency: donanemab > aducanumab  $\geq$  lecanemab >> gantenerumab
- Table 2 provides the model-estimated fold increases in  $K_{out}$  for the target dose studied in phase 3 trials for the mAbs

Table 1: Parameter table of model fit

Parameter	Unit	Value	RSE	Bootstrap estimate*
Additive residual error (SD)	-	6.43	11.2%	6.16 (4.88, 7.48)
Log( $K_{in}$ )	CL/day	-3.58	2.4%	-3.56 (-3.73, -3.41)
Log( $K_{out}$ )	1/day	-8.13	1.4%	-8.11(-8.31, -7.92)
IMAX	-	1*	-	-
$\text{AUC}_{50}$ verubecestat	$\mu\text{M}\cdot\text{h}$	0.402	59%	0.433 (0.0755, 0.897)
slope aducanumab	$\text{mM}^{-1} \text{day}^{-1}$	715	11.9%	705 (566, 900)
slope donanemab	$\text{mM}^{-1} \text{day}^{-1}$	907	14.1%	914 (672, 1330)
slope lecanemab	$\text{mM}^{-1} \text{day}^{-1}$	602	12.9%	598 (477, 760)
slope gantenerumab	$\text{mM}^{-1} \text{day}^{-1}$	395	24.3%	395 (245, 759)

\* fixed; \*median (2.5,97.5 percentile)

Figure 2: Goodness of fit plot of plaque time course data

Gray symbols/line: observed; black lines: model fit. PBO: placebo; QD: once daily; Q2W: every 2 weeks; Q4W, every 4 weeks.

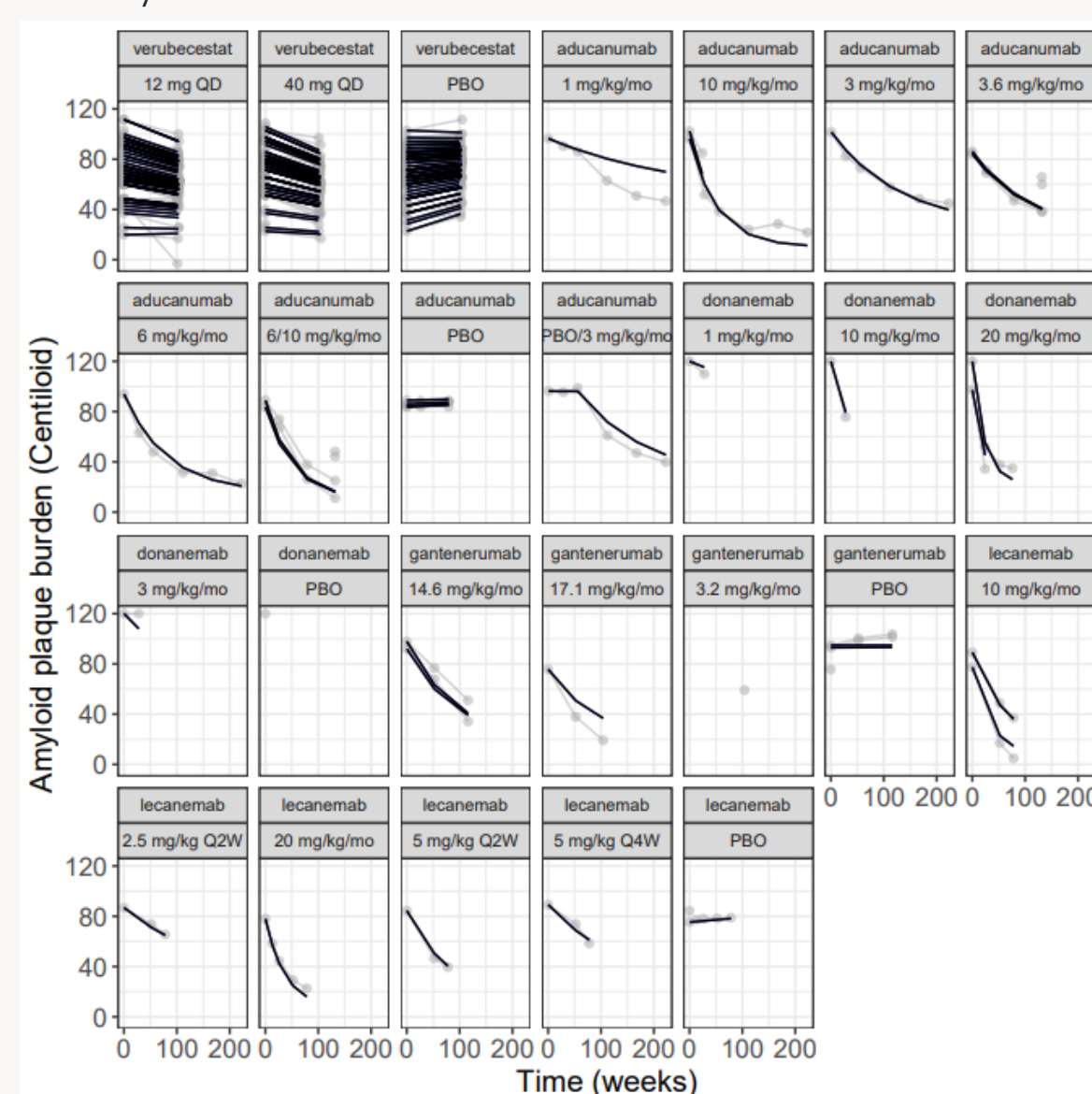


Table 2: Fold increase in  $K_{out}$

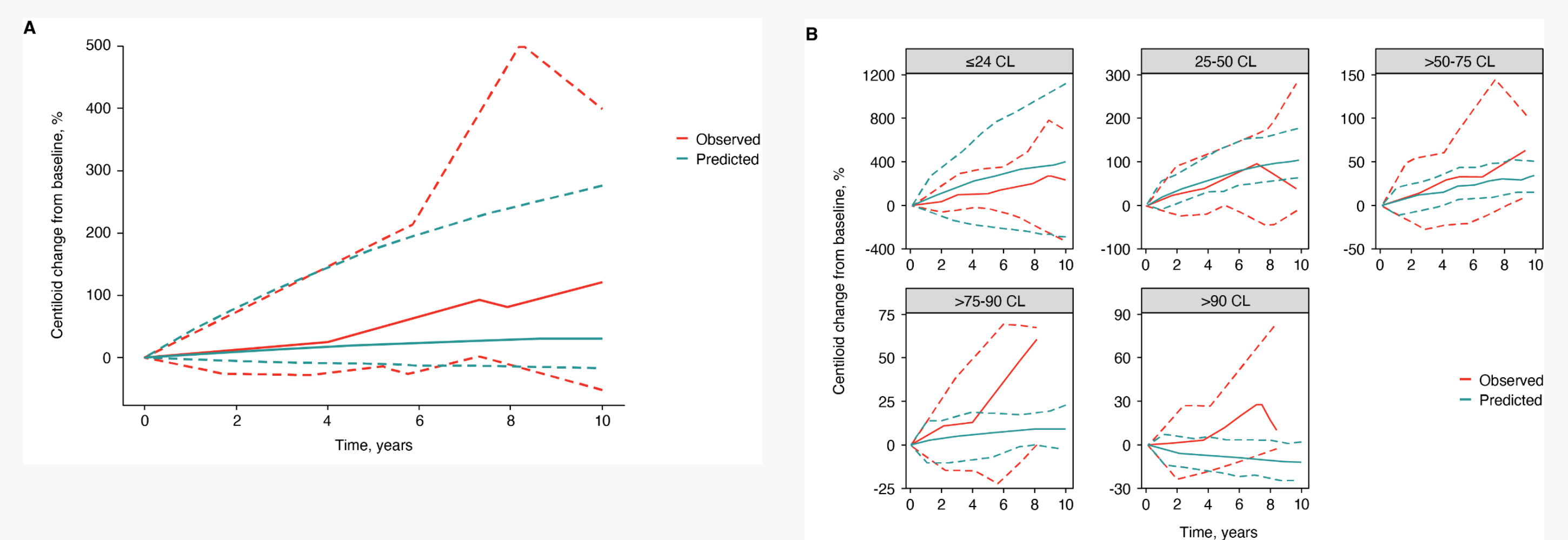
mAb regimen	Fold increase median (95% CI)
Aducanumab 10 mpk Q4W	9.3 (7.4-11.1)
Gantenerumab 1200 mg Q4W	5.3 (3.2-7.2)
Lecanemab 10 mpk Q2W	13.7 (10.7-16.7)
Donanemab 1400 mg Q4W	15.2 (11.5-19.1)

## Results (ctd)

- External Validation
  - The model showed good predictive performance in describing amyloid progression over 6 years in the ADNI natural history dataset. (Figure 3)

Figure 3: External validation

Comparing model with ADNI data (A) overall and (B) stratified by baseline plaque load. Solid and dashed lines represents medians and 10<sup>th</sup> and 90<sup>th</sup> percentiles, respectively, of the amyloid plaque values. ADNI: Alzheimer's Disease Neuroimaging Initiative.



- Comparative Predictions
  - Verubecestat (BACE1 inhibitor) led to a modest reduction in amyloid plaque over 24 months
  - Anti-amyloid mAbs achieved greater plaque reduction over the same period (Figure 4)
  - Lecanemab and donanemab were predicted to yield similar plaque reductions by 18 months, despite lecanemab's lower potency (Figure 5):
    - Due to lecanemab's faster ramp-up (20 mg/kg monthly, or 10 mg/kg Q2W)
    - Versus donanemab's slower titration (10 mg/kg over 3 months)
  - Aducanumab was predicted to show less plaque reduction than lecanemab at 18 months (Figure 5):
    - Attributed to a 6-month titration to 10 mg/kg Q4W
    - Despite slightly higher efficacy
  - Gantenerumab showed the lowest predicted reduction (Figure 5):
    - Due to lower efficacy
    - Combined with a slow 9-month titration to ~15 mg/kg

Figure 4: Effect of BACE1 inhibition and mAb treatment

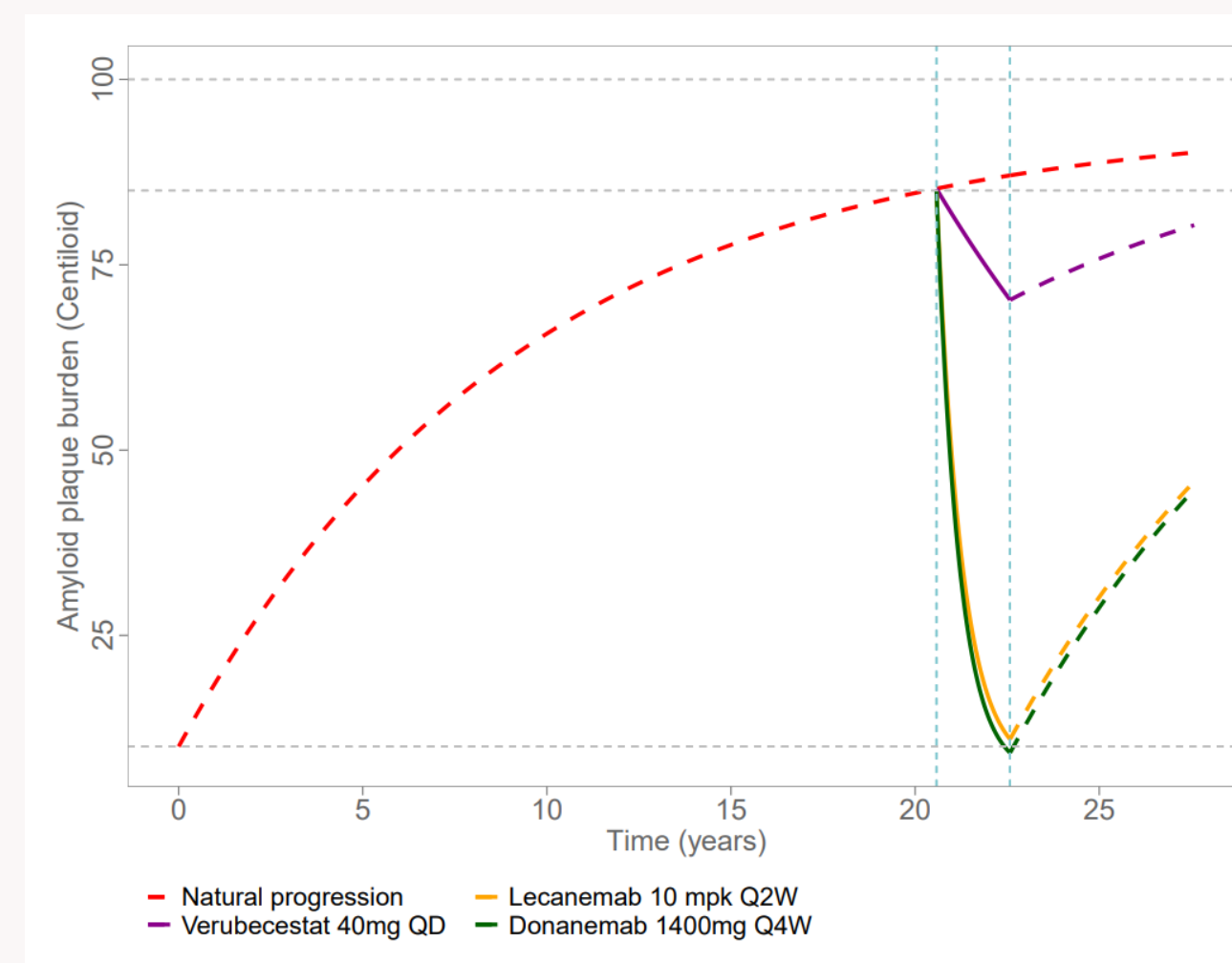
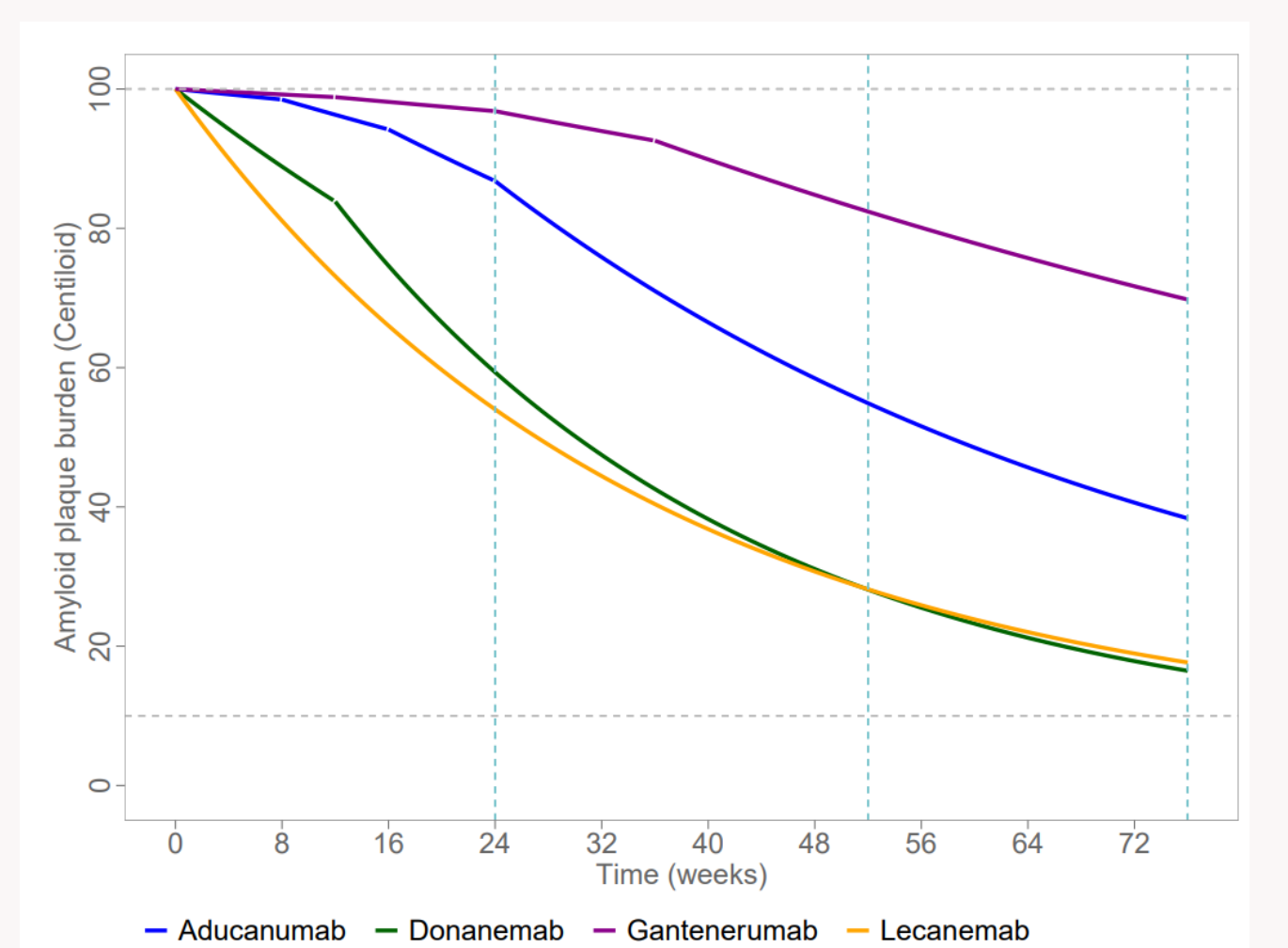


Figure 5: Impact of mAb's dose titration



## Conclusions

### Joint Turnover Model for Amyloid Plaque Dynamics

- Successfully linked drug exposure to amyloid plaque dynamics, capturing both natural progression and treatment responses
- Enabled estimation of the underlying plaque turnover rate
- Facilitated cross-study comparisons by integrating data across diverse compounds and study designs
- Supported prediction of alternative dosing regimens and therapeutic strategies, accounting for:
  - Dosing and titration schedules
  - Mechanism of action

### Applications:

- The model can be used to simulate early intervention strategies and unstudied regimens, including combinations of monoclonal antibodies and verubecestat (Stone J., AAIC, July 19, 2023)

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