Quantitative Systems Pharmacology Amyloid Platform: Multiscale Computational Modeling of Aβ Biology and Its Interaction with Lecanemab Pharmacology

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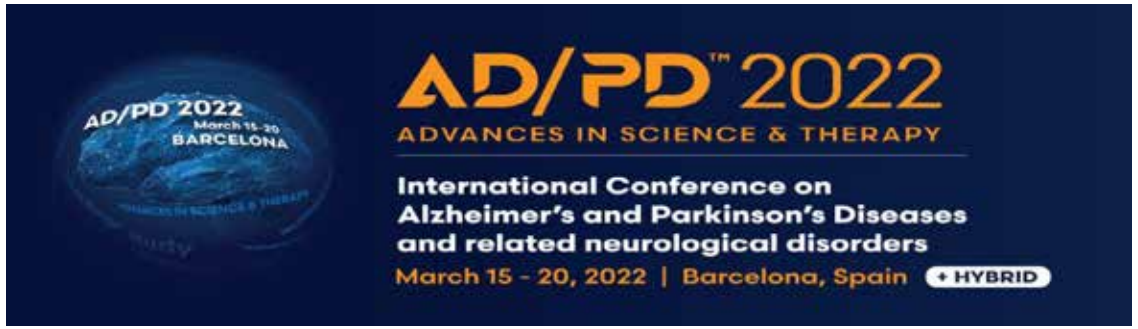
Presenter Disclosures



	No, Nothing to disclose
X	Yes, please specify

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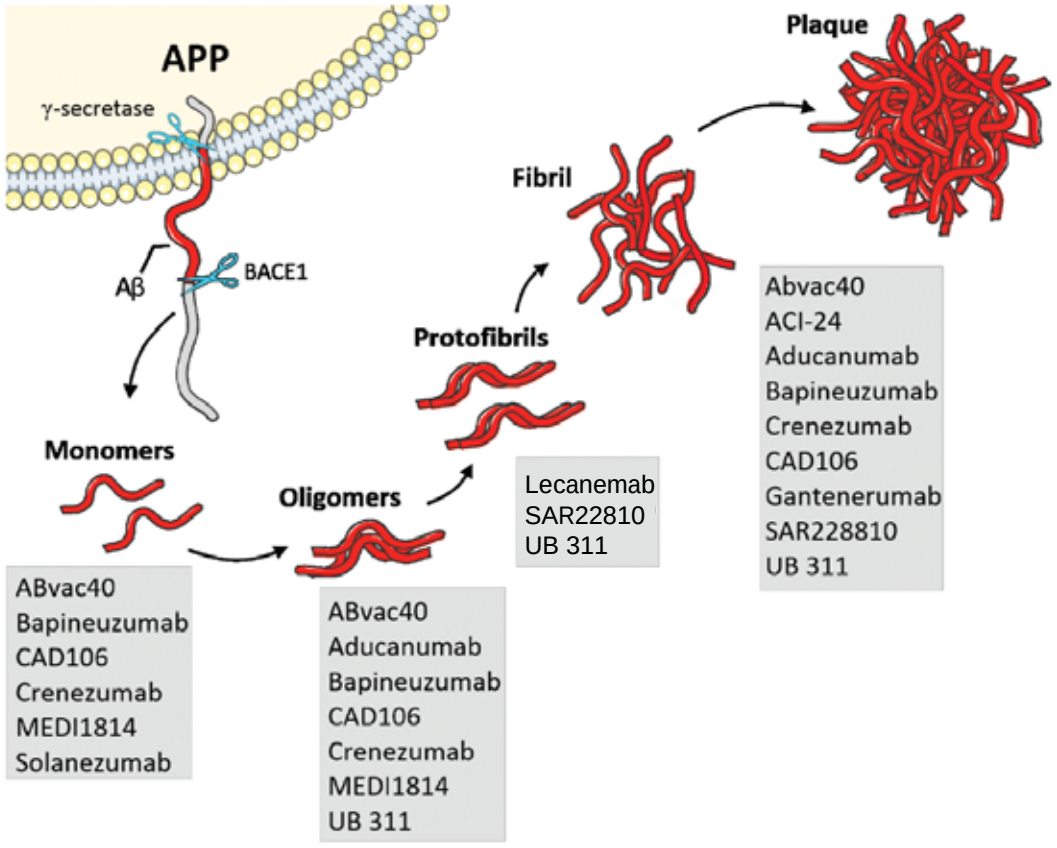
Overview

- **Aβ QSP Platform Model**
  - Background
  - Account of the model components and assumptions
  - Model qualification using existing clinical data
- **Simulations using Aβ QSP Platform**
  - Extent of Aβ species removal from different monoclonal antibody treatments and assessment of biomarkers
  - Account of ARIA-E model components and assumptions
  - Simulated QSP incidence of ARIA-E for APOE carriers and non-carriers

Aβ, amyloid beta; APOE, apolipoprotein E; ARIA-E, amyloid-related imaging abnormalities-edema; QSP, Quantitative Systems Pharmacology.

Targeting Amyloid



Adapted from Zampar & Wirths, *Alzheimer's Disease Drug Discovery* 2020

- Amyloid aggregates are characterized based on size and solubility into monomers, oligomers, protofibrils, and fibrils.
- Anti-amyloid monoclonal antibodies differ in their affinity for each of these species, potentially leading to different levels of SUVr reduction and potentially different clinical outcomes.

Monoclonal antibody affinity for Aβ species used in the QSP model

Antibody	Monomer*1 K_D (nM)	Oligomer*2 K_D (nM)	Protofibril*3 K_D (nM)	Fibril*4 K_D (nM)
Solanezumab	0.60	NA*5	NA*5	NA*5
Bapineuzumab	6.97	6.97*6	0.09	0.2
Crenezumab	7.16	0.72*7	14.4	NA*5
Gantenerumab	1270	30.7	2.51	0.69
Lecanemab	2290	67.3	0.16	1.79

*1: Monomer K_D were obtained by Biacore assay using Aβ1-28 (Unpublished data)
*2: Oligomer K_D were obtained by literature or Biacore assay with cross-linked Aβ1-42 6-8 mers (Unpublished data)
*3: Protofibril K_D were obtained by literature or Biacore assay with recombinant Aβ1-42 large protofibrils (Unpublished data)
*4: Fibril K_D were obtained by literature or Biacore assay with recombinant Aβ1-42 fibrils (Unpublished data)
*5: NA were replaced with 20 μM in model simulations (Unpublished data)
*6: Oligomer K_D of Bapineuzumab were assumed to be same as monomer (Unpublished data)
*7: Oligomer K_D of Crenezumab were assumed to be 1/10 of monomer (Meilandt et al. 2019)

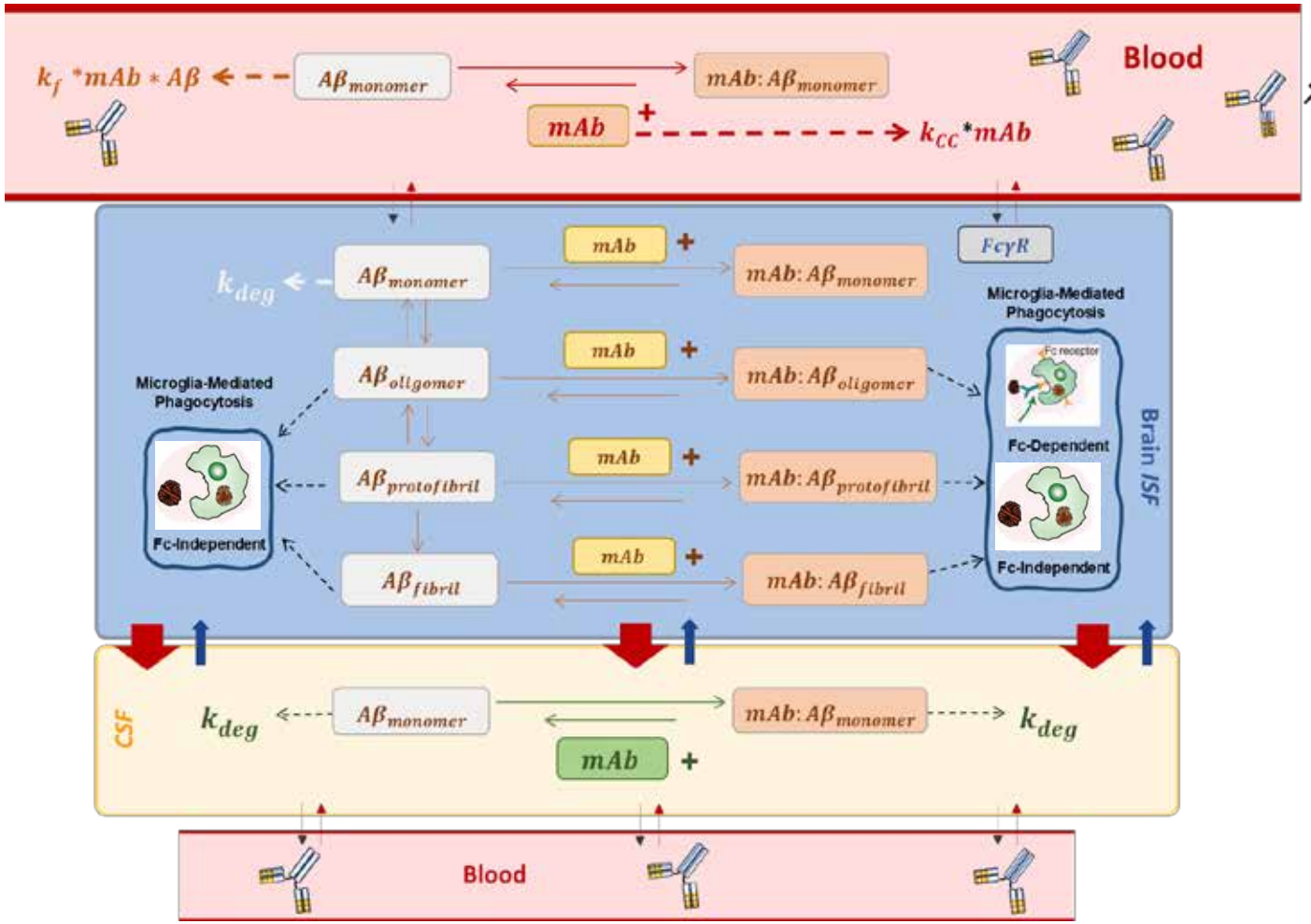
Aβ, amyloid beta; APP, amyloid precursor protein; BACE, beta-site amyloid precursor protein cleaving enzyme 1; QSP, Quantitative Systems Pharmacology; SUVr, standardized uptake value ratio.

Amyloid QSP Model

Ab Aggregation Platform

Model Assumptions:

1) Monoclonal antibody concentrations are simulated using a qualified PBPK model derived from Chang et al., 2019.
2) Oligomers, Protofibrils, and Fibrils are cleared from the ISF by:
   i. Non-Fc & Fc-mediated activation of microglia
   ii. Antibody mediated activation of microglia
3) Monomers are cleared from the CSF by a first order degradation kinetics
4) ApoE4+ genotype implemented with a 50% lower basal clearance rate and a 60% higher EC_{50} for $A\beta_{40}$ and $A\beta_{42}$ peptides based on Lin et al., 2018.
5) Amyloid PET tracers bind primarily to fibrils, with additional binding to protofibrils.



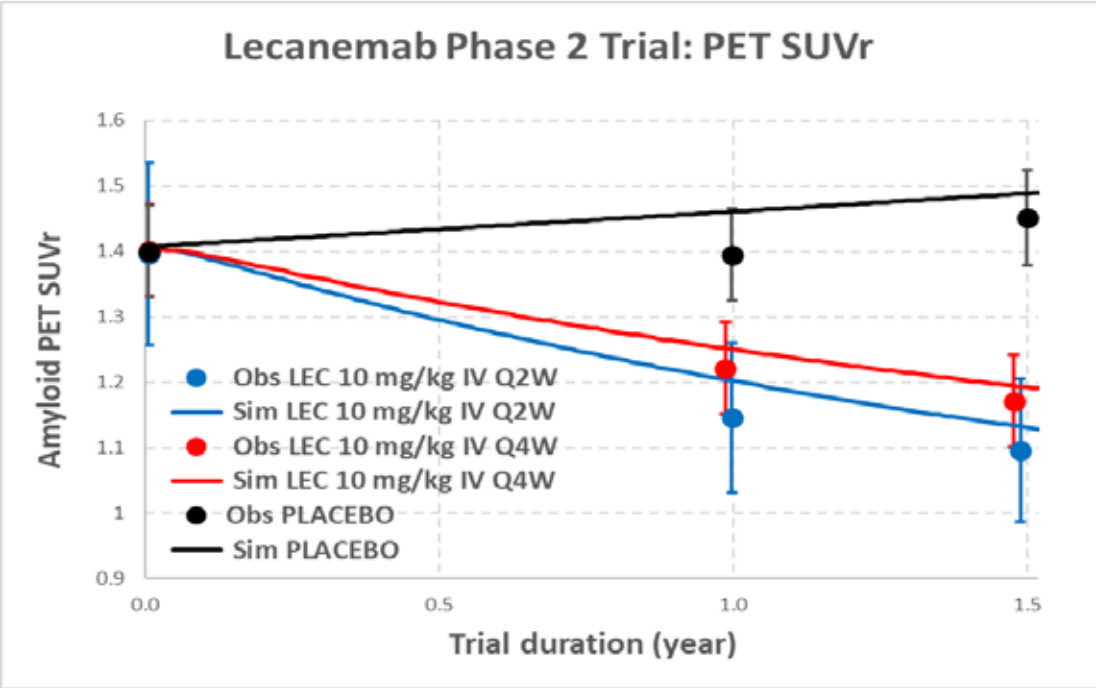
Different biological processes involved in Ab_{40} & Ab_{42} aggregation dynamics. Oligomers (c_i , i = 2 …16), protofibrils (c_i , i = 17 …24), and fibrils (c_i , $i \geq 25$) are eliminated assuming microglia-dependent clearance

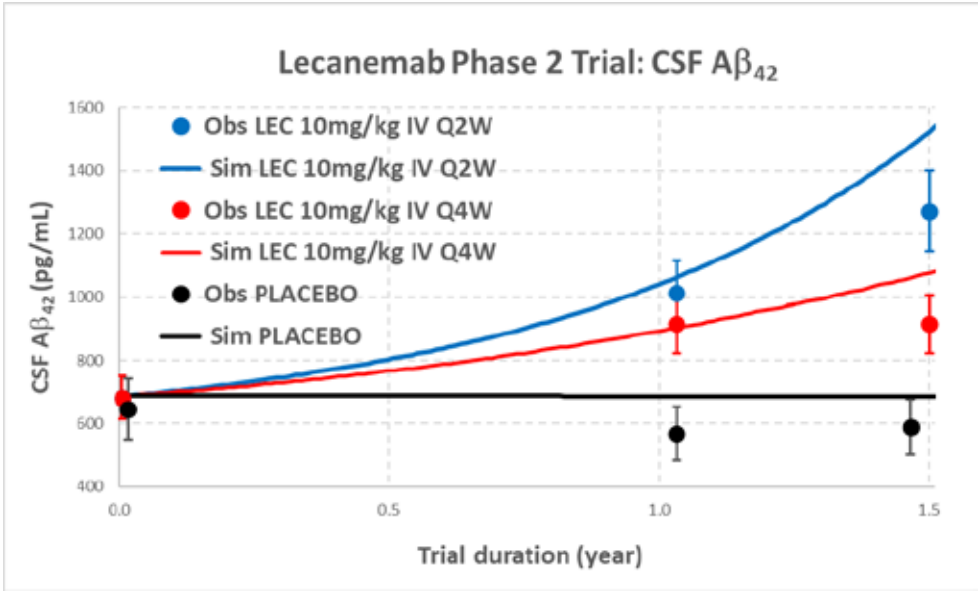
Aβ, amyloid beta; APOE4, apolipoprotein E4; CSF, cerebrospinal fluid; ISF, interstitial fluid; mAb, monoclonal antibody; PBPK, physiological based pharmacokinetic modeling and simulation; PET, positron emission tomography; QSP, Quantitative Systems Pharmacology; SUVr, standardized uptake value ratio.

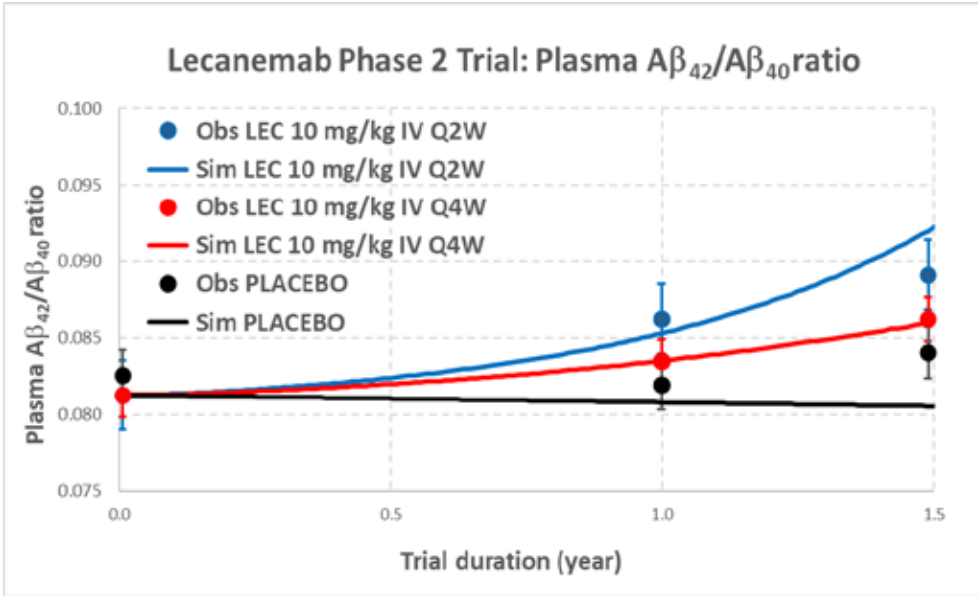
Model PK-PD Qualification: Lecanemab

QSP Model adequately replicates biomarker data from the lecanemab Phase 2 Study 201.

- Amyloid PET SUVr
- CSF Biomarker (Aβ42 Concentration)
- Plasma Biomarkers (Aβ42/Aβ40 ratio)





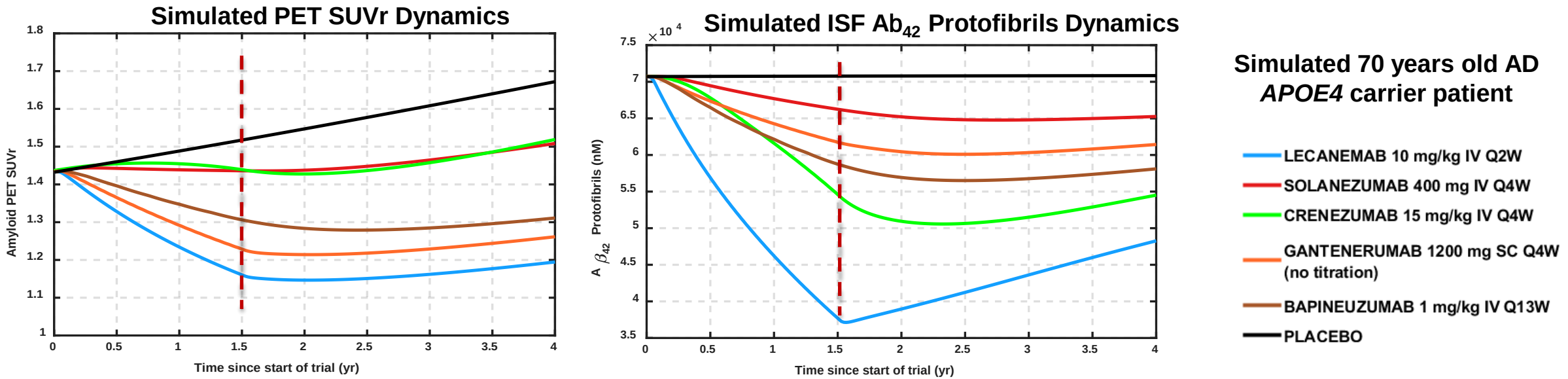


Simulated data represents 70 years old AD *APOE4* carrier patient

Aβ, amyloid beta; CSF, cerebrospinal fluid; PET, positron emission tomography; PK-PD, pharmacokinetic–pharmacodynamic; QSP, Quantitative Systems Pharmacology; SUVr, standardized uptake value ratio.

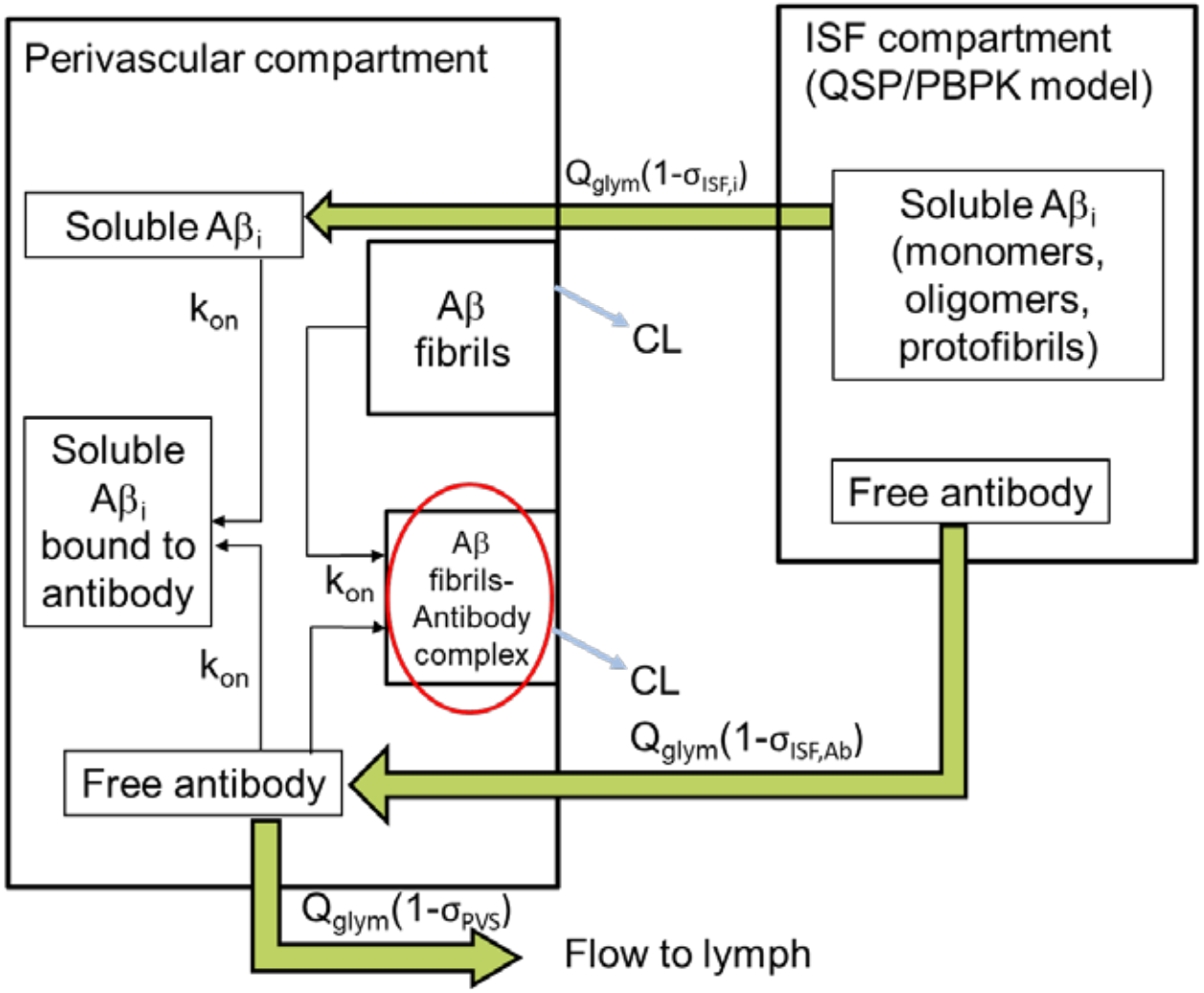
Simulated Changes in Amyloid Profiles Differ Between Antibodies

- Change in oligomers, protofibrils, and SUVr were simulated for several anti-amyloid monoclonal antibodies for 18-months on treatment, followed by 2.5 years of observation (4 years total). A constant dose was used throughout the simulation (ie, no titration regimen for any molecule)
- The simulated treatment extent of Aβ species removal and their return to baseline depends primarily on the monoclonal antibody binding affinity to aggregated Aβ species
- At clinical doses, lecanemab produced pronounced reductions in protofibrils and SUVr, consistent with the affinity profile
- Solanezumab and Crenezumab have the least pronounced predicted SUVr reduction. Crenezumab (IgG4 antibody) does not benefit from the increase in microglial mediated clearance, while Solanezumab has low affinity to aggregated Aβ species



Aβ, amyloid beta; APOE4, apolipoprotein E4; IV, intravenous; PET, positron emission tomography; SUVr, standardized uptake value ratio.

ARIA-E Implementation



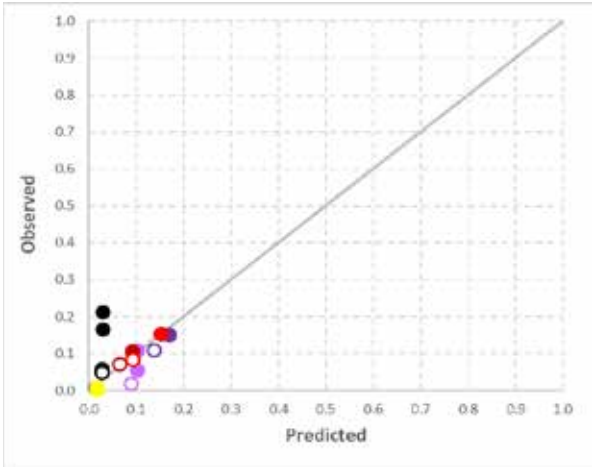
- Administration of anti-amyloid monoclonal antibodies has been associated with ARIA-E
- Time-to-event models were developed linking the amount of amyloid-antibody complex in the perivascular compartment to the risk of ARIA-E
- Key model assumptions:
  - Fibril/protofibril concentrations in perivascular space were similar to those in ISF at treatment baseline
  - Clearance of fibrils and fibril-antibody complex was due to macrophages (instead of the microglia-driven clearance in ISF)
  - Clearance of fibril-antibody complex was calibrated based on data from reported clinical trials of solanezumab, bapineuzumab, crenezumab, gantenerumab, and lecanemab
  - Model assumes that macrophage-based clearance differs in ApoE4 carriers/noncarriers.

Aβ, amyloid beta; APOE4, apolipoprotein E4; ARIA-E, amyloid-related imaging abnormality-edema; ISF, interstitial fluid; PBPK, physiological based pharmacokinetic modeling and simulation; PET, positron emission tomography; QSP, Quantitative Systems Pharmacology.

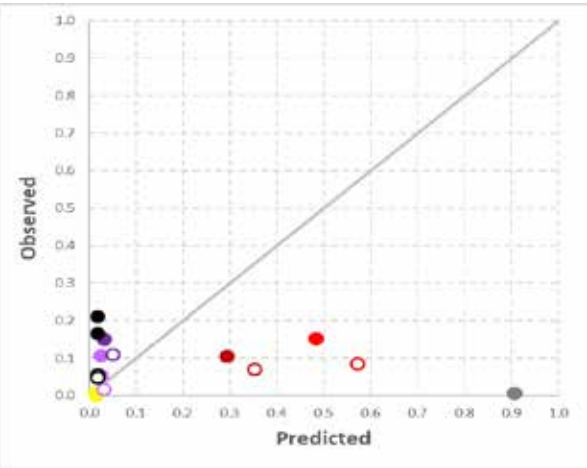
Gaining Insights Into Potential ARIA-E Mechanisms

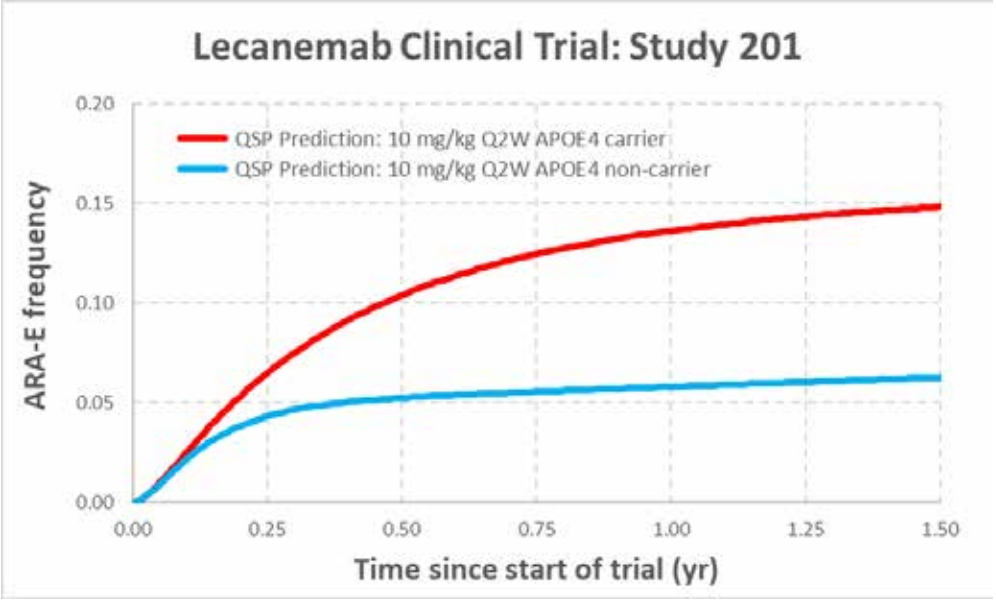
- Different models were tested to evaluate whether concentrations of fibril-antibody complex or protofibril - antibody complex were better predictors of ARIA-E risk
  - Fibril-antibody complex (left) was shown to be the best predictor of ARIA-E risk, and was incorporated into the final QSP model
- Model adequately characterized the incidence of ARIA-E observed in lecanemab Study 201
  - Different rates of ARIA-E in ApoE4 carriers/noncarriers could potentially be explained by different amounts of fibrils in the PVS at the start of treatment, and the amount of fibril-antibody complex during treatment

ARIA-E incidence model driven by mAb- bound fibril concentration



ARIA-E incidence model driven by mAb-bound protofibril concentration





APOE4, apolipoprotein E4; ARIA-E, amyloid-related imaging abnormality-edema; mAb, monoclonal antibody; QSP, Quantitative Systems Pharmacology.

Conclusions

- **Aβ QSP Platform has been developed, implemented and qualified**
  - It captures the known features of Aβ aggregation process, including protofibrils
  - It is integrated with the mechanisms of action driving the pharmacology of drugs targeting the modulation of Aβ pathology for the treatment of Alzheimer's Disease
  - It adequately replicates clinical PK/PD data for several monoclonal antibodies: lecanemab, gantenerumab, solanezumab, bapineuzumab, and crenezumab
- **The simulated PK and PD results generated using the *Aβ QSP Platform* show pronounced differences in oligomer, protofibril, and plaque reduction between several monoclonal antibodies**
  - Difference in affinity for various amyloid species drives changes in SUVr response between various antibodies
  - Better estimation of protofibril and oligomer concentrations in ISF with response to monoclonal antibody treatment may provide insight into appropriate maintenance dosing following plaque clearance
- **Incidence of ARIA-E can be related to the amount of antibody-fibril complex in the perivascular space**
  - Model adequately replicates clinical data
  - Potentially provides insight into mechanism leading to ARIA-E: fibril-antibody complex in the perivascular space is a good predictor of ARIA-E, protofibril-antibody complex is not

Aβ, amyloid beta; ARIA-E, amyloid-related imaging abnormalities-edema; ISF, interstitial fluid; PK/PD, pharmacokinetic/pharmacodynamic; QSP, Quantitative Systems Pharmacology; SUVr, standardized uptake ratio.