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RESEARCH ARTICLE

Systematic in silico analysis of clinically tested drugs for reducing amyloid-beta plaque accumulation in Alzheimer's disease

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Abstract

Introduction: Despite strong evidence linking amyloid beta (Aβ) to Alzheimer's disease, most clinical trials have shown no clinical efficacy for reasons that remain unclear. To understand why, we developed a quantitative systems pharmacology (QSP) model for seven therapeutics: aducanumab, crenezumab, solanezumab, bapineuzumab, elenbecestat, verubecestat, and semagacestat.

Methods: Ordinary differential equations were used to model the production, transport, and aggregation of Aβ; pharmacology of the drugs; and their impact on plaque.

Results: The calibrated model predicts that endogenous plaque turnover is slow, with an estimated half-life of 2.75 years. This is likely why beta-secretase inhibitors have a smaller effect on plaque reduction. Of the mechanisms tested, the model predicts binding to plaque and inducing antibody-dependent cellular phagocytosis is the best approach for plaque reduction.

Discussion: A QSP model can provide novel insights to clinical results. Our model explains the results of clinical trials and provides guidance for future therapeutic development.

KEYWORDS
aducanumab, amyloid beta pathway, amyloid plaque reduction, bapineuzumab, crenezumab, elenbecestat, model-informed drug development, quantitative systems pharmacology model, semagacestat, solanezumab, verubecestat

1 | INTRODUCTION

Amyloid beta (Aβ) plaque accumulation is a known pathological hallmark of Alzheimer's disease (AD) and has been the focus of drug development for AD in the past decades. Different approaches and hypotheses have been proposed around modulation of the Aβ pathway. The main modalities of Aβ-modulating drugs are antibody-based immunotherapies (mAbs)[1] and small molecule inhibitors.[2] The potential mechanism of actions include inhibition of Aβ monomer production; inhibition of Aβ plaque formation; actively removing Aβ

RESEARCH IN CONTEXT

1. **Systematic review:** The authors reviewed published literature, conference abstracts, and clinical trial press releases to curate available clinical data. Most of the trials with amyloid beta (Aβ)-modulating therapies have shown no clinical efficacy, and the reasons remain unclear. The relevant publications have been appropriately cited.
2. **Interpretation:** We developed a dynamical systems model describing Aβ biology and the pharmacology of seven drugs. The model captured pharmacokinetics of these drugs and their effect on amyloid plaque. Our work demonstrates the utility of mathematical modeling to help explain the results of Alzheimer's disease trials and to help design effective therapies and clinical trials in the future.
3. **Future directions:** Several areas remain open for future model expansion: (a) Including Aβ40 and Aβ42 isoforms in the model and describing the dynamics of plaque formation in the course of disease progression, (b) creating virtual patients to capture variability in the trial, and (c) linking plaque reduction to clinical outcomes.

plaque through antibody-dependent cellular phagocytosis (ADCP); and "peripheral sink hypothesis," which hypothesizes that binding of all/most of the soluble Aβ in the circulation affects the equilibration of soluble Aβ between brain and blood, leading to a reduction of Aβ in the brain without a requirement for mAbs to enter the brain.[3]

Despite strong evidence linking elevated Aβ levels to AD,[4] clinical trial outcomes of Aβ-modulating therapies have been disappointing.[5,6] The reasons for lack of efficacy of anti-Aβ agents are unclear, but may include (1) insufficient drug exposure at the site of target expression (i.e., the brain), (2) the wrong patient population or timing of therapy, (3) ineffective drug mechanism of action (MOA; e.g., binding to Aβ monomers, oligomers, or plaques), or (4) incomplete or incorrect disease understanding (e.g., invalid Aβ plaque hypothesis). Just as the causes for failure vary, the appropriate response to each of these failures may also be different. For example, the first two causes can be addressed by conducting additional clinical studies with existing drug candidates (e.g., by either adjusting dosing regimen or enrolling a different patient population), while the latter two require developing new drugs or identifying new drug targets. Unfortunately, clinical trials for AD are particularly costly due to the long treatment period needed (more than 12 months)[7] to observe potential functional changes, the expensive and complex brain imaging technologies required for biomarker collection, and the large patient numbers required to observe significant changes in cognitive function in a heterogeneous population. For all the above-stated reasons, understanding the reasons for failure in completed AD trials will lead to better drug design and more effective clinical study design in the future.[8]

Quantitative systems pharmacology (QSP) modeling integrates different types of quantitative information mechanistically and provides an opportunity to systematically analyze data from various clinical trials and drug modalities within a self-consistent modeling framework. QSP models can also be used to determine drug dosing frequencies, dosing amounts, and to define the patient population most likely to respond to the treatment. In recent years, there has been an increase in the application of QSP modeling to decision making in drug discovery and development.[9–13] Several QSP models in AD have also been published. For example, a multi-compartment model was built capturing Aβ production and transport between plasma and cerebrospinal fluid (CSF) to understand the underlying changes in Aβ kinetics for presenilin (PSEN) mutation carriers.[14] A recent QSP model for AD includes both pharmacology of the drug and disease biology but focuses on the dysregulation of lipid metabolism.[15] Another QSP model for AD captures the pharmacokinetics–pharmacodynamics (PK/PD) relationship for crenezumab.[16] Several PK/PD models have been published for beta-secretase (BACE) inhibitors,[17,18] describing the relationship between drug exposure and soluble Aβ changes in CSF from monkeys. All of these models address specific questions and include different aspects of AD biology and drug pharmacology. A key limitation of these models is that they were all developed for a single drug. Because QSP models tend to include many parameters, and data in the brain are often limited, calibrating a model to multiple drugs potentially results in more robust model parameterization and better model predictions.

Direct comparison of the pharmacologic effects of multiple drugs is often challenging because drugs have different MOAs, dosing frequencies, and other PK parameters. QSP models when calibrated to multiple drugs accommodate this complexity and enable more meaningful comparisons of the PD data. For example, small molecule BACE or γ-secretase inhibitors lead to decreased Aβ concentrations in CSF and plasma,[19–21] while anti-Aβ antibodies lead to increased plasma Aβ concentrations.[1] Different anti-Aβ antibodies bind to different forms of Aβ species with different affinities.[22,23] Aducanumab is designed to bind to Aβ oligomer and plaque but has weak binding affinity for Aβ monomer. Preclinical studies suggest that aducanumab, once bound, activates ADCP to clear Aβ.[24] On the other hand, solanezumab is designed to bind to Aβ monomer, but not its aggregated forms.[25] Bapineuzumab is designed to bind to monomer, oligomer, and plaque and also induce ADCP.[26] In clinical trials, aducanumab was administered up to 10 mg/kg intravenously (IV) every 4 weeks in its phase 3 trial, while bapineuzumab was administered only up to 2 mg/kg every 13 weeks in its phase 3 trials.[26] Even though nearly all of these therapeutics, with the possible exception of aducanumab, did not achieve a slowing of cognitive decline in AD,[5,6] it is difficult to attribute the outcomes to a specific reason for failure.

Here, a QSP platform model was developed to generate hypotheses for the causes of clinical failure and to understand the modeled mechanisms for plaque reduction. The model integrates Aβ biology with the MOA of seven published drugs that modulate Aβ biology. The drugs included in this work are selected based on the understanding of their MOA and the data availability to enable model parameterization. The model development approach was to use a common Aβ biology

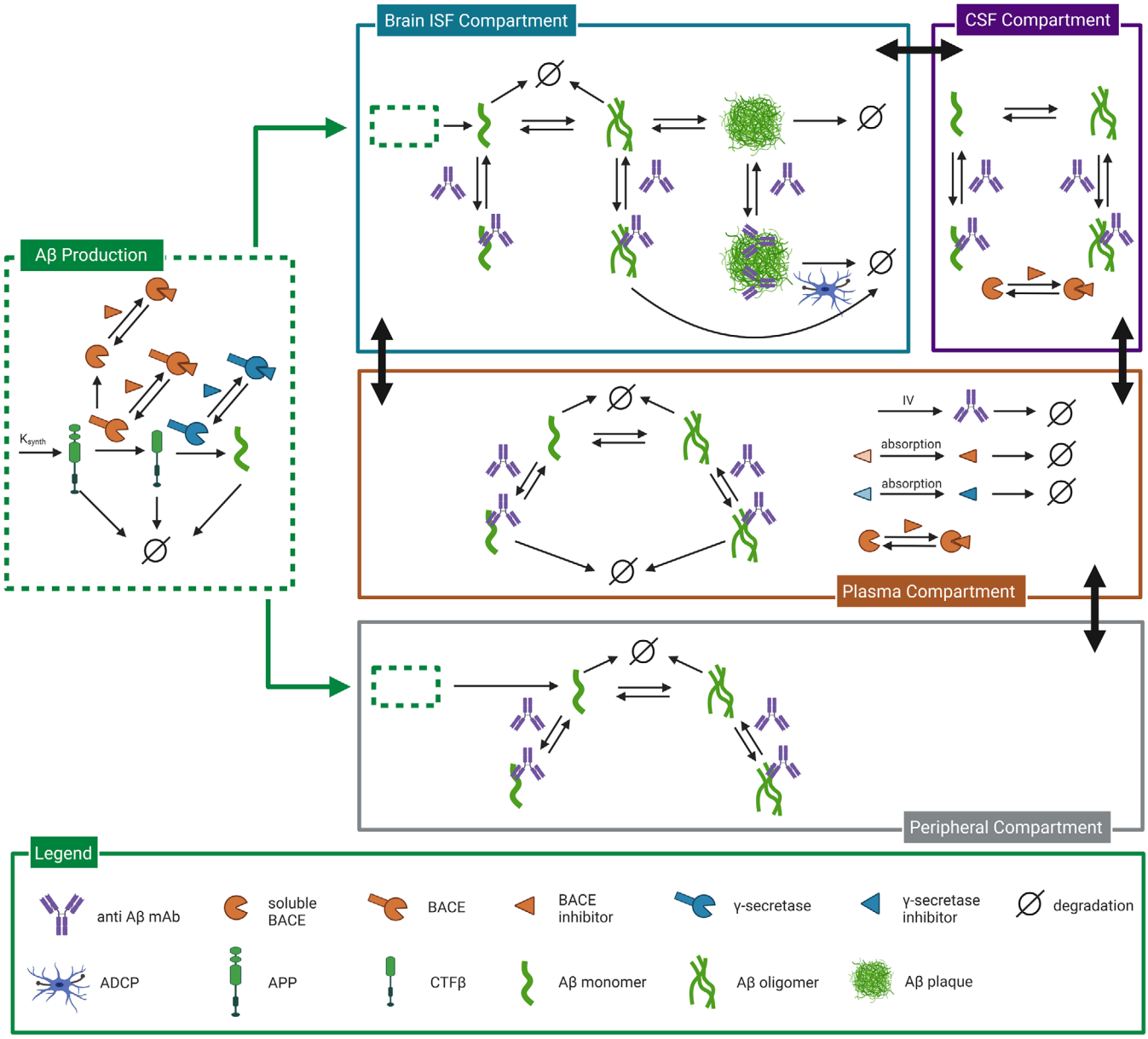

FIGURE 1 Schematic model diagram. There are four compartments in the model, a circulating plasma compartment, a peripheral compartment, a brain interstitial fluid (ISF) compartment, and a cerebrospinal fluid (CSF) compartment. Anti-Aβ mAbs, BACE inhibitors, and γ-secretase inhibitor are also represented in the diagram. Aβ, amyloid beta; BACE, beta-secretase; ADCP, antibody-dependent cellular phagocytosis

submodel allowing only drug-related parameters (e.g., PK and drug binding affinity to target) to vary among drugs. After model calibration to drug PK and observed PD including Aβ plaque changes measured by positron emission tomography (PET) imaging, the model was systematically analyzed. We expect this model, calibrated to multiple drugs of related mechanisms, to provide actionable insights into the reasons underlying clinical trial failures and to guide future drug and clinical study design.

2 | METHODS

Figure 1 describes the key mechanisms captured in the model. The common Aβ biology submodel includes four compartments: a circulation plasma compartment, a peripheral tissue compartment, a brain interstitial fluid (ISF) compartment, and a CSF compartment. Aβ is produced in brain ISF and peripheral tissue compartments through sequential cleavage of amyloid precursor protein (APP) by BACE followed by γ-secretase to form an Aβ monomer. In this model, Aβ monomer represents the sum of two major forms, Aβ40 and Aβ42, because both forms showed similar production and clearance rates in CSF based on stable isotope labeling kinetic (SILK) experiment[27] and the therapeutics included in the current work induced similar dynamic changes between the two forms in both CSF or plasma based on the available literature data. Aβ monomer aggregates to form soluble Aβ oligomer in all compartments. However, plaque formation from soluble oligomers is limited to only brain ISF. Formation of soluble oligomer

and plaque are reversible, but the rates of reverse reaction from plaque to oligomer is much slower than the forward aggregation reactions. Aβ monomer and oligomer can transport between peripheral and circulation compartments, as well as among circulation, brain ISF, and CSF compartments.

The MOA of seven drugs are included: four anti-Aβ mAbs: aducanumab, crenezumab, solanezumab, and bapineuzumab; two small-molecule BACE inhibitors: elenbecestat and verubecestat; and one small-molecule γ-secretase inhibitor: semagacestat. Aducanumab is a high affinity, fully human immunoglobulin (IgG)1 monoclonal antibody that binds to the N-terminal region of the Aβ molecule. It is known to bind to aggregated forms of Aβ (oligomer and plaque) with higher affinity than to Aβ monomer.[24,28] Once bound to oligomer or to plaque, aducanumab induces clearance of these complexes due to Fc receptor binding and ADCP. In the model, we describe this mechanism as a drug–oligomer and drug–plaque complex binding to Fcγ receptor in brain ISF followed by clearance of these complexes. Crenezumab is an IgG4 monoclonal antibody that binds to Aβ oligomer and plaque with higher affinity than to monomer[29,30] and also induces ADCP of drug–plaque and drug–oligomer complexes. Because IgG4 antibodies are known to induce less potent effector functions than IgG1 antibodies,[31] the model assumes that the binding to the Fc receptor is four-fold weaker and ADCP-mediated clearance of Fcγ receptor-bound drug–Aβ oligomer or plaque complex for crenezumab is less than the clearance rate for aducanumab and bapineuzumab. Solanezumab is a humanized monoclonal IgG1 antibody directed against the mid-domain of the Aβ peptide. It binds to Aβ monomer and Aβ oligomer, but it does not bind to Aβ plaque. Bapineuzumab is a humanized IgG1 antibody that binds Aβ monomer, oligomer, and plaque and induces ADCP. It is known to bind to all Aβ species with comparable affinity.[22,32] In the model, anti-Aβ mAbs bind to Aβ monomer, oligomer, and plaque with different affinities depending on each mAb. BACE and γ-secretase inhibitors are incorporated in the model as a competitive reversible binding to its target.

Publicly available PK and PD data from phase 1–3 clinical trials of these seven drugs were used for model development (summarized in Table S1 in supporting information). PD data included total Aβ in circulation and CSF, and Aβ plaque reduction measured by amyloid PET imaging, BACE activity in CSF for BACE inhibitors (fitting results were not shown). Data were digitized from publications. Most of the studies were conducted with patients with mild–moderate AD. Phase 1 studies for BACE and γ-secretase inhibitors were healthy volunteer studies. Model parameters for each appropriate population are used for simulations. Details of data processing are described in supporting information.

In addition to clinical trial data, other literature data and information were also used to inform the model. SILK studies[27] were used to inform Aβ synthesis and transport rate constants. Aβ concentration in brain ISF was based on semi-quantitative data, which indicated highest concentration of Aβ to be in insoluble oligomer (i.e., plaque), followed by soluble oligomer and then monomer.[33,34] Protein turnover half-lives for APP,[35] BACE,[36] and γ-secretase[37] were derived from in vitro or in vivo measurements reported in the literature. Antibody drug concentration ratio at steady state between CSF and circulation was set to be 0.1%.[38]

Further details about model structure, details of data processing, model calibration, and model simulation and analysis are described in supporting information.

3 | RESULTS

3.1 | A single model can recapitulate clinical PK and PD data for seven therapeutics

The core Aβ biology submodel was fit to the Aβ dynamics in CSF from the SILK experiment as shown in Figure S1 in supporting information. The healthy and AD individuals are differentiated via a single model parameter, that is, faster transport of Aβ from CSF to circulation (1.4X of *k31Abeta*) for healthy individuals. In addition, the Aβ biology submodel recapitulates the known concentrations or relative abundance of different Aβ species in mild–moderate AD patients base on literature as shown in Table S2 in supporting information.

To simulate drug treatment, the model parameters for either healthy or AD individuals were applied depending on the population from which the data were collected. Figures 2 and 3 summarize the key model fitting results for the four mAb drugs and three small molecule inhibitors, respectively. Specifically, the figures show model simulations of single-dose PK, total Aβ (monomer and oligomer in unbound and drug bound state in case of mAb treatment) in circulation and in CSF, as well as percent plaque reduction in ISF. Figure 2A pertains to Aducanumab, 2B pertains to Bapineuzumab, 2C to Crenezumab, and 2D to Solanezumab. Figure 3A pertains to Elenbecestat, 3B to Verubecestat, and 3C to Semagecestat. When there are no data, only simulations are shown. For each plot, simulations shown are consistent with dosing regimens tested in clinical trials from which the data were collected. Final model parameter values describing Aβ biology and drug MOA are summarized in Tables S3, S4 and S5 in supporting information. For elenbecestat, normalized percent standardized uptake value ratio (SUVR) difference between 50 mg/day and placebo groups at the end of 18 months treatment was 40.8% in its phase 2 study.[39] However, about half of the SUVR reduction was reported at 40 mg for verubecestat,[40] even though near complete Aβ reduction in CSF was reported for both elenbecestat and verubecestat at those doses. The model was not able to match the Aβ reduction in CSF for both elenbecestat and verubecestat while also matching measured SUVR changes for these two drugs. Therefore, the final calibrated model predicts less SUVR reduction compared to data for elenbecestat while it predicts greater SUVR change compared to data for verubecestat. For semagacestat, Aβ levels in plasma decrease initially, recover, and then rise above baseline levels. The model captures the decrease of Aβ in plasma. However, it is not able to capture the overshoot, which has been hypothesized to be a stimulatory effect of the drug at low concentrations while an inhibitory effect is expected at high concentration.[20,41] Because this work is intended to support the design of future drug development and clinical study design, no effort was made to capture the rebound of Aβ

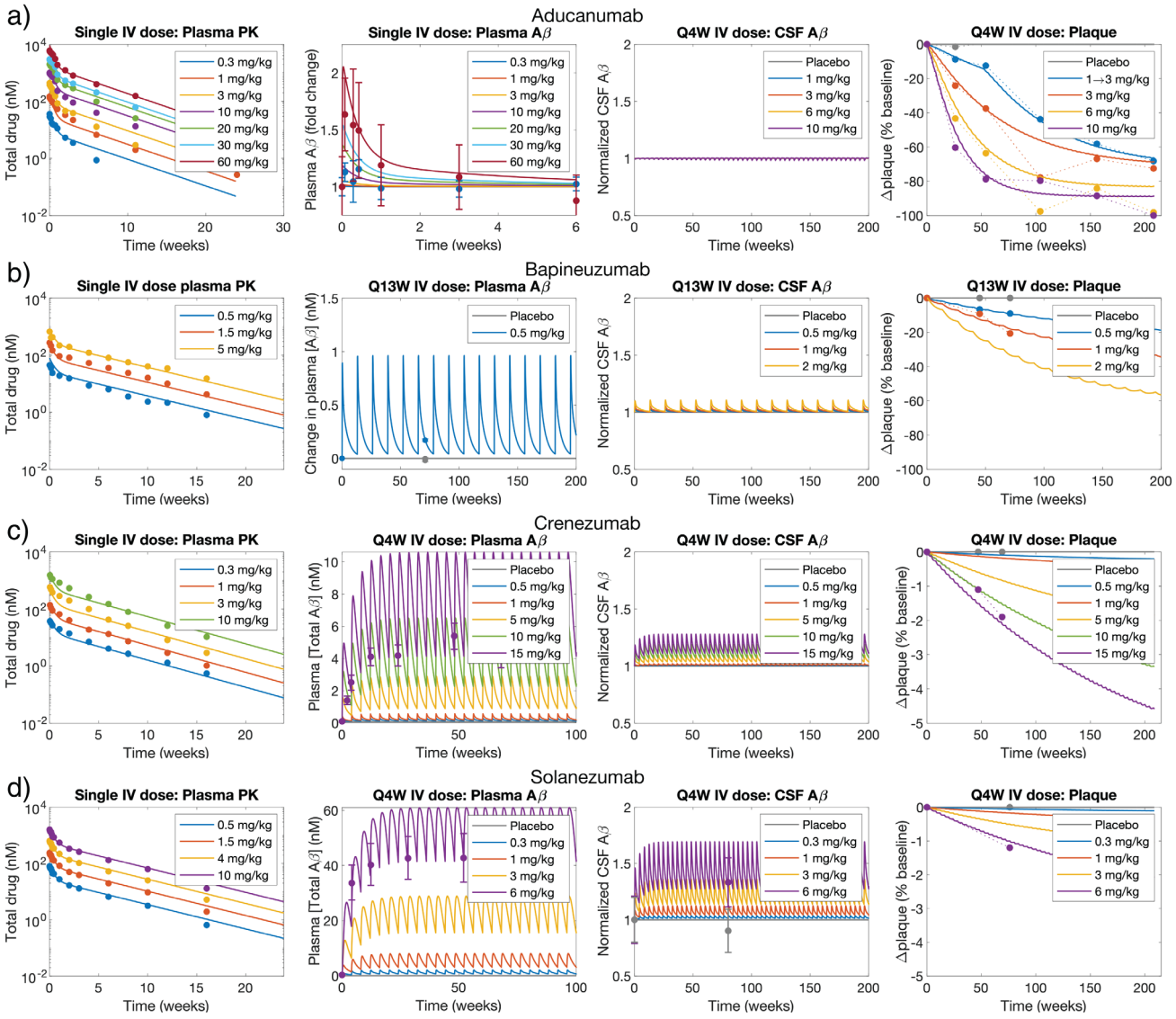

FIGURE 2 Model fitting results to clinical PK and PD data for anti-Aβ mAbs. (A) aducanumab, (B) bapineuzumab, (C) crenezumab, and (D) solanezumab. Closed circles are digitized clinical data (if data are available) and lines are model simulation. Dose levels are indicated in the legend and dosing regimen are indicated in the title of the plot. The duration of model simulations and scale of the plot was selected to best demonstrate the dynamics of the measured time course data. For plaque reduction, simulations were run for 200 weeks for all drugs. Aβ, amyloid beta; CSF, cerebrospinal fluid; IV, intravenous; mAbs, monoclonal antibodies; PD, pharmacodynamics; PK, pharmacokinetics

plasma levels because current drug development is not focused on γ-secretase inhibition as a mechanism of treating AD. Subsequently, the model prediction on plaque reduction for semagacestat was not compared to the SUVR data because the model is likely to overpredict the effect.

Overall, the model adequately captures the majority of PK and PD data for the seven compounds with the same underlying Aβ biology model. Total Aβ levels in circulation increase after dosing with anti-Aβ mAbs due to a slower clearance of drug–Aβ monomer and drug–Aβ oligomer complexes compared to unbound Aβ species. Total Aβ level in CSF is predicted to also increase with anti-Aβ mAbs treatment due to the slower transport rate of drug–Aβ monomer and drug–Aβ oligomer complexes from CSF to circulation. Small-molecule BACE and γ-secretase inhibitors lead to Aβ level decrease in both plasma and CSF due to inhibition of Aβ production in the brain and peripheral compartments. Among all seven drugs modeled, aducanumab had the greatest plaque reduction from baseline with clinically tested doses and dosing regimens. For aducanumab, the model a priori predicted the plaque reduction for the 1–3 mg/kg titration schedule. In addition, the aducanumab model predicts a dose-dependent effect on plaque reduction, with the 10 mg/kg dose leading to a faster and larger plaque reduction than the 6 mg/kg dose. Crenezumab and solanezumab were predicted to have < 5% plaque decrease from baseline after 200 weeks of treatment. Both elenbecestat and verubecestat are predicted to have reached near maximum BACE inhibition with the highest clinically tested doses. The model predicts that maximum BACE inhibition leads to near 60% plaque reduction after 4 years of treatment.

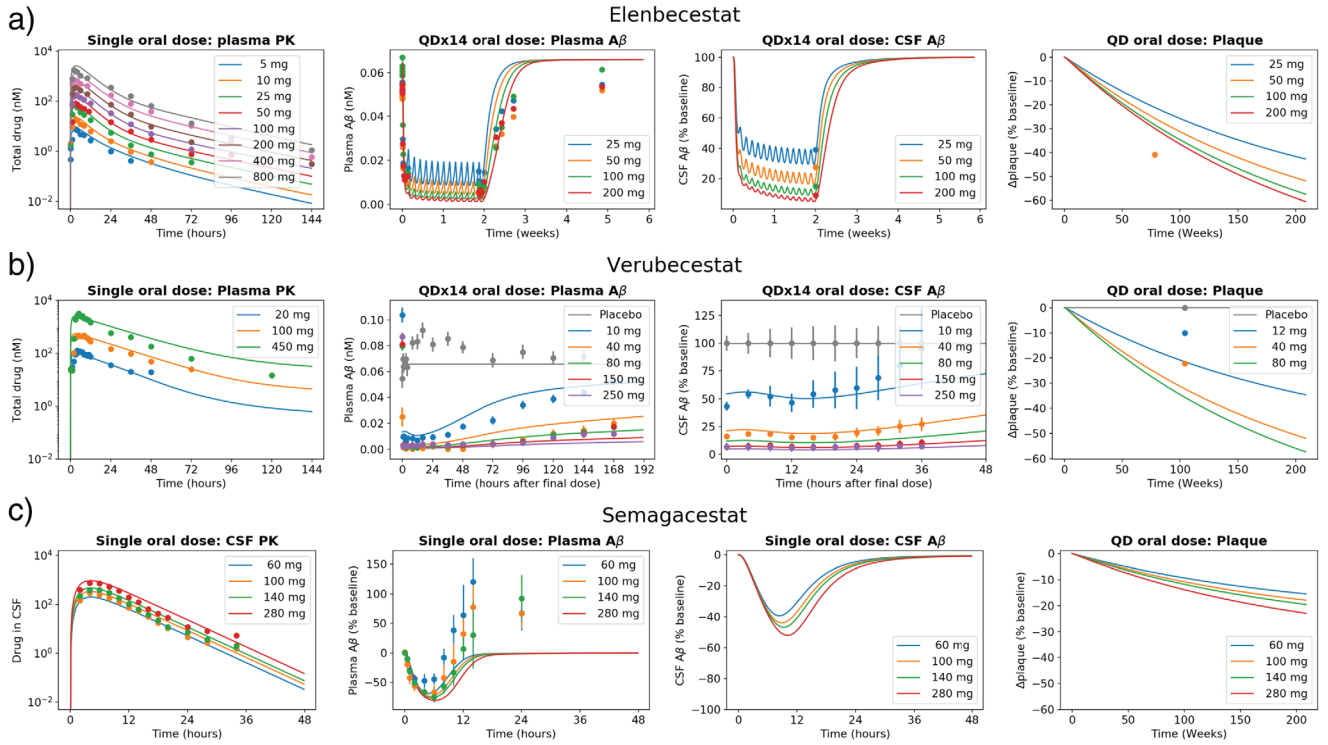

FIGURE 3 Model fitting results to clinical pharmacokinetics and pharmacodynamics data for small molecule inhibitors: (A) elenbecestat, (B) verubecestat, and (C) semagacestat. Closed circles are digitized clinical data (if data are available) and lines are model simulation. Dose levels are indicated in the legend and dosing regimen are indicated in the title of the plot. The duration of model simulations and scale of the plot was selected to best demonstrate the dynamics of the measured time course data. For plaque reduction, simulations were run for 200 weeks for all drugs. Aβ, amyloid beta; CSF, cerebrospinal fluid; IV, intravenous; mAbs, monoclonal antibodies; PD, pharmacodynamics; PK, pharmacokinetics

3.2 | Model comparison of anti-Aβ mAbs at the same dosing regimen

In clinical studies, the four anti-Aβ mAbs were tested at different doses as well as with different dosing frequencies. After model calibration to clinical data, model simulations were run to compare the effects of the four mAbs administered at the same dose and dosing frequency. In model simulations, all mAbs are given as IV Q4W for 4 years at dose levels ranging from 1 to 20 mg/kg. Model predictions of total drug concentration in plasma, total Aβ (both drug bound and unbound monomer and oligomer) in plasma and CSF and percent plaque reduction are shown in Figure 4. When mAbs are given at the same dose, all four antibodies have comparable exposure. Total Aβ increase in circulation is highest for solanezumab because it has the highest affinity for Aβ monomer, followed by bapineuzumab, which has the second highest affinity. The most pronounced plaque reduction is predicted for bapineuzumab and aducanumab. In phase 3 clinical trials for bapineuzumab, the highest dose tested is 2 mg/kg every 13 weeks. The dose was limited by amyloid-related imaging abnormalities (ARIA) safety events.[26] Our model prediction suggests that if higher doses can be administered safely, bapineuzumab treatment can lead to significant plaque reduction.

3.3 | Model comparison of plaque reduction with different anti-Aβ antibody binding profiles

The four anti-Aβ mAbs have different binding affinities to Aβ monomer, oligomer, and plaque (Table S4). To better understand which of these binding events are most critical for plaque reduction, we used the model to simulate hypothetical antibodies based on aducanumab; however, they solely bind to a single Aβ species, either monomer, oligomer, or plaque. For mAbs binding to oligomer or plaque, the model simulation also includes the ADCP-mediated clearance of the drug–Aβ complex. For mAbs binding to Aβ monomer, drug–Aβ complex is cleared out of the brain through transport mechanisms. For each simulation, binding K_d for one Aβ species was set to a non-zero value while association binding rate constant *kon* for the other two were set to zero. A range of binding K_ds and doses are tested for each of the binding mechanisms with IV dosing Q4W for four years (Figure 5). For a mAb solely binding to monomer, even with K_d in the subnanomolar range and at very high doses of 20 mg/kg, the model predicts that only up to 20% monomer is bound by drug; subsequently, the reduction in oligomer and plaque is minimal (Figure 5C and 5F). For a mAb solely binding to oligomer, greater than 80% reduction of oligomer is predicted for subnanomolar K_d and doses higher than 10 mg/kg

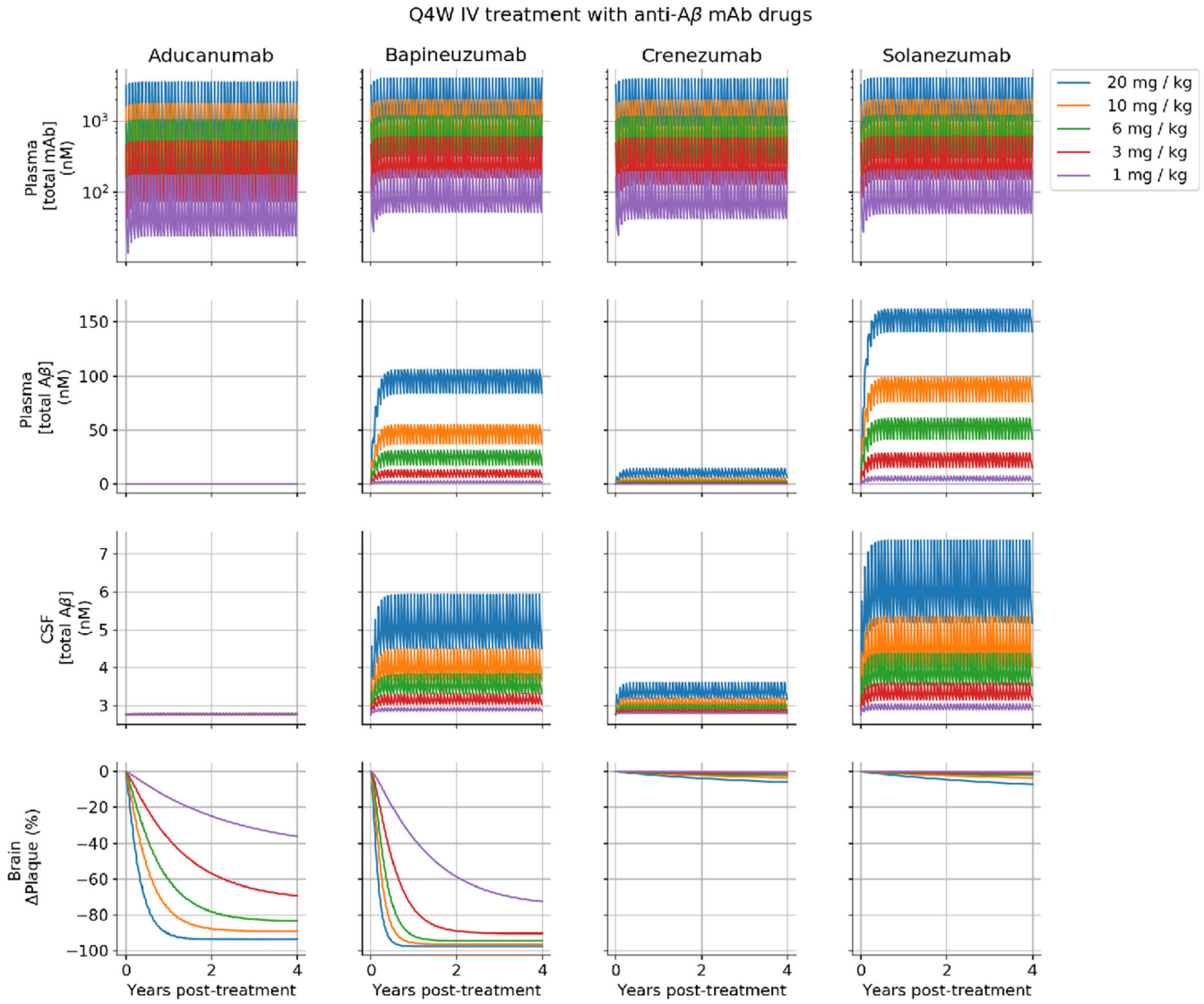

FIGURE 4 Model simulations of pharmacokinetics (PK) and pharmacodynamics (PD) with aducanumab, crenezumab, solanezumab, and bapineuzumab at the same doses and dosing regimen. All the antibodies are administered from 6 to 50 mg/kg intravenously every 4 weeks for 4 years. Plots show model simulated PK (top row), total Aβ in plasma (second row), total Aβ in CSF (third row), and percent plaque reduction from baseline (bottom row). Aβ, amyloid beta; CSF, cerebrospinal fluid; IV, intravenous; mAbs, monoclonal antibodies

(Figure 5E). In this scenario, the plaque reduction at the end of 4 years is predicted to be greater than 50% (Figure 5B). MAb binding to plaque with ADCP with a K_d of 10 nM induces near complete plaque elimination that is comparable to the effect of aducanumab at 10 mg/kg. The two-dimensional plot with mAb binding to plaque (Figure 5A) also suggests that with a tighter binding affinity to plaque, a lower dose is sufficient to achieve the same plaque reduction. Because administration of all the mAbs have been accompanied by ARIA as a side effect,[1] our model simulation results suggest that modification of aducanumab to achieve higher affinity plaque binding may reduce the dose needed to achieve desired plaque reduction while limiting ARIA safety events.

3.4 | Slow plaque turnover rate determines the plaque reduction rate for BACE inhibitors

To identify potential reasons why drugs that inhibit plaque formation (e.g., BACE inhibitor, mAbs binding to Aβ monomer or oligomer) are not as effective with regard to plaque reduction as drugs that directly induce plaque clearance, we analyzed our model to generate hypotheses. Slow plaque turnover rate was identified as a sensitive model parameter. As shown in Figure 6A, if endogenous plaque turnover rate is modified from a half-life of 10 years to 2.75 years or 1 year, the plaque reduction with 200 mg daily elenbecestat, which relies on endogenous plaque turnover for elimination, is predicted to be faster,

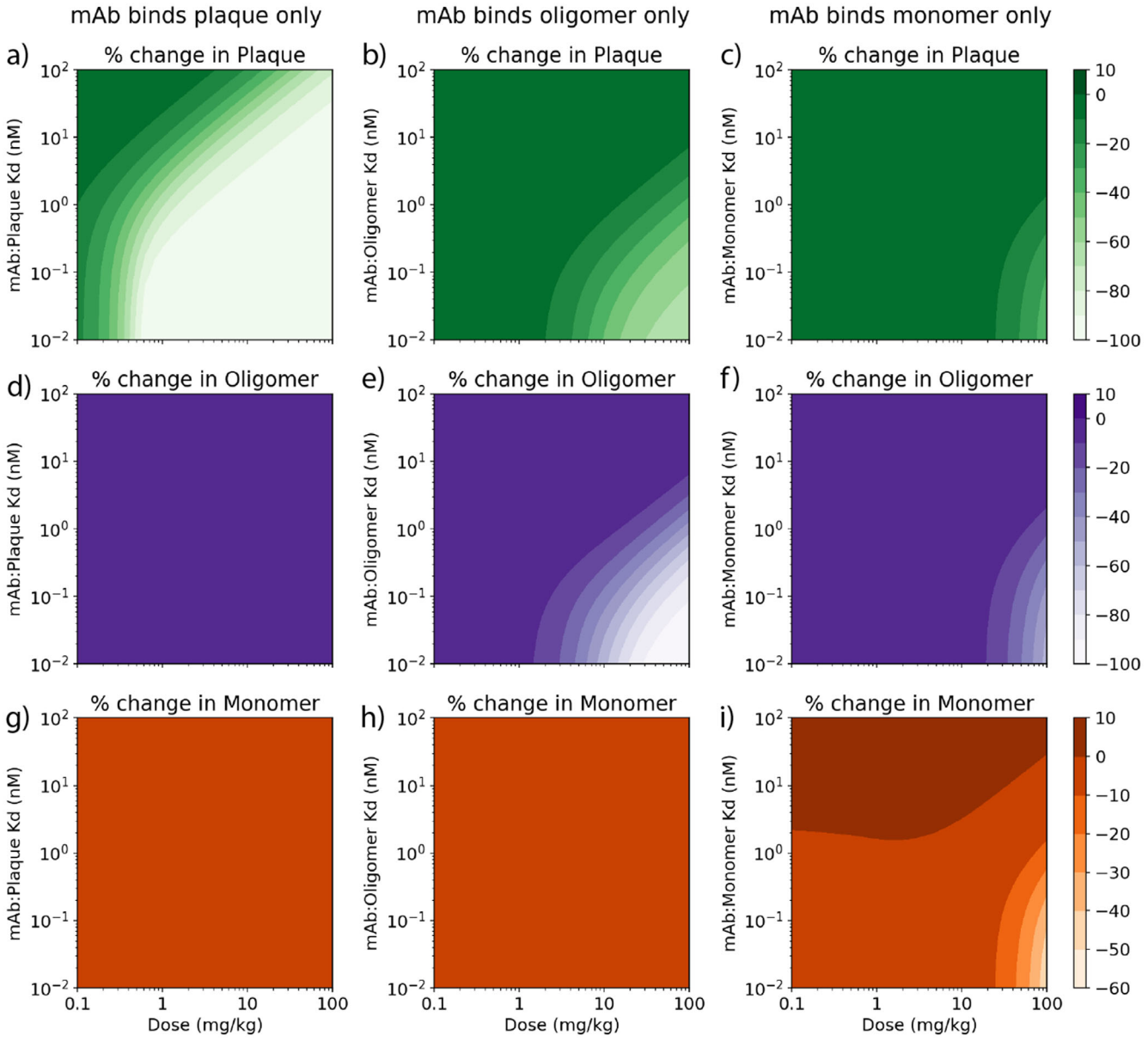

FIGURE 5 Impact of K_d and dose on plaque reduction with hypothetical antibodies binding to different Aβ species. Two-dimensional parameter scans of binding K_d and dose was performed with hypothetical antibodies only bind to Aβ plaque (A, D, G), oligomer (B, E, H), or monomer (C, F, I). Antibodies are administered as IV dosing every 4 weeks for a total of 4 years at various dose levels. The color on the plot represents percent plaque level change from baseline at the end of 4 years (A, B, C) or average percent free oligomer change from baseline during the last dosing period (D, E, F) or average percent free monomer change from baseline during the last dosing period. Aβ, amyloid beta; CSF, cerebrospinal fluid; IV, intravenous; mAbs, monoclonal antibodies

leading to higher percent plaque reduction at the end of 4 years. On the other hand, endogenous plaque turnover rate has a lesser effect on the rate of plaque reduction by aducanumab because plaque reduction is mostly driven by aducanumab binding to plaque and inducing ADCP.

3.5 | Model simulations do not support peripheral sink hypothesis

Testing of the peripheral sink hypothesis in a clinical trial has been limited by the potency of the available mAbs and the highest clinically feasible doses. Based on our model simulation (Figure 5I), greater than 50 mg/kg of mAb with subnanomolar potency for monomer is needed to maintain less than 40% free Aβ monomer from baseline. Our model predicts that the doses tested in the clinic for solanezumab do not lead to a sustained reduction in free Aβ monomer either in circulation or in brain ISF (Figure S2 in supporting information). This is consistent with the reported slight free Aβ reduction in CSF with solanezumab.[42] Using the model, we tested the sink hypothesis by artificially changing the Aβ clearance rate in circulation to be faster than nominal (by increasing the parameters *kclearAbeta_plasma* and *kclearAolig_plasma*) to allow quick removal of Aβ in plasma. As shown in Figure 6B, an increase of Aβ

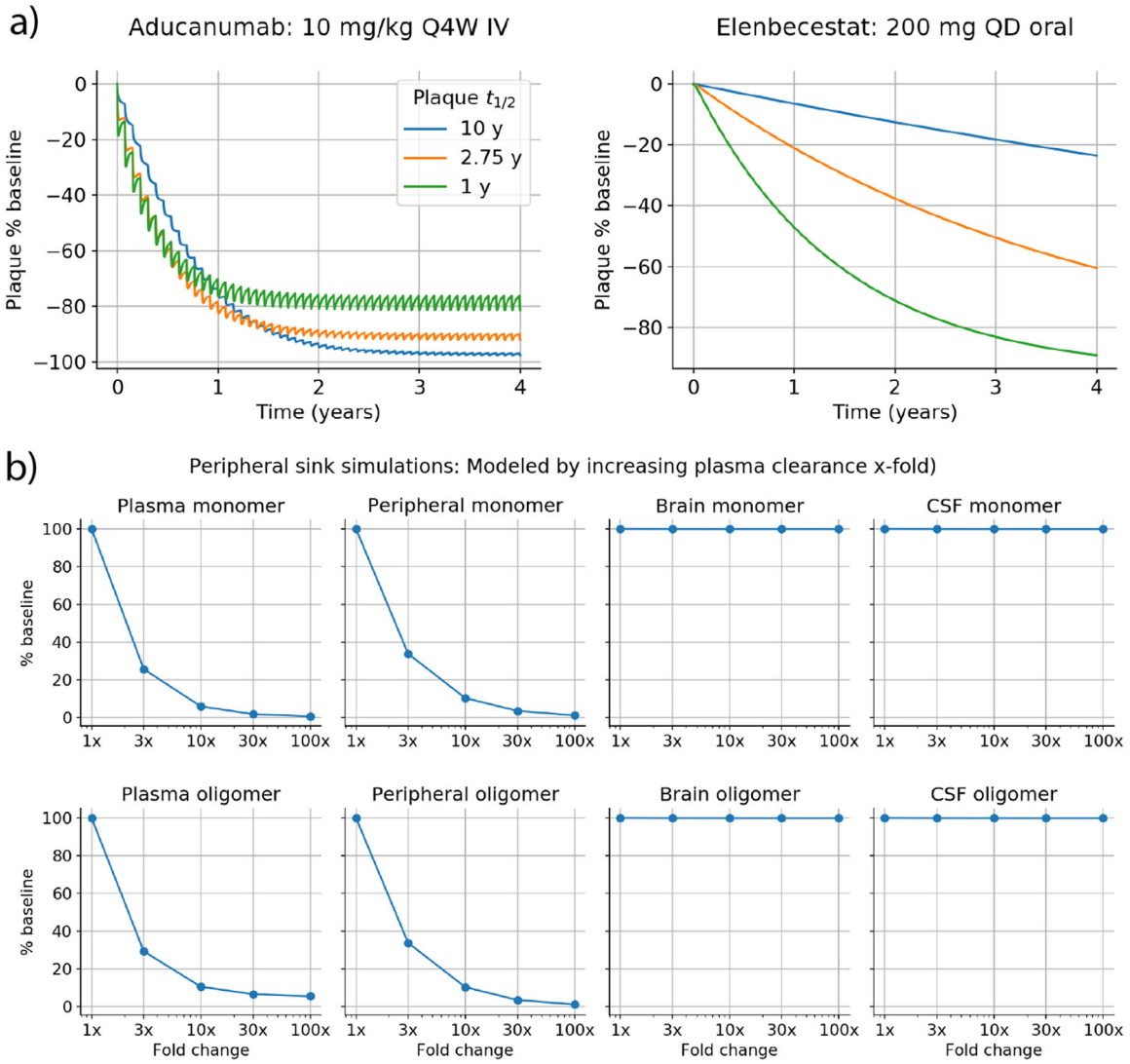

FIGURE 6 Model simulations to test the effect of endogenous plaque turnover on plaque reduction (A) and peripheral sink hypothesis (B). A, Model simulated plaque reduction with 4 years treatment of Q4W 10 mg/kg IV of aducanumab and oral daily 200 mg dose of elenbecestat with endogenous Aβ plaque turnover half-life at 1, 2.75, and 10 years. All other parameter values are unchanged for each simulation. B, Model simulations of Aβ monomer and oligomer reduction in circulation, peripheral, CSF, and ISF with varying intrinsic clearance rate of Aβ monomer and oligomer in circulation up to 100-fold of the nominal value. Aβ, amyloid beta; CSF, cerebrospinal fluid; ISF, interstitial fluid; IV, intravenous; mAbs, monoclonal antibodies

clearance rate leads to different levels of reduction of both Aβ monomer and oligomer in circulation as well as in the peripheral compartment. However, minimal changes of Aβ species in ISF and CSF are predicted. Consequently, plaque reduction is predicted to be negligible (data not shown). Therefore, our simulation results do not support the peripheral sink hypothesis.

4 | DISCUSSION

To better understand the causes of prior failure of clinical studies with various drugs targeting the Aβ pathway, and to provide guidance for future clinical development of AD therapies, we developed a single QSP model to analyze treatment effects of anti-Aβ antibodies, BACE, and γ-secretase inhibitors on Aβ monomer, oligomer, and plaque. The Aβ biology module matched available data for Aβ dynamics in CSF from SILK experiments. The drug pharmacology modules together with the Aβ biology module captured the available PK and PD data for seven drugs. Model analysis revealed that binding to plaque and the induction of active clearance of plaque, potentially through ADCP, could be the most effective approach to reduce amyloid plaque. The model predicted bapineuzumab and aducanumab to induce the fastest plaque reduction when given at the same dose and regimen among the four mAbs. Unfortunately, the clinically tested doses for bapineuzumab were not high enough to observe significant plaque reduction. The safety profile of bapineuzumab at the tested doses prevented its further dose escalation. For drugs aiming at preventing plaque formation (e.g., BACE inhibitors and mAbs binding to Aβ monomer and oligomer,

such as solanezumab), the reduction rate of existing plaque is limited by the endogenous turnover rate of plaque. The predicted slow speed of this process (half-life of ≈2.75 years), could explain the relatively small magnitude of plaque reduction observed with BACE inhibitors after 2 years of treatment. A shorter plaque turnover half-life of 1 year together with near complete inhibition of BACE with 200 mg elenbecestat could result in ≈90% plaque reduction after 4 years (Figure 6). Crenezumab is a IgG4 antibody that doesn't induce a strong ADCP effect. Therefore, even though it binds to plaque with relatively high affinity, not much plaque reduction is observed in clinical studies.

Model simulations described an increase in the rate and magnitude of plaque reduction with an aducanumab dose increase from 6 to 10 mg/kg for a nominal patient. Based on model simulation, the rate of plaque reduction could be further increased by doses higher than 10 mg/kg. However, due to the potential ARIA toxicity, higher doses have not been tested clinically.[24] The model was used to explore strategies for the development of future anti-Aβ mAbs to achieve greater plaque reduction at lower doses. The model predicts that either tighter drug binding to plaque (Figure 5A) and/or greater induction of ADCP (data not shown) will lead to an increased rate of plaque reduction, which could lead to a lower dose required for clinically relevant plaque reduction. This suggests that future generations of anti-Aβ mAb may be improved in two ways: increased drug binding affinity to plaque, and Fc region enhancement to increase ADCP.

The model is also used to test the "peripheral sink" hypothesis, which assumes that Aβ can be removed from the brain as a consequence of increased Aβ clearance in circulation. Our simulations suggest that removing Aβ from circulation does not change CSF Aβ levels because Aβ from circulation mostly originates from peripheral tissue and the transport rates of Aβ between plasma and ISF is slow. Our simulations are consistent with results in mice showing that blocking Aβ production with a BACE inhibitor that cannot penetrate into the brain does not reduce Aβ levels in CSF.[43]

A bigger question in the field is whether targeting plaque reduction is the right approach to improve cognitive function. Our model predicted that aducanumab at 10 mg/kg leads to significant plaque reduction. However, its effect on cognitive function improvement based on the latest clinical studies is still debatable. In addition, studies linking plaque levels as measured by PET-SUVR to cognition scores have consistently shown a weak but measurable relationship between the changes in plaque levels and cognition.[44,45] Combining our simulation results with clinical results suggests that targeting amyloid plaque alone may have modest clinical effects on the treatment of AD. In addition to plaque reduction, the model also predicts Aβ monomer and soluble oligomer reduction in ISF, which is difficult to measure experimentally. For elenbecestat and verubecestat, the model is predicting > 70% reduction of both monomer and oligomer in ISF at the phase 2 and 3 tested doses (Figures S3 and S4 in supporting information). However, given the lack of change in clinical endpoint, it suggests that targeting these soluble species will probably not be effective either.

Typical PK/PD models developed for a single drug cannot be used to compare effects of different drugs with different mechanisms of action. By including seven drugs with a range of mechanisms in our model calibration, while maintaining a single underlying biology model, this approach provides more constraints on model parameters and model structure, hence more confidence in model predictions. For example, the inclusion of semagacestat in this model critically informed model parameters related to γ-secretase dynamics and was therefore included despite the fact that development of γ-secretase inhibitors for AD was stopped 10 years ago. Earlier availability of clinical data for the drugs included here together with an earlier development of this platform model could have informed optimal clinical trial design and reduced clinical development costs eliminating trials predicted not to be successful. Moreover, a similar modeling exercise, performed preclinically, could have helped generate hypotheses and influenced critical thinking, even without the full dataset in the early development process (e.g., enabling lead generation).

The work presented here illustrates results from a "typical" AD patient. Comparison of SUVR values from different trials and using different tracers can be challenging. Therefore, this work is meant to capture the general trend of various treatments and is not meant to provide accurate predictions of PD changes for a given treatment. In future work, access to more clinical data will improve the accuracy of model predictions for each drug. In addition, access to individual patient clinical data will allow us to create virtual patients to capture between-patient variability, including effects of the apolipoprotein E genotype. The model can also be expanded in the future to connect the plaque change to clinical endpoints. Due to the current lack of understanding on how amyloid plaque buildup may contribute to cognitive function decline, this connection will be based on a data-driven approach in which we will derive an empirical relationship between plaque SUVR measurements and cognitive function scores through meta-analysis of multiple studies.

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CONFLICTS OF INTEREST

BTH has a family member works for Novartis, owns Novartis stock, also serves on scientific advisory boards for Biogen, Takeda, Novartis, Dewpoint, and Cell Signaling. His laboratory has a Sponsored research agreement with Abbvie.

All other authors declare that there are no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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