Supplemental material for:

Passive Immunotherapies Targeting Amyloid-β in Alzheimer's Disease: A Quantitative Systems Pharmacology Perspective

Molecular Pharmacology MOLPHARM-MR-2023-000726

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Supplemental Data

The ordinary differential equations (ODE) used in Drug A scenario, where a drug binds the Aβ monomer alone are as follows:

Mass of the Drug A in the Central compartment:

$$\frac{d(CENT)}{dt} = -\frac{CENT}{Vc} * CL - CENT * kcp + kpc * PER$$

Mass of Drug A in the Peripheral compartment:

$$\frac{d(PER)}{dt} = CENT * kcp - kpc * PER$$

Drug A concentration in the brain compartment:

$$\frac{d(D)}{dt} = -\frac{CENT}{Vc} * kpb - konDT * D * T + koffDT * DT - kbp * D$$

Monomer-drug A complex in the brain:

$$\frac{d(DT)}{dt} = konDT * D * T - \ koffDT * DT - keD * DT$$

Monomer concentration in the brain:

$$\frac{d(T)}{dt} = ksynT - \frac{RmaxTT * T}{KdTT + T} + \ koffTT * TT \ - konDT * D * T + koffDT * DT - keT * T$$

Dimer concentration in the brain:

$$\frac{d(TT)}{dt} = \frac{RmaxTT * T}{KdTT + T} - \ koffTT * TT \ - \frac{RmaxTTT * TT}{KdTTT + TT} + koffTTT * TTT$$

Tetramer concentration in the brain:

$$\frac{d(TTT)}{dt} = \frac{RmaxTTT * TT}{KdTTT + TT} - \ koffTTT * TTT \ - \frac{RmaxO * TTT}{KdO + TTT} + koffO * O$$

Oligomer concentration in the brain:

$$\frac{d(O)}{dt} = \frac{RmaxO * TTT}{KdO + TTT} - koffO * O - \frac{RmaxP * O}{KdP + O} + koffP * P$$

Protofibril concentration in the brain:

$$\frac{d(P)}{dt} = \frac{RmaxP * O}{KdP + O} - koffP * P - \frac{RmaxF * P}{KdF + P} + koffF * F$$

Fibril concentration in the brain:

$$\frac{d(F)}{dt} = \frac{RmaxF * P}{KdF + P} - koffF * F - \frac{RmaxA * F}{KdA + F} + koffA * A$$

Aggregated plaque concentration in the brain:

$$\frac{d(A)}{dt} = \frac{RmaxA * F}{KdA + F} - koffA * A$$

The ODEs used in Drug B scenario are similar to Drug A, but with additional ODEs for drug binding to all amyloid species, not just the monomer:

Mass of the Drug B in the Central compartment:

$$\frac{d(CENT)}{dt} = -\frac{CENT}{Vc} * CL - CENT * kcp + kpc * PER$$

Mass of Drug B in the Peripheral compartment:

$$\frac{d(PER)}{dt} = CENT * kcp - kpc * PER$$

Drug B concentration in the brain compartment:

$$\frac{d(D)}{dt} = -\frac{CENT}{Vc} * kpb - konDT * D * T + koffDT * DT - kbp * D - konDTT * D * TT + koffDTT * DTT - konDTTT * D * TTT + koffDTTT * DTTT - konDO * D * O + koffDO * DO - konDP * D * P + koffDP * DP - konDF * D * F + koffDF * DF - konDA * D * A + koffDA * DA$$

Monomer-Drug B complex in the brain:

$$\frac{d(DT)}{dt} = konDT * D * T - koffDT * DT - keD * DT$$

Monomer concentration in the brain:

$$\frac{d(T)}{dt} = ksynT - \frac{RmaxTT * T}{KdTT + T} + koffTT * TT - konDT * D * T + koffDT * DT - keT * T$$

Dimer concentration in the brain:

$$\frac{d(TT)}{dt} = \frac{RmaxTT * T}{KdTT + T} - koffTT * TT - \frac{RmaxTTT * TT}{KdTTT + TT} + koffTTT * TTT - konDTT * D * TT + koffDTT * DTT$$

Tetramer concentration in the brain:

$$\frac{d(TTT)}{dt} = \frac{RmaxTTT * TT}{KdTTT + TT} - koffTTT * TTT - \frac{RmaxO * TTT}{KdO + TTT} + koffTTT * TTT - konDTTT * D * TTT + koffDTTT * DTTT$$

Oligomer concentration in the brain:

$$\frac{d(O)}{dt} = \frac{RmaxO * TTT}{KdO + TTT} - koffO * O - \frac{RmaxP * O}{KdP + O} + koffP * P - konDO * D * O + koffDO * DO$$

Protofibril concentration in the brain:

$$\frac{d(P)}{dt} = \frac{RmaxP * O}{KdP + O} - koffP * P - \frac{RmaxF * P}{KdF + P} + koffF * F - konDP * D * P + koffDP * DP$$

Fibril concentration in the brain:

$$\frac{d(F)}{dt} = \frac{RmaxF * P}{KdF + P} - koffF * F - \frac{RmaxA * F}{KdA + F} + koffA * A - konDF * D * F + koffDF * DF$$

Aggregated plaque concentration in the brain:

$$\frac{d(A)}{dt} = \frac{RmaxA * F}{KdA + F} - koffA * A - konDA * D * A + koffDA * DA$$

Concentration of Drug B complex with dimer:

$$\frac{d(DTT)}{dt} = konDTT * D * TT - koffDTT * DTT$$

Concentration of Drug B complex with tetramer:

$$\frac{d(DTTT)}{dt} = konDTTT * D * TTT - koffDO * DO$$

Concentration of Drug B complex with oligomer:

$$\frac{d(DO)}{dt} = konDO * D * O - koffDO * DO$$

Concentration of Drug B complex with protofibril:

$$\frac{d(DP)}{dt} = konDP * D * P - koffDP * DP$$

Concentration of Drug B complex with fibril:

$$\frac{d(DF)}{dt} = konDF * D * F - koffDF * DF$$

Concentration of Drug B complex with aggregated plaque:

$$\frac{d(DA)}{dt} = konDA * D * A - koffDA * DA$$

The ODEs used for model building of Drug C are similar to those for Drug B, but without drug binding to the monomer, dimer, tetramer, oligomer.

Mass of the Drug C in the Central compartment:

$$\frac{d(CENT)}{dt} = -\frac{CENT}{Vc} * CL - CENT * kcp + kpc * PER$$

Mass of Drug C in the Peripheral compartment:

$$\frac{d(PER)}{dt} = CENT * kcp - kpc * PER$$

Drug C concentration in the brain compartment:

$$\frac{d(D)}{dt} = -\frac{CENT}{Vc} * kpb - kbp * D - konDP * D * P + koffDP * DP - konDF * D * F + koffDF * DF - konDA * D * A + koffDA * DA$$

Monomer concentration in the brain:

$$\frac{d(T)}{dt} = ksynT - \frac{RmaxTT * T}{KdTT + T} + koffTT * TT - keT * T$$

Dimer concentration in the brain:

$$\frac{d(TT)}{dt} = \frac{RmaxTT * T}{KdTT + T} - koffTT * TT - \frac{RmaxTTT * TT}{KdTTT + TT} + koffTTT * TTT$$

Tetramer concentration in the brain:

$$\frac{d(TTT)}{dt} = \frac{RmaxTTT * TT}{KdTTT + TT} - koffTTT * TTT - \frac{RmaxO * TTT}{KdO + TTT} + koffO * O$$

Oligomer concentration in the brain:

$$\frac{d(O)}{dt} = \frac{RmaxO * TTT}{KdO + TTT} - koffO * O - \frac{RmaxP * O}{KdP + O} + koffP * P$$

Protofibril concentration in the brain:

$$\frac{d(P)}{dt} = \frac{RmaxP * O}{KdP + O} - koffP * P - \frac{RmaxF * P}{KdF + P} + koffF * F - konDP * D * P + koffDP * DP$$

Fibril concentration in the brain:

$$\frac{d(F)}{dt} = \frac{RmaxF * P}{KdF + P} - koffF * F - \frac{RmaxA * F}{KdA + F} + koffA * A - konDF * D * F + koffDF * DF$$

Aggregated plaque concentration in the brain:

$$\frac{d(A)}{dt} = \frac{RmaxA * F}{KdA + F} - koffA * A - konDA * D * A + koffDA * DA$$

Concentration of Drug C complex with protofibril:

$$\frac{d(DP)}{dt} = konDP * D * P - koffDP * DP$$

Concentration of Drug C complex with fibril:

$$\frac{d(DF)}{dt} = konDF * D * F - koffDF * DF$$

Concentration of Drug C complex with aggregated plaque:

$$\frac{d(DA)}{dt} = konDA * D * A - koffDA * DA$$

The ODEs used for model building of Drug D also include an effector function:

Mass of the Drug D in the Central compartment:

$$\frac{d(CENT)}{dt} = -\frac{CENT}{Vc} * CL - CENT * kcp + kpc * PER$$

Mass of Drug D in the Peripheral compartment:

$$\frac{d(PER)}{dt} = CENT * kcp - kpc * PER$$

Drug D concentration in the brain compartment:

$$\frac{d(D)}{dt} = -\frac{CENT}{Vc} * kpb - kbp * D - konDP * D * P + koffDP * DP - konDF * D * F + koffDF * DF - konDA * D * A + koffDA * DA$$

Monomer concentration in the brain:

$$\frac{d(T)}{dt} = ksynT - \frac{RmaxTT * T}{KdTT + T} + koffTT * TT - keT * T$$

Dimer concentration in the brain:

$$\frac{d(TT)}{dt} = \frac{RmaxTT * T}{KdTT + T} - koffTT * TT - \frac{RmaxTTT * TT}{KdTTT + TT} + koffTTT * TTT$$

Tetramer concentration in the brain:

$$\frac{d(TTT)}{dt} = \frac{RmaxTTT * TT}{KdTTT + TT} - koffTTT * TTT - \frac{RmaxO * TTT}{KdO + TTT} + koffO * O$$

Oligomer concentration in the brain:

$$\frac{d(O)}{dt} = \frac{RmaxO * TTT}{KdO + TTT} - koffO * O - \frac{RmaxP * O}{KdP + O} + koffP * P$$

Protofibril concentration in the brain:

$$\frac{d(P)}{dt} = \frac{RmaxP * O}{KdP + O} - koffP * P - \frac{RmaxF * P}{KdF + P} + koffF * F - konDP * D * P + koffDP * DP$$

Fibril concentration in the brain:

$$\frac{d(F)}{dt} = \frac{RmaxF * P}{KdF + P} - koffF * F - \frac{RmaxA * F}{KdA + F} + koffA * A - konDF * D * F + koffDF * DF$$

Aggregated plaque concentration in the brain:

$$\frac{d(A)}{dt} = \frac{RmaxA * F}{KdA + F} - koffA * A - konDA * D * A + koffDA * DA$$

Concentration of Drug D complex with protofibril:

$$\frac{d(DP)}{dt} = konDP * D * P - koffDP * DP - keDP * DP$$

Concentration of Drug D complex with fibril:

$$\frac{d(DF)}{dt} = konDF * D * F - koffDF * DF - keDF * DF$$

Concentration of Drug D complex with aggregated plaque:

$$\frac{d(DA)}{dt} = konDA * D * A - koffDA * DA - keDA * DA$$

Supplemental Tables

Table 1. Antibody affinity towards different amyloid species

Antibody affinity towards amyloid species [nM]							
Amyloid species	**Parameter name**	**Aducanumab**	**Bapineuzumab**	**Crenezumab**	**Gantenerumab**	**Lecanemab**	**Solanezumab**
Monomer	KdDT	7300 [1]	6.97 [2]	4 [3]	1300 [1]	2300 [1]	0.6 [2]
Oligomer	KdO	2.23 [2]	6.97 [2]	0.5 [3]	1.2 [4]	67.3 [2]	20000 [2]
Protofibril	KdP	0.79 [1]	0.09 [2]	14.4 [2]	2.50 [1]	0.16 [1]	20000 [2]
Fibril	KdF	3.3 [1]	0.2 [2][b]	20000 [2][b]	0.69 [4]	1.8 [1]	20000 [2]
Plaque	KdA	3.3 [1][a]	0.2 [2]	20000 [2]	0.69 [4][a]	1.8 [1][a]	20000 [2]

[a] assumed same as fibril

[b] assumed same as plaque

Table 2. Physiological parameters and parameters for non-linear amyloid aggregation cascade

	Definition	Value	Unit	Reference
T_0	Monomer initial state	0.75	nM	[5]
TT_0	Dimer initial state	1	nM*	Assumed
TTT_0	Tetramer initial state	1	nM*	Assumed
O_0	Oligomer initial state	1	nM*	Assumed
P_0	Protofibril initial state	1	nM*	Assumed
F_0	Fibril initial state	1	nM*	Assumed
A_0	Plaque initial state	1	nM*	Assumed
k_eT	Monomer elimination rate	0.05	1/h	[6]
$k_{syn}T$	Monomer synthesis rate	ksyn= T_0*keT = 0.0375	1/h	Calculated
$R_{max}T$	the maximum rate achieved by the system	0.00002	nM/h	Optimized using natural disease progression
K_dT	the constant equal to Aβ species at which the R_{max} is at half-maximum	0.05	nM	Optimized using natural disease progression
k_{offTT}	the first-order rate constant for the Aβ dimer dissociation	0.000005	1/h	Assumed
k_{offTTT}	the first-order rate constant for the Aβ tetramer dissociation	$0.1\cdot k_{offTT}$	1/h	Assumed
k_{offO}	the first-order rate constant for the Aβ oligomer dissociation	$0.1\cdot k_{offTTT}$	1/h	Assumed
k_{offP}	the first-order rate constant for the Aβ protofibil dissociation	$0.1\cdot k_{offO}$	1/h	Assumed
k_{offF}	the first-order rate constant for the Aβ fibril dissociation	$0.1\cdot k_{offP}$	1/h	Assumed
k_{offA}	the first-order rate constant for the Aβ aggregate dissociation	$0.1\cdot k_{offA}$	1/h	Assumed
Y	$R_{max\_higher\_species}=Y*R_{max\_lower\_species}$	0.675	Unitless	Optimized using natural disease progression
Z	$K_{dhigher\_species}=Z*K_{d\_lower\_species}$	1	Unitless	Optimized using natural disease progression

*Initial concentrations were assumed to be 1 nM due to high variability in literature sources [7–9], as well as in initial values used in previously developer QSP models [2,5,10]. If more data becomes available, adjusting the Y and Z can be used to re-calibrate the model further.

Table 3. Antibody molecular weight used to calculate dose

Antibody	Molecular weight (g/mol)
Aducanumab	145912.34
Bapineuzumab	145871.99
Crenezumab	144884.91
Gantenerumab	146274.65
Lecanemab	147181.62
Solanezumab	144082.24

Table 4. PK parameters used in model validation

Antibody	References for the clinical PK data used	CL, Clearance (L/h)	Vc, Central Volume (L)	Vp, Periferal Volume (L)	Optimized against plasma data (Phoenix WinNonlin™)
Aducanumab	[11]	0.035	6.3	10.5	
Bapineuzumab	[12]	0.018	8.6	6.2	
Crenezumab	[13]	14.71	1.54	0.008	
Gantenerumab	[14]	0.029	14.8	5.3	
Lecanemab	[15]	0.002	2.5	0.9	
Solanezumab	[16]	0.009	3.0	4.4	

Table 5. PD endpoint used in model validation

Antibody	References for the clinical PET SUVR data	Unit
Aducanumab	[17–19]	relative to baseline
Bapineuzumab	[20,21]	relative to baseline
Crenezumab	[22]	relative to baseline
Gantenerumab	[23]	relative to baseline
Lecanemab	[24]	relative to baseline
Solanezumab	[25,26]	relative to baseline

Table 6. Parameters used in the simulation of Drug A, B, C and D scenario

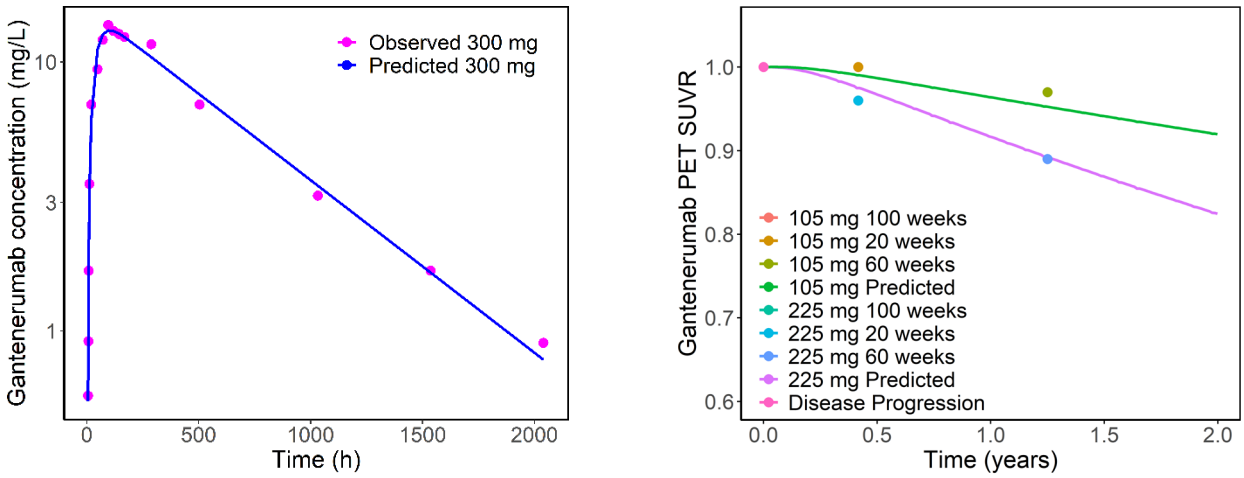
Parameter	Definition	Drug	Value	Unit	Reference
kpb	Plasma to brain distribution rate	A-D	1	1/h	Assumed
kbp	brain to plasma distribution rate		kpb*1000	1/h	to account for the exposure of 0.1 % of total antibody in the brain [27]
keDO	Constant of antibody-oligomer elimination through ADCP	D	0.000001	1/h	Manually adjusted
keDP	Constant of antibody-protofibril elimination through ADCP	D	0.000001	1/h	Manually adjusted
keDF	Constant of antibody-fibril elimination through ADCP	D	0.000001		Manually adjusted
keDA	Constant of antibody-plaque elimination through ADCP	D	0.000001		Manually adjusted
k_{on}DT	Drug-monomer binding rate constant	A, B	3.96	1/nM*h	[5]
k_{on}DTT	Drug-dimer binding rate constant	B	0.001	1/nM*h	Assumed for hypothetical drug
k_{on}DTTT	Drug-tetramer binding rate constant	B	0.001	1/nM*h	Assumed for hypothetical drug
k_{on}DO	Drug-oligomer binding rate constant	B-D	0.001	1/nM*h	Assumed for hypothetical drug

$k_{on}DP$	Drug-protofibril binding rate constant	B-D	0.001	1/nM*h	Assumed for hypothetical drug
$k_{on}DF$	Drug-fibril binding rate constant	B-D	0.001	1/nM*h	Assumed for hypothetical drug
$k_{on}DA$	Drug-plaque binding rate constant	B-D	0.001	1/nM*h	Assumed for hypothetical drug
$k_{off}DTT$	Drug-dimer unbinding rate constant	B	0.001	1/h	Assumed for hypothetical drug (faster than higher species)
$k_{off}DTTT$	Drug-tetramer unbinding rate constant	B	0.001	1/h	Assumed for hypothetical drug (faster than higher species)
$k_{off}DO$	Drug-oligomer unbinding rate constant	B-D	0.001	1/h	Assumed for hypothetical drug (faster than higher species)
$k_{off}DP$	Drug-protofibril unbinding rate constant	B-D	0.00001	1/h	Assumed for hypothetical drug
$k_{off}DF$	Drug-fibril unbinding rate constant	B-D	0.00001	1/h	Assumed for hypothetical drug
$k_{off}DA$	Drug-plaque unbinding rate constant	B-D	0.00001	1/h	Assumed for hypothetical drug

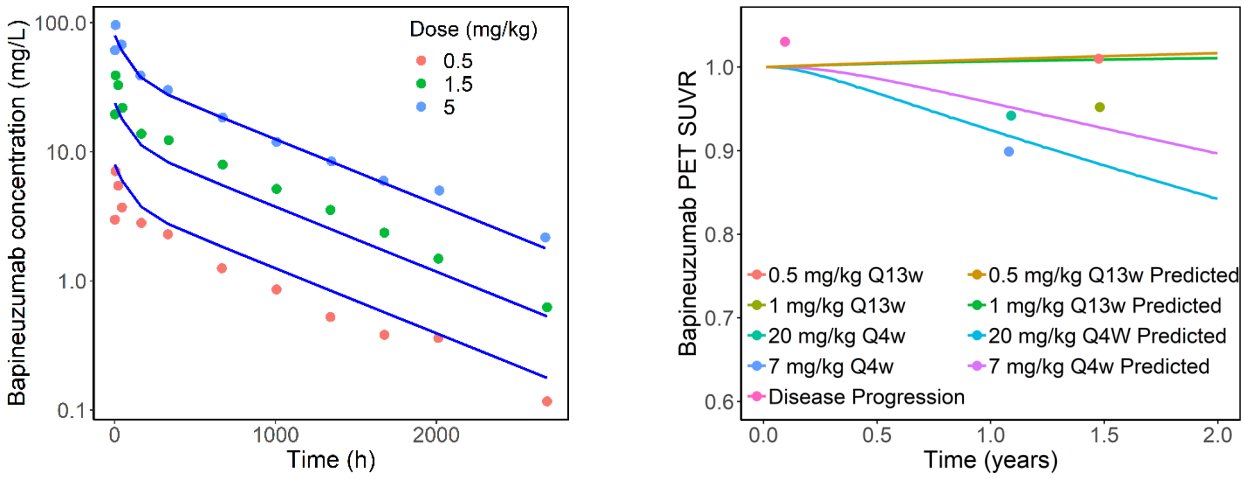
Volume of brain interstitial fluid was assumed to be constant for all cases 0.25 L. This is derived from the fact that 15-20 % of 1130cm^3 (1.13 L) for women, and slightly higher for men is ~0.25 L [28,29].

Supplemental Figures

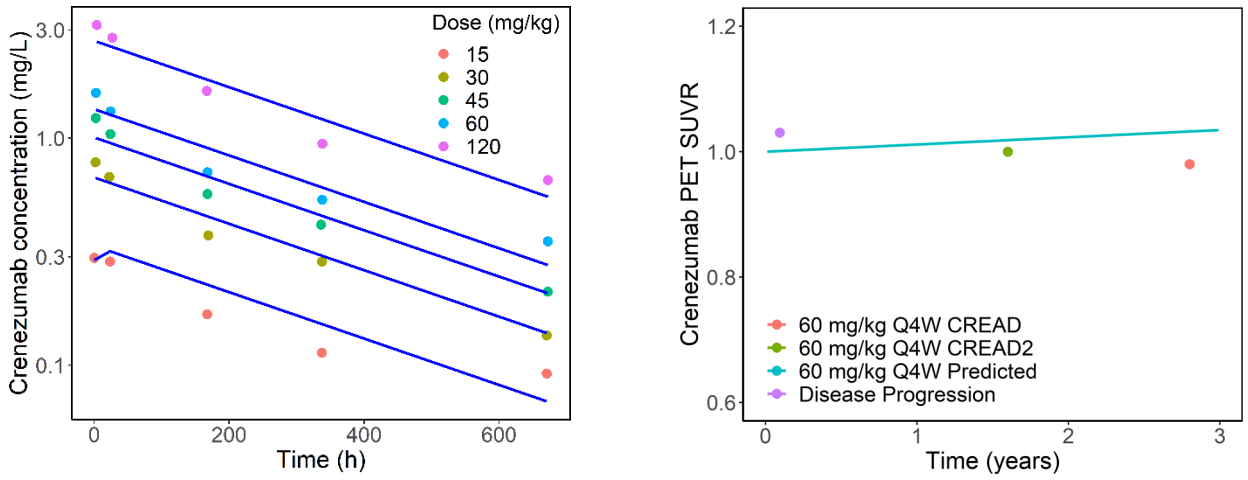
PK/PD relationship of 4 remaining antibodies used for model validation is presented in Supplementary Figures 1-4:



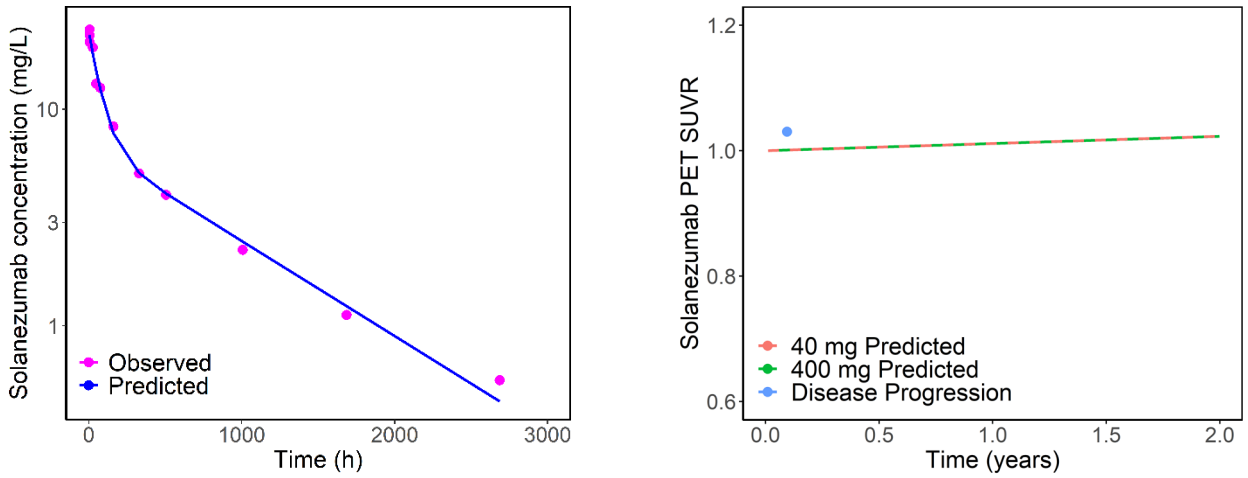
Supp. Fig. 1. Observed vs. Predicted values for Gantenerumab PK (left panel) and changes in the amyloid PET SUVR (right panel).



Supp. Fig. 2. Observed vs. Predicted values for Bapineuzumab PK (left panel) and changes in the amyloid PET SUVR (right panel).



Supp. Fig. 3. Observed vs. Predicted values for Crenezumab PK (left panel) and changes in the amyloid PET SUVR (right panel).



Supp. Fig. 4. Observed dose/weight-normalized solanezumab concentration (after single doses of 0.5, 1.5, 4 and 10 mg/kg) vs. Predicted (1 mg/kg dose) values for PK (left panel) and changes in the amyloid PET SUVR (right panel).

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