Population Pharmacokinetics and Exposure-Response Analyses of Amyloid PET SUVr and Plasma Biomarkers Aβ42/40 ratio and p-tau181 for Lecanemab in Subjects with Early Alzheimer's Disease

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Introduction

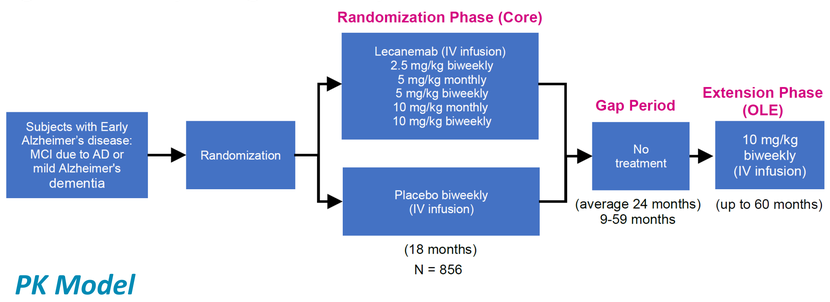
- Lecanemab (BAN2401) is a humanized IgG1 monoclonal antibody that preferentially targets soluble aggregated Aβ species (protofibrils) with activity at insoluble fibrils.
- Changes in amyloid plaques are assessed by amyloid positron emission tomography (PET), a well-established imaging biomarker to visualize brain amyloid load for Alzheimer's disease (AD). Changes in plasma biomarkers such as Aβ42/40 ratio and phosphorylated-tau181 (p-tau181) are potential surrogate markers for amyloid reduction.
- The objective of this analysis was to describe the population pharmacokinetics (PK) and exposure-response (E-R) relationship for change in amyloid plaques, as measured using PET, and plasma biomarkers of amyloid pathology as evidenced by changes in plasma Aβ42/40 ratio and p-tau181 following IV administration of lecanemab in subjects with early Alzheimer's disease (EAD).

Methods

Clinical Study

- Phase 2 Study 201 Core was an 18-month, double-blind, placebo-controlled study evaluating 5 lecanemab dosing regimens and placebo in patients with EAD (mild cognitive impairment [MCI] due to AD or mild AD dementia).[1)] Study 201 open-label extension (OLE) was initiated following completion and analysis of the Core double-blind treatment period to allow patients to receive open-label lecanemab 10 mg/kg-biweekly for up to 60 months. There was a gap period of average 24 months (9-59 months) without treatment between the last dose in the Core Study and the first dose in the OLE Phase (Figure 1).

Figure 1. Study Design of Study 201 Core and OLE



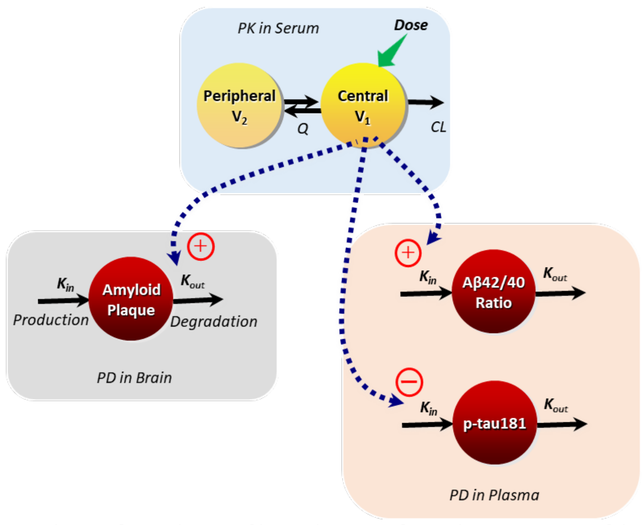
PK Model

- A 2-compartment linear model parameterized for clearance (CL), volumes of distribution of the central (V1) and peripheral (V2) compartments and inter-compartmental clearance (Q) was fit to pooled data from two Phase 1 studies and Study 201 Core and OLE.
- Evaluated covariates were: sex, age, race, body weight (BW), albumin and *APOE4* carrier status. Effect of anti-drug antibody (ADA) status as a categorical time-variant covariate and ADA titer as a continuous time-variant covariate on CL were also evaluated.

Exposure-Response Model

- E-R analyses for amyloid PET standard uptake ratio (SUVr) and plasma Aβ42/40 ratio and p-tau181 were performed on data from subjects with EAD receiving either lecanemab or placebo who participated in Study 201 Core and OLE. Time course of amyloid PET SUVr and plasma Aβ42/40 ratio and p-tau181 were described using indirect response models. Structures and equations of the models are shown in Figure 2.
- Covariates tested were BW, sex, *APOE4* carrier status, AD diagnosis (MCI or mild AD-D), ADA and neutralizing ADA (NAb) at subject level.

Figure 2. Schematic of PK and E-R Models for Lecanemab



K_{in} = zero-order rate for production of biomarker; K_{out} = first-order rate constant of degradation of biomarker; The equation for SUVr model is presented below:

$$\frac{dSUVr}{dt} = K_{in} - SUVr(t) \cdot K_{out} \cdot \left[1 + \frac{E_{max} \cdot Conc}{EC_{50} + Conc}\right]$$

Estimated parameters included baseline SUVr, K_{in}, maximum exposure effect (E_{max}) and lecanemab concentration resulting in half of the maximum drug effect (EC_{50}), where $K_{out} = K_{in}$/baseline.
The equations for Aβ42/40 ratio and p-tau181 models are presented below:

$$\textbf{Aβ42/40 ratio}: \frac{dR}{dt} = K_{in} \cdot [1 + Slope \cdot Conc] - R(t) \cdot K_{out}$$

$$\textbf{p-tau181}: \frac{dR}{dt} = K_{in} \cdot [1 - Slope \cdot Conc] - R(t) \cdot K_{out}$$

For both Aβ42/40 ratio and p-tau181 estimated parameters included baseline, K_{out} and slope for exposure effect, where $K_{in} = K_{out}$*baseline.

Covariate Testing

- Covariates were tested using a stepwise approach. Univariate analysis was performed first for the effect of each covariate at a significance level of α = 0.01. Subsequently, significant covariates were pooled in a full multivariate model which was followed by backward elimination at a significance level of α = 0.001.

Modeling Software

- Population PK and E-R analyses were conducted using the first-order conditional estimation with interaction method as implemented in the NONMEM software system (version 7.4.3). R software (version 4.0.3) was used for the graphical visualization and simulations.

Model Evaluation

- Final population PK and E-R models were evaluated for performance using goodness-of-fit plots, simulated prediction-corrected visual predictive checks (pcVPC) and non-parametric bootstrapping.

Simulations to Explore the Maintenance Dosing Regimens

- To explore the impact of potential maintenance dosing regimens, time profiles of biomarkers were simulated for the following 4 dosing scenarios:

(1) 10 mg/kg bi-weekly (Q2W) for 42 months
(2) 10 mg/kg Q2W for 18 months, followed by 24 months treatment discontinuation
(3) 10 mg/kg Q2W for 18 months, followed by 10 mg/kg monthly for 24 months
(4) 10 mg/kg Q2W for 18 months, followed by 10 mg/kg every 3 months for 24 months.

Results

PK Outcomes

- PK dataset included 9027 serum lecanemab observations, from 725 subjects.
- Lecanemab PK profiles were well described by a 2-compartment model with linear elimination. Final PK model contained covariate effects of ADA positive status, sex, body weight and albumin on CL and sex, body weight on V1 and Japanese on V2. The final population PK parameter estimates are presented in Table 1.

Table 1. Parameter Estimates and Bootstrap Confidence Intervals for Final Lecanemab PK Model

Parameter	Estimate	%RSE	Bootstrap Median (95% CI)
Clearance: CL			
Basal CL (L/h)	0.0181	2.55	0.0181 (0.0175 – 0.0188)
Effect of sex on CL (ratio)	0.792	3.43	0.790 (0.735 – 0.825)
Effect of BW on CL (exponent)	0.403	9.73	0.393 (0.217 – 0.495)
Effect of albumin on CL (exponent)	-0.243	17.2	-0.237 (-0.405 – -0.0771)
Effect of ADA on CL (ratio)	1.09	0.586	1.09 (1.05 – 1.12)
Central volume of distribution: V1			
Basal V1 (L)	3.22	1.18	3.22 (3.15 – 3.28)
Effect of BW on V1 (exponent)	0.606	7.52	0.603 (0.548 – 0.663)
Effect of sex on V1 (ratio)	0.893	1.75	0.893 (0.870 – 0.919)
Inter-compartment Clearance: Q			
Basal Q (L/h)	0.0349	8.02	0.0349 (0.0294 – 0.0396)
Peripheral volume of distribution: V2			
Basal V2 (L)	2.19	7.21	2.20 (2.00 – 2.40)
Effect of Japanese on V2 (ratio)	0.455	24.4	0.450 (0.338 – 0.583)
Relative bioavailability (F1)*	0.998	4.07	0.999 (0.950 – 1.06)
Inter-individual variability (%CV)			
CL	38.9	6.69	38.9 (36.7 – 40.4)
V1	14.0	8.38	14.0 (12.7 – 15.1)
V2	99.5	7.91	99.8 (84.4 – 109)
F	34.2	17.7	34.1 (28.7 – 37.4)
Residual variability			
Proportional Study 101 (%CV)	14.0	3.49	14.0 (12.6 – 15.1)
Proportional Study 104 (%CV)	19.7	4.66	19.6 (16.9 – 22.1)
Proportional Study 201 (%CV)	30.3	0.803	30.2 (28.7 – 31.2)

Abbreviations: %RSE=percent relative standard error of the estimate = SE/parameter estimate * 100; ADA= anti-drug antibody; BW=body weight; CL=clearance; V1=central volume of distribution; Q=inter-compartment clearance; V2= peripheral volume of distribution; CI = confidence interval; CV% = Square root of variance *100. * F = relative bioavailability of the formulation used in the Study 201 OLE to the formulation used in Study 201 Core and earlier studies;
Eta shrinkage (%): ETA_CL: 9.96%; ETA_V1: 30.5%; ETA_V2: 31.7%; ETA_F1: 63.2%

Exposure-Response Outcomes

- Amyloid PET SUVr E-R dataset included 1213 observations from 374 subjects from Study 201 Core and OLE.
- There was a total of 1254 observations from 284 subjects in the plasma Aβ42/40 ratio dataset and a total of 2021 observations from 562 subjects in the plasma p-tau181 dataset, both from Study 201 Core and OLE.
- Parameter estimates for the final model PET SUVr are presented in Table 2. Covariates in the SUVr model indicate that *APOE4* carrier subjects have higher baseline SUVr, and older subjects have higher maximum plaque removal (E_{max}) by lecanemab.
- Based on E-R analysis for amyloid PET SUVr, the population estimate of K_{out} (=K_{in}/Baseline PET SUVr) is 0.173/year and thus the degradation half-life is estimated to be approximately 4 years, suggesting that it will take approximately 16-20 years for amyloid to re-accumulate and return to its value prior to treatment initiation with lecanemab.
- Parameter estimates for the final models for plasma Aβ42/40 ratio and p-tau181 are presented in Table 3. The half-life of plasma Aβ42/40 ratio is estimated to be approximately 1.9 years which is comparable to that for plasma p-tau181 (approximately 1.5 years) but shorter than that for amyloid PET SUVr.

Table 2. Parameter Estimates and Bootstrap Confidence Intervals for Final E-R Model for Amyloid PET SUVr

Parameter	Estimate	%RSE	Bootstrap Median (95% CI)
Baseline PET SUVr	1.34	0.873	1.34 (1.31 – 1.38)
Effect of *APOE4* carrier on Baseline (ratio)	1.04	1.04	1.04 (1.02 – 1.07)
K_{in} (/year)	0.232	11.1	0.232 (0.174 – 0.277)
E_{max}	1.54	11.8	1.56 (1.10 – 2.01)
Effect of age on E_{max} (exponent)	1.58	20.9	1.60 (0.972 – 2.07)
EC_{50} (ug/mL)	75.0	19.6	77.1 (38.5 – 121)
Inter-individual variability (%CV)			
Baseline	10.9	8.12	11.0 (9.79 – 11.9)
Correlation Baseline ~ E_{max} (R)	0.669	11.5	0.674 (0.556 – 0.713)
E_{max}	50.3	12.0	50.8 (42.1 – 59.7)
Residual variability			
Proportional (%CV)	5.01	2.75	5.02 (4.48 – 5.59)

Abbreviations: E_{max} = maximum drug effect; EC_{50} = lecanemab concentration at which 50% of maximum drug effect is achieved; K_{in} = rate of production;
Eta shrinkage (%): ETA_Baseline: 6.94%; ETA_E_{max}: 27.7%

Table 3. Parameter Estimates and Bootstrap Confidence Intervals for Final E-R Models for Plasma Aβ42/40 Ratio and p-tau181

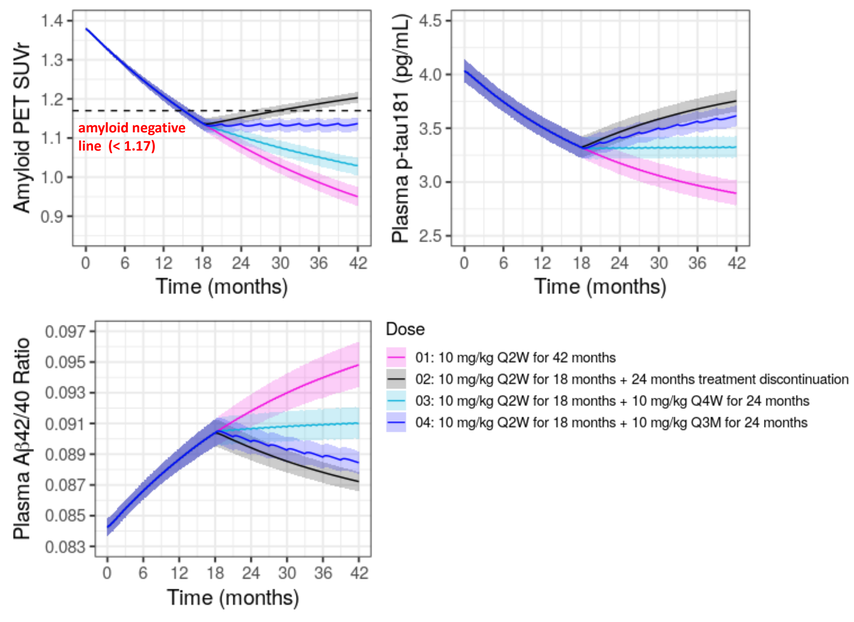
	Parameter	Estimate	%RSE	Bootstrap Median (95% CI)
Aβ42/40 ratio	Baseline: Aβ42/40 ratio	0.0842	4.28	0.0843 (0.0834 - 0.0852)
	K_{out} (/year)	0.367	1.97	0.368 (0.255 - 0.521)
	Slope (1/ug/mL)	0.00155	9.32	0.00155 (0.00110 - 0.00213)
	Inter-individual variability			
	Baseline (%CV)	6.78	16.1	6.73 (4.58 – 8.76)
	Slope (%CV)	44.1	11.1	44.3 (21.4 – 58.9)
	Residual: Proportional (%CV)	6.41	2.82	6.42 (6.03 – 6.82)
p-tau181	Baseline: p-tau181 (pg/mL)	4.06	1.61	4.06 (3.97 – 4.14)
	K_{out} (/year)	0.468	20.7	0.502 (0.183 – 0.934)
	Slope (1/ug/mL)	0.00313	15.6	0.00328 (0.00178 – 0.00596)
	Effect of BW on Slope (exponent)	-0.300	24.2	-0.304 (-0.439 – -0.211)
	Inter-individual variability			
	Baseline (%CV)	35.1	5.63	35.1 (33.0 – 37.4)
	Slope (SD)	0.00151	50.2	0.00162 (0.000662 – 0.00280)
	Residual: Proportional (%CV)	19.4	2.39	19.4 (18.3 – 20.6)

Abbreviations: K_{out} = rate constant of degradation;
Aβ42/40 ratio - Eta shrinkage (%): ETA_Baseline: 11.9%; ETA_Slope: 63.1%
p-tau181 - Eta shrinkage (%): ETA_Baseline: 4.65%; ETA_Slope: 68.4%

Simulations to Explore the Maintenance Dosing Regimens

- Lecanemab 10 mg/kg Q2W for 18 months results in amyloid negativity (PET SUVr: <1.17).
- Low brain amyloid level is predicted to be maintained with less frequent monthly or every 3 months maintenance dosing whereas plasma p-tau181 and Aβ42/40 ratio are predicted to be maintained with monthly dosing.

Figure 3. Simulations to Explore the Maintenance Dosing Regimens



Notes: Black dashed line in SUVr plot represents SUVr = 1.17, indicating amyloid negative line. Solid line and shaded area: predicted median and 95% CI.

Conclusions

- PK of lecanemab was well-characterized in patients with AD by two-compartment models and detected covariates were consistent with other monoclonal antibodies.
- The developed E-R models provide insights in the effect of lecanemab dosing on the extent of brain amyloid removal and plasma biomarkers of amyloid and tau pathology. These models can be used to inform lecanemab dose regimens in future clinical studies.

Acknowledgments

Funding for the studies and analyses was provided by Eisai Co Ltd.

Disclosures

All authors are employees of Eisai Inc. Eisai Ltd, or Eisai Co Ltd.

References

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Presented at Population Approach Group Europe (PAGE 2022), June 28 – July 1, 2022, Ljubljana, Slovenia.