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Preliminary population pharmacokinetic modeling of PF-04360365, a humanized anti-amyloid monoclonal antibody, in patients with mild-to-moderate Alzheimer's disease

Timothy Nicholas,[1] William Knebel,[2] Marc R. Gastonguay,[2] Martin M. Bednar,[1] Bill Billing,[1] Jaren W. Landen,[1] James W. Kupiec, Brian Corrigan,[1] Rene Laurencot,[1] Qinying Zhao[1]

[1]Pfizer Global Research and Development, New London, CT, USA; [2]Metrum Research GP LLC, Tariffville, CT, USA

Introduction

- PF-04360365 is a humanized anti-amyloid IgG2 monoclonal antibody that recognizes amino acids 33–40 of the beta-amyloid (Aβ) 1–40 peptide, and requires a free carboxy terminus for binding.
- In transgenic mice that overexpress amyloid precursor protein, the murine analog of PF-04360365 has been observed to decrease Aβ levels in the central nervous system and to improve their performance in various models of learning and memory.
- PF-04360365 is currently undergoing clinical testing in patients with Alzheimer's disease (AD) as a potential disease modifying agent to reduce brain Aβ burden and to improve clinical outcomes.
- A robust population pharmacokinetic (PK) model at an early stage of drug development can be critical in helping design more efficient clinical studies.

Objective

- To develop a PK modeling approach for evaluating the effect of PF-04360365 in patients with AD.

Methods

- Plasma PK data were obtained from patients with mild-to-moderate AD (Mini Mental State Examination score 16–26) participating in a randomized, double-blind, placebo-controlled, dose-escalation (0.1–10 mg/kg) study.
- Patients received either a single intravenous dose of PF-04360365 (n=26) or placebo (n=11).
- Plasma drug concentrations were analyzed by ELISA – the analytical range was 156–10,000 ng/mL. Both inter- and intra-assay precisions were within 10% and the accuracy, as determined by percent relative error, was ≤16.0%. Concentration measurements that were missing or below the limit of quantification were excluded from the analysis. Individuals with no concentration data were not included in the analysis.
- A population PK model was developed using non-linear mixed effects modeling methodology with NONMEM software version VI, Level 2.0 (ICON Development Solutions). Models were developed on a Mac workstation utilizing the Mac OS X operation system and the GNU Fortran compiler, GCC-3.4.0. First order conditional estimation method with interaction was used. Allometric scaling was implemented using a reference weight of 70 kg. Given the limited number of patients (n=26) and the relatively narrow age range (60–80 years), covariate analysis was limited to the effects of weight.
- Predictive checks and visual predictive checks were evaluated based on 500 Monte Carlo simulation replicates of the original data.

Results

- The PK profile of PF-04360365 appeared linear with moderate inter-individual variability following administration of single doses ranging from 0.1–10 mg/kg.
- The PK of PF-04360365 was best described by a two-compartment model.
- The model was parameterized as clearance (CL), central volume of distribution (V1), inter-compartmental clearance (Q), and peripheral volume of distribution (V2) and implemented using ADVAN 3 TRANS4.
- Inter-individual random effects were modeled with exponential variance models. Covariance was described with a full block omega matrix.
- Additive and proportional error structures were examined and a proportional error model was utilized for the residual error model.
- Fixed and random parameters are shown in Table 1. Fixed parameters (CL, V1, Q and V2) were precisely estimated, as seen by low percent standard error (SE) in the range of 3–10%, with exception of the allometric power exponent on Q and V2. Inter-individual variances were estimated with moderate precision.
- Diagnostic plots and visual predictive checks for the model indicated a good fit with minimal bias. Figure 1 plots observed versus the population predictions of PF-04360365 concentration. Figure 2 displays the observed drug concentrations versus the individual predicted drug concentration. In both cases the data appear symmetric about the line of identity.

Table 1. Demographic characteristics of individuals included in the study

Parameter	Fixed effect parameter (% SE)	Asymptotic 95% CI
CL (L/h) = Θ_1	0.00684 (6)	(0.00597, 0.00771)
(WT/70)$^{a}_{5}$	0.911 (37)	(0.370, 1.45)
V1 (L) = Θ_2	3.16 (3)	(2.95, 3.37)
(WT/70)$^{a}_{6}$	0.573 (34)	(0.194, 0.951)
Q (L/h) = Θ_3	0.0210 (10)	(0.0170, 0.0250)
(WT/70)$^{a}_{7}$	0.236 (126)	(–0.346, 0.817)
V2 (L) = Θ_4	5.34 (8)	(4.49, 6.18)
(WT/70)$^{a}_{8}$	0.590 (54)	(–0.0288, 1.20)
Inter-individual variance (% SE)		
Ω1.1 CL	0.0714 (44)	(0.00931, 0.134)
Ω1.2 COV $_{(CL-V1)}$	0.0268 (69)	(–0.00960, 0.0632)
Ω2.2 V1	0.0312 (36)	(0.00929, 0.0531)
Ω1.3 COV $_{(CL-V2)}$	0.0756 (42)	(0.0134, 0.138)
Ω2.3 COV $_{(V1-V2)}$	0.0465 (57)	(–0.00501, 0.0981)
Ω3.3 V2	0.184 (53)	(–0.00676, 0.374)
Ω1.4 COV $_{(CL-Q)}$	0.0421(76)	(–0.0205, 0.105)
Ω2.4 COV $_{(V1-Q)}$	0.0424 (54)	(–0.00267, 0.0874)
Ω3.4 COV $_{(V2-Q)}$	0.107 (61)	(–0.0217, 0.237)
Ω4.4 Q	0.0895 (55)	(–0.00663, 0.186)
Residual variance (% SE)		
σ^2_{prop}	0.00998 (11)	(0.00778, 0.0122)

Figure 1. Observed vs. population predicted PF-04360365 concentrations

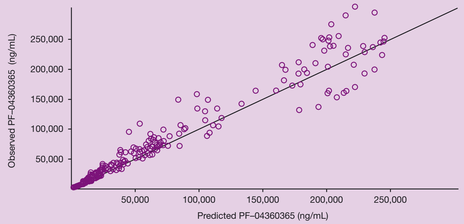
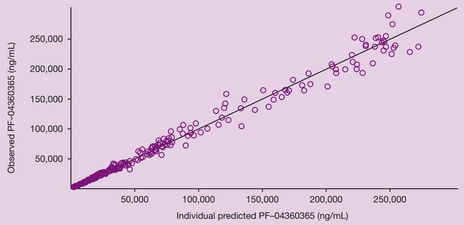


Figure 2. Observed vs. individual predicted PF-04360365 concentrations



- Weighted residuals and conditional weighted residuals are plotted versus the population predicted PF-04360365 concentrations in Figures 3 and 4, respectively. No clear trend in the residuals was observed that would suggest an ill fitting model.
- The distributions of the inter-individual random effects are shown in Figure 5.

Figure 3. Weighted residual vs. population predicted PF-04360365 concentrations

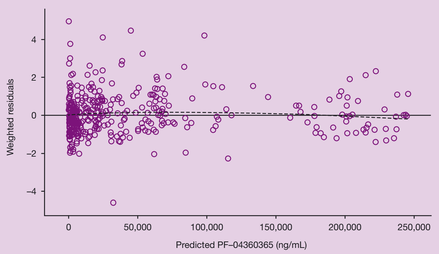


Figure 4. Conditional weighted residual vs. population predicted PF-04360365 concentrations

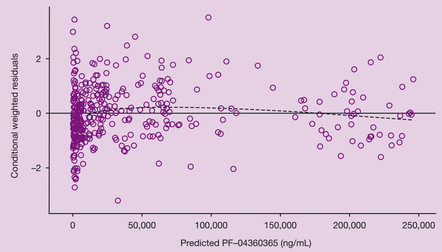
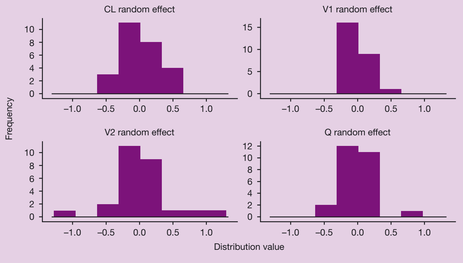
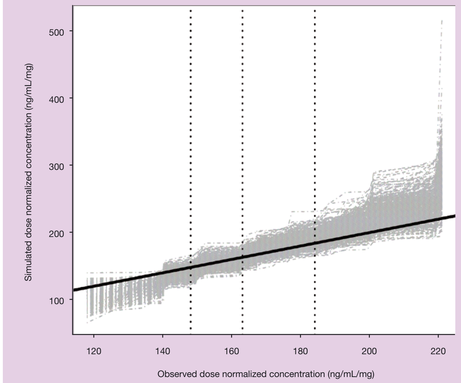


Figure 5. Distribution of inter-individual random effects



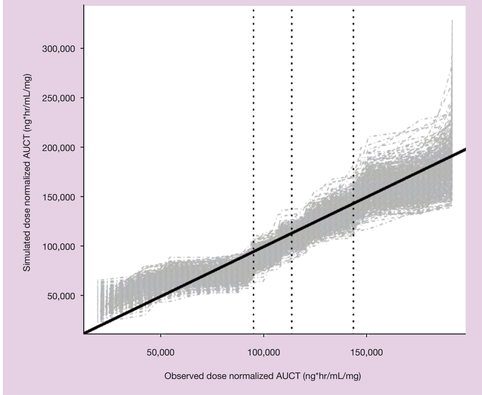
- Predictive checks showed that the model accurately described PF-04360365 exposure across the observed dosing range. The predictive check for dose normalized mean PF-04360365 concentration quantile-quantile (Q-Q) plot is shown in Figure 6.

Figure 6. Predictive check for dose normalized mean PF-04360365 concentration Q-Q plot



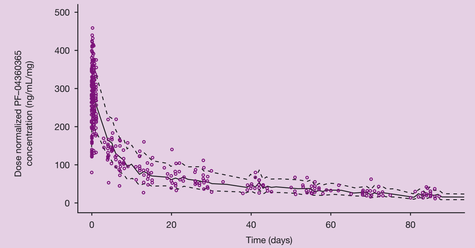
- Predictive check for dose normalized PF-04360365 area under the concentration–time curve Q-Q plot is displayed in Figure 7.

Figure 7. Predictive check for dose normalized PF-04360365 AUCT: Q-Q plots



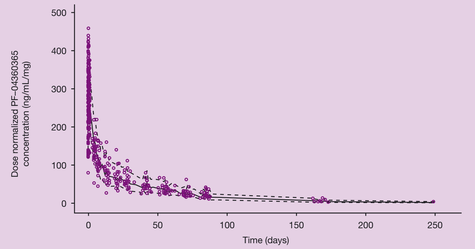
- The visual predictive checks for plasma PF-04360365 concentrations, with an 80% prediction interval are shown in Figures 8 and 9, covering day 1 to 85 and all data, respectively.

Figure 8. Visual predictive check plot for dose normalized PF-04360365 concentrations with 80% prediction interval: day 1 to day 85



Values are represented by open circle. Median simulated concentrations are presented as a solid black line with 80% prediction interval represented as dashed lines.

Figure 9. Visual predictive check plot for dose normalized PF-04360365 concentrations with 80% prediction interval: all data



Values are represented by open circle. Median simulated concentrations are presented as a solid black line with 80% prediction interval represented as dashed lines.

Conclusions

- The PK model evaluation provided evidence that the final PK model was consistent with the observed data.
- This preliminary model describing the PK profile of PF-04360365 will be refined as more data are collected.
- The PK model would be suitable for simulation.
- Simulated exposure and concentration–time profiles of different dosing regimens based on the model can provide a better understanding of clinical trial designs including optimal doses and dosing frequency.

Disclosures

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