



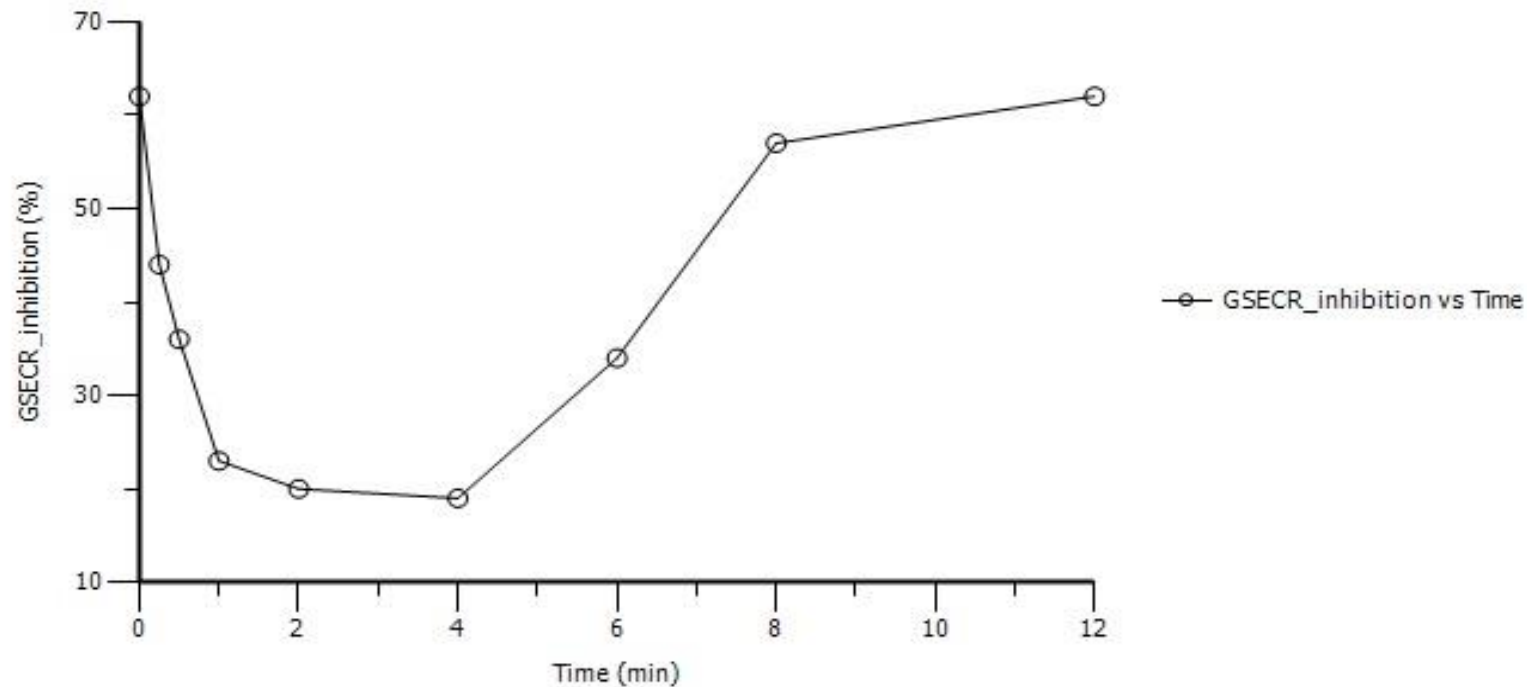
**PML Library:
PD12 - Modeling
inhibition of enzyme
activity by means of
Turnover**

PD12: Study Background

- APP mice produce excess human Amyloid Precursor Protein.
- Cleavage of APP initiates a cascade of secretases, including gamma secretase (GSECR), that results in the formation of amyloid peptide fragments that deposit to form insoluble plaques in the brain.
- By inhibiting GSECR, one hopes to produce less plaque formation via a decrease in formation of amyloid peptide fragments.
- Concentration of soluble beta-amyloid in brain serves as a biomarker of GSECR enzyme activity.

PD12: Exploratory Data Analysis

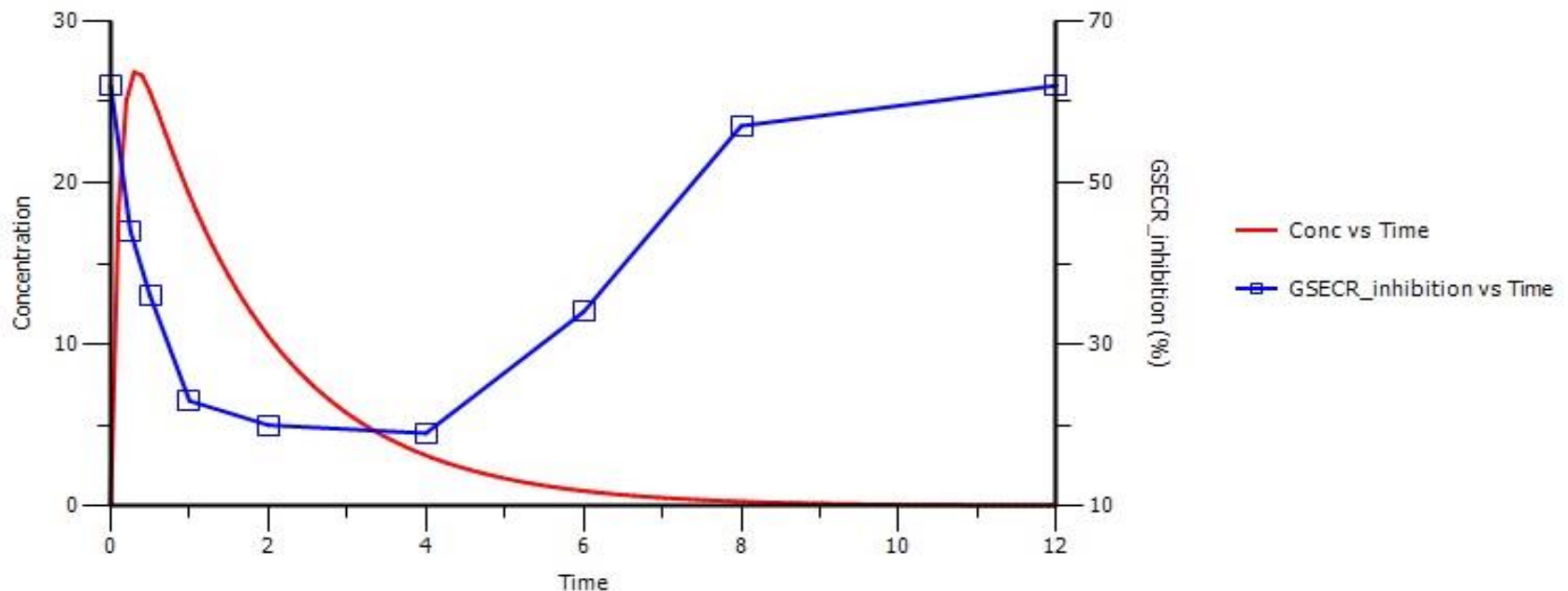
- Characterize the turnover-driven response to a gamma secretase (GSECR) inhibitor in mice
- Response is measured as % decrease in the biomarker beta-amyloid vs time



Gabrielsson & Weiner, Pharmacokinetic and Pharmacodynamic Data Analysis - Concepts and Applications, 5th Edition, Swedish Pharmacology Press (2015)

PK12: Protocol

- Previous studies show a delay between peak inhibitor concentration and maximum inhibitory response, suggesting an indirect response model.

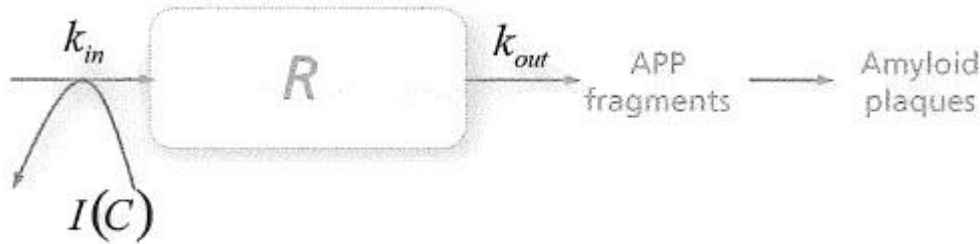


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PD12 Objective: use PK from previous study to simulate concentrations

- PK: use fixed parameters from a 1-compartment model obtained from a previous study to simulate concentrations.
- Extravascular 1-compartment model:
- $dC/dt = \text{Dose} \cdot k_a / V \cdot (k_a - k_e)$
 - K_a = absorption rate constant, 8.8 1/hr
 - K_e = elimination rate constant, 0.605 1/hr
 - V = volume of distribution, 3.05 L
- Solve concentration function at different time points for a given dose level.

PD12: Objective: Construct mechanistic Turnover model



- Rate of production is inhibited by the function $I(C)$
- Indirect response is modeled using $dR/dt = k_{in} \cdot I(C) - k_{out} \cdot R$
 - k_{in} = zero order rate of production
 - k_{out} = first order rate of loss
 - $I(C)$ = mechanistic inhibition of k_{in}

PD12: Objective: Model drug mechanism using Inhibitory function

- $I(C)$ – typical inhibitory I_{max} function
- Inhibitory function $I(C) = 1 - I_{max} * C^{\gamma} / (IC50^{\gamma} + C^{\gamma})$
 - I_{max} = maximum inhibitory response
 - $IC50$ = concentration at which 50% of maximum inhibition occurs
 - γ = exponent for sigmoid I_{max} model

PD12: Objective: Full mechanistic Turnover model

- Full model, substituting in the mechanistic inhibition function:
- $dR/dt = K_{in} * (1 - I_{max} * C^{\gamma} / (C^{\gamma} + IC_{50}^{\gamma})) - K_{out} * R$
- Get final estimates for the following parameters:
 - K_{in} = zero order rate of production
 - K_{out} = 1st order loss
 - I_{max} = maximum inhibition
 - IC_{50} = concentration at which 50% of maximum inhibition occurs
 - γ = exponent for sigmoid I_{max} function

PD12: Built-in PK/indirect: inhibition of production

Population? | Structure | Parameters | Input Options | Initial Estimates | Run Options | Model Text | Plots | no warnings

Type: PK/Indirect Set WNL Model

Parameterization: Micro | Absorption: Extravascular | Num Compartments: 1

tlag? Ka = Ke ? Elim. Cpt.?

Closed form? Freeze PK?

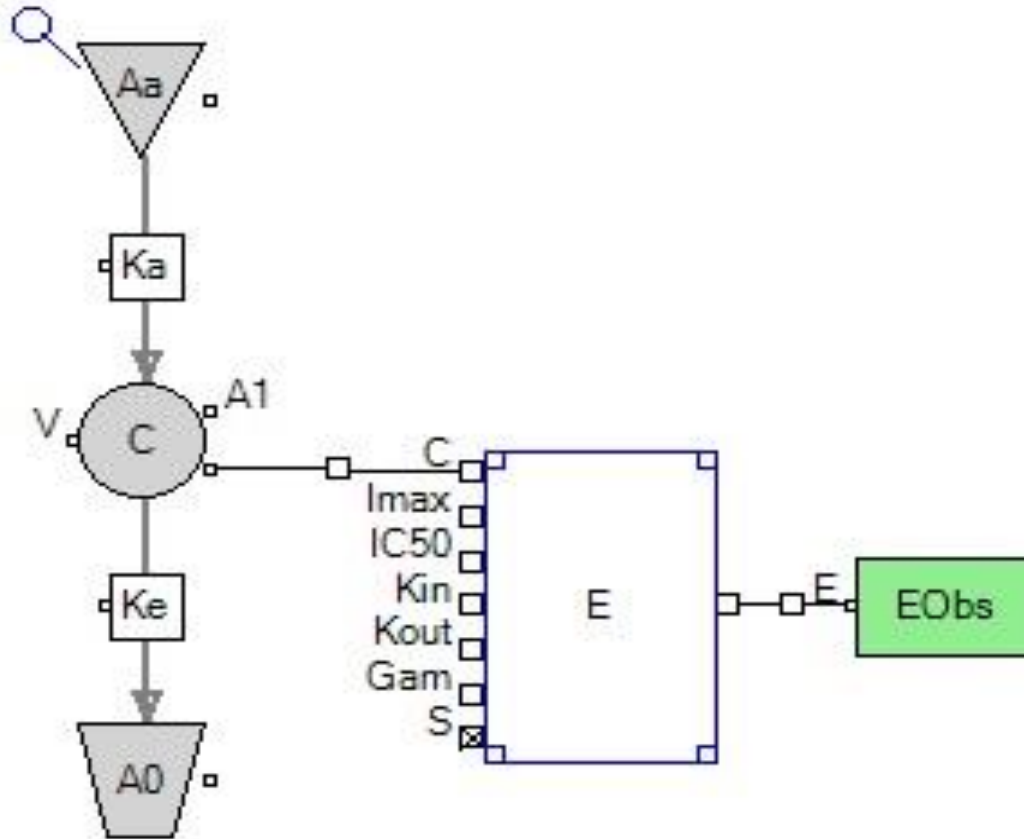
Indirect: Inhib. Limited OF Build-up
Exponent Freeze Indirect?

Residual Error: E | EObs | EEps = Additive BQL?
Stdev: 1 0.81236 Accept Freeze

Parameters:	Statements:
Ka	deriv(Aa = - Ka * Aa)
V	deriv(A1 = Ka * Aa - Ke * A1)
Ke	deriv(E = Kin * (1 - Imax * C ^ gam / (C ^ gam + IC50 ^ gam)) -
Kin	dosepoint(Aa)
Kout	C = A1 / V
Imax	sequence{E = Kin / Kout}
IC50	error(EEps = 1)
gam	observe(EObs = E + EEps)

Gabrielsson & Weiner, Pharmacokinetic and Pharmacodynamic Data Analysis - Concepts and Applications, 5th Edition, Swedish Pharmacology Press (2015)

PD12: Graphical Model



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PD12: Indirect Response Model: PML Code

```
1 test(){
2   # differential eq's for PK model
3   deriv(Aa = - Ka * Aa)
4   deriv(A1 = Ka * Aa - Ke * A1)
5   # differential eq for indirect response model
6   deriv(E = Kin * (1 - Imax * C ^ gam / (C ^ gam + IC50 ^ gam)) - Kout * E)
7   # extravascular dose administration
8   dosepoint(Aa)
9   # concentration in the central compartment
10  C = A1 / V
11  # baseline response R0
12  sequence{E = Kin / Kout}
13  # observed response and error model
14  error(EEps = 1)
15  observe(EObs = E + EEps)
16  # PK parameters as frozen fixed effects
17  fixef(Ka(freeze) = c(, 8.8, ))
18  fixef(V(freeze) = c(, 3.05, ))
19  fixef(Ke(freeze) = c(, 0.605, ))
20  # Indirect response parameters with initial estimates
21  fixef(Kin = c(, 60, ))
22  fixef(Kout = c(, 1, ))
23  fixef(Imax = c(, 0.67, ))
24  fixef(IC50 = c(, 1, ))
25  fixef(gam = c(, 1, ))
26 }
```

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PD12: Initial Estimates

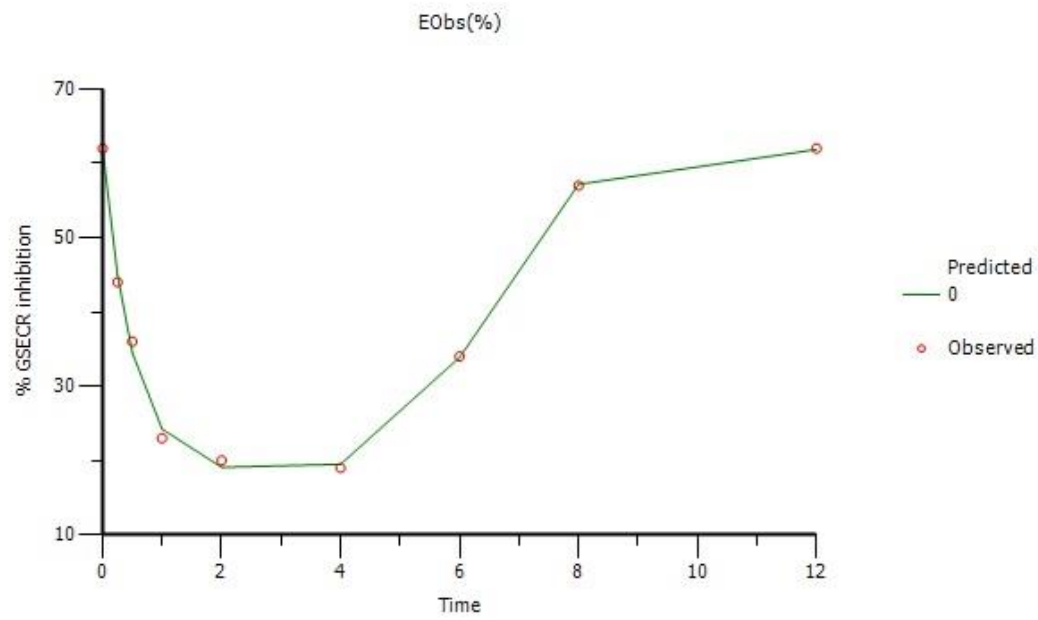
- $IC_{50} = 1$, derived from overlay plot at 50% inhibition
- Γ = exponent, arbitrarily set to 1 (from reduced model)
- $R_0 = 60$, from exploratory plot response at time = 0
- $k_{out} = 1$, derived from slope of downswing in exploratory plot
- $k_{in} = R_0 \cdot k_{out} = 60$
- $\Delta R = R_0 - R_{min} = 60 - 20 = 40$
- $I_{max} = \Delta R \cdot k_{out} / k_{in} = 40 / 60 \sim 0.67$



Demo

PD12: Results

- Fit



- Final Parameter Estimates

	Parameter	Estimate	Units	Stderr	CV%	2.5% CI	97.5% CI	Var. Inf. factor
1	tvKa	8.8	1/min	0	0	8.8	8.8	0
2	tvV	3.05		0	0	3.05	3.05	0
3	tvKe	0.605	1/min	0	0	0.605	0.605	0
4	tvKin	123.196	%/(min)	6.4234726	5.2140269	102.75387	143.63813	62.232
5	tvKout	1.99168	1/min	0.097173042	4.8789485	1.6824354	2.3009246	0.014285
6	tvImax	0.705753		0.011407454	1.6163521	0.66944979	0.74205621	0.00020058
7	tvIC50	0.965352		0.046750401	4.8428346	0.816573	1.114131	0.0032631
8	tvgam	2.49622		0.25736744	10.310287	1.677171	3.315269	0.10257
9	stdev0	0.81236		0.19147585	23.570319	0.20300512	1.4217149	

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PD12: Summary

- Fix PK parameters from previous study
- Develop an indirect response model
- Derive initial estimates
- Fit the model to the data
- Review results
- Simulate response at different dose levels

Questions?



PML School: Materials

- Each model will be made available in Certara Forum
 - Link to live webinar and presentation slides
 - <https://support.certara.com/forums/forum/34-pml-school/>
 - Model text as file download
 - Can be imported into Phoenix model object to be run on a new dataset
 - Questions and comments can be exchanged in the Forum
 - Or can be entered into the Certara Support portal at:
 - <https://support.certara.com/support>
 - Or can be sent as emails to support@certara.com
- PML School on Twitter: @PML_School
 - Notifications on updates of materials, Q&A and discussions
 - Announcements of new sessions
- PML School on Youtube:
 - <https://www.youtube.com/user/CertaraLP/videos>

- A wide range of On Demand and Classroom courses are available through Certara University:
 - Introductory, intermediate and advanced instruction in Phoenix WinNonlin, Population Modeling using NLME, IVIVC Toolkit
 - Fundamentals of Pharmacokinetics and Pharmacodynamics
 - Noncompartmental data analysis
 - Programming Bootcamp
 - Partner Lectures and Webinar series
- Please visit our [Certara University](#) web site for more information

Coming up...

Modeling PK/PD Systems with Distributed Delays

Speaker(s): Wojciech Krzyzanski

Date: May 16, 2017

Time: 11 am EST

Duration: 1 hour



Effect Compartment III: IV infusion

Model response-time data with a link-model

May 11, 2017 | 10am EST

Presenter: Bernd Wendt