The Exposure-Response-Driven Development Program: Application to an Anti-inflammatory Compound

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Introduction

-Pharmacometric approaches to optimizing drug development have been gaining greater usage and acceptance. However, these approaches have been employed less frequently in early-phase clinical development.

-Early-phase decision making tends to be empirical and deterministic, does not integrate all of the available nonclinical and clinical data, and fails to consider the impact of uncertainty.

-We advocate a pharmacometric approach to early-phase drug development that addresses these issues. Employing quantitative methods based on modeling and simulation to integrate the available data permits more informed decision-making that enables optimization of early phase development.

Objective

-To provide a model for pharmacometrically-informed early clinical development with exposure-response serving as the unifying basis.

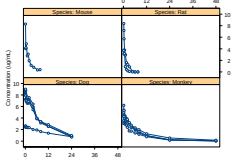
-An example using an anti-inflammatory compound in clinical development will demonstrate how assessment of exposure-response using pharmacometric approaches was applied to drive early-phase clinical development.

Methods

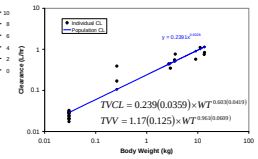
1. Use a nonlinear mixed effects pharmacokinetic (PK) modeling approach to allometric interspecies scaling.[1,2]
2. Model in vitro inhibition of lipopolysaccharide (LPS)-induced cytokine (TNFα shown) production in whole blood.
3. Model exposure-based pharmacodynamics (PD) of drug in a rat adjuvant-induced arthritis (AIA) model for endpoints such as bone resorption, paw weight, and inflammation.
4. Implement simulation model integrating nonclinical data for projection of human results, including impact of absorption-related assumptions and uncertainty in PK projections on PK and PD outcomes. Compare simulated exposure distributions with relevant PD and toxicology endpoints to select optimal starting dose and dose range for First-in-Human (FIH) study.
5. Perform real-time PK and PD analysis to adjust later stages of FIH study (Fed/Fasted, Females, Multiple Dose). No changes were required (results not shown).
6. Model PK-PD results from FIH study to optimize selection of doses for a study in patients with acute coronary syndrome undergoing percutaneous coronary intervention (PCI) administered once daily doses of drug for 5 days peri-PCI.

Nonclinical Results & Modeling

Concentration vs. Time by Species



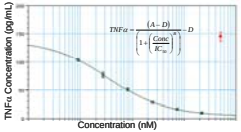
Population and Individual Clearance vs. WT



$$TVCL = 0.239(0.0359) \times WT^{0.603(0.0419)}$$

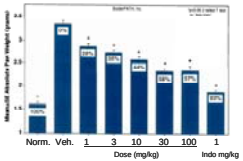
$$TVV = 1.17(0.125) \times WT^{0.863(0.0609)}$$

In vitro Inhibition of LPS-stimulated TNFα

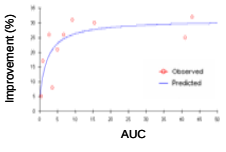


$$TNF\alpha = \frac{(A-D)}{\left(1+\left(\frac{Conc}{IC_{50}}\right)^{n}\right)} + D$$

Paw Weight Response In Rat AIA Model

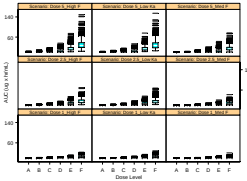


Emax Model Results for AIA, Paw Weight



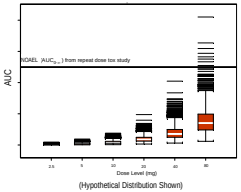
First-In-Human Study Simulations

Simulated Distribution of AUC by Dose Level for Various Starting Doses and Absorption Assumptions



A=1x, B=2x, C=4x, D=8x, E=16x, F=32x

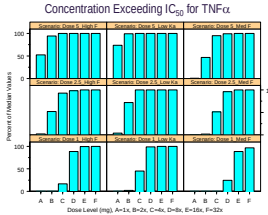
Simulated Distribution of AUC by Dose Shown Relative to NOAEL



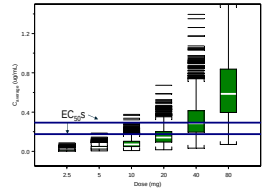
(Hypothetical Distribution Shown)

First-In-Human Study Simulations

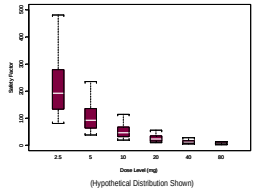
Probability of Median 24-hour Post-dose Concentration Exceeding IC_{50} for TNFα



Simulated Distribution of Average Concentration by Dose Relative to EC_{50}s for Two Endpoints from AIA



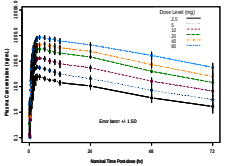
Simulated Distribution of a NOAEL-based Safety Factor



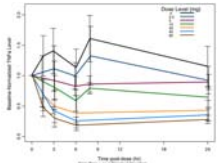
(Hypothetical Distribution Shown)

Healthy Subject Results & Modeling

Observed Drug Concentration vs. Time



Baseline-Normalized TNFα vs. Time



Healthy Subject Population PK Model

$$\frac{dAl_{ijk}}{dt} = -\left(\frac{Amax_{i}}{Km_{i,j} + Al_{ijk}}\right) \times Al_{ijk}$$

$$\frac{dA2_{ijk}}{dt} = \left(\frac{Amax_{i}}{Km_{i,j} + Al_{ijk}}\right) \times Al_{ijk} - \left(\frac{CL_{ijk}}{V_{ij}}\right) \times A2_{ijk}$$

$$C_{ijk} = \frac{A2_{ijk}}{V_{ij}}$$

$$C_{ijk} = \hat{C}_{ijk} + \varepsilon 1_{ijk} + \varepsilon 2_{ijk}$$

$$CL_{ij} = \theta 1 \times \exp\left(\eta 1_{i} + \kappa 1_{i,j}\right)$$

$$V_{ij} = (\theta 2 + \theta 7 \times (WT_{i} - 75.2)) \times \exp\left(\eta 2_{i} + \kappa 2_{i,j}\right)$$

$$Amax_{i} = \theta 3 \times \exp\left(\eta 3_{i}\right)$$

$$Km_{ij} = \theta 4 \times \exp\left(\eta 4_{i} + \kappa 3_{i,j}\right)$$

$$Lag_{i,j} = \left(\theta 5 \times \left(1 + \theta 6 \times FAST_{ij}\right)\right) \times \exp\left(\eta 5_{i} + \kappa 4_{i,j}\right)$$

$$\eta_{i} \sim N(0, \omega_{i}^{2}) \quad \kappa_{ij} \sim N(0, \omega_{ij}^{2}) \quad \varepsilon_{ij} \sim N(0, \sigma^{2})$$

Healthy Subject Population PD Model

$$E_{i,j,k} = \hat{E}_{i,j,k} + \varepsilon_{i,j,k}$$

$$\hat{E}_{i,j,k} = E0_{i,j,k} \times \left(1 - \frac{Emax_{i} \times Conc_{i,j,k}}{IC50_{i} + Conc_{i,j,k}}\right)$$

$$CMC_{i,j,k} = \left(MonocyteCount_{i,j,k} - median\left(MonocyteCount\right)\right)$$

$$E0_{i,j,k} = \left(\beta_{0} + b_{0,i} + b_{0(i),j}\right) + \left(\beta_{1} + b_{1,i}\right) \times CMC_{i,j,k}$$

$$Emax_{i} = \beta_{2} + b_{2,i}$$

$$IC50_{i} = \beta_{3} + b_{3,i}$$

$$b_{i} \sim N\left(0, \omega_{bn}^{2}\right) \quad b_{0(i)} \sim N\left(0, \omega_{b0(1)}^{2}\right) \quad \varepsilon_{i,j,k} \sim N\left(0, \sigma^{2} \left| \hat{E}_{i,j,k} \right|^{2\delta}\right)$$

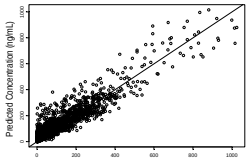
Population PK Parameter Estimates

PK Parameter	Description	Estimate	Units	IIV^1	IOV^2
CL	Clearance	3.75	L/hr	25.1%	9.0%
V	Volume at median body weight	72.8	L	15.5%	11.4%
	Change in volume w.r.t body weight	0.825	L/kg	--	--
Amax	Max absorption rate	38	mg/hr	81.7%	--
Km	Amount of drug in gut resulting in 50% of max rate	24.9	mg	75.4%	75.2%
Lag	Oral absorption lag time in fed state	0.454	hr	6.2%	4.2%
	Change in lag time in fasted state	-46.9	%	--	--

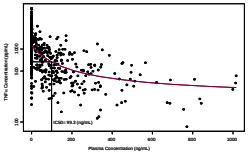
Population PD Parameter Estimates

Parameter	Units	TNFα Estimate	TNFα IIV^1	TNFα IOV^2	Estimate
IC_{50}	ng/mL	99.3	45.9	--	58.9
E_{max}		0.807	0.047	--	0.812
E0 Intercept	pg/mL	1120	283	148	2680
E0 w.r.t. Monocyte Count	pg/ml/10^-6 cells	2310	919	--	6560

Population Predicted vs. Observed Drug Concentration



Population Predicted and Observed TNFα Concentration vs. Drug Concentration

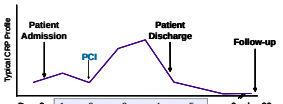


References

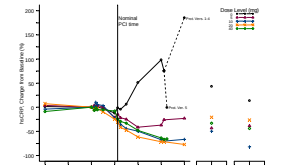
[1]Cosson VF, et al., Mixed Effect Modeling of Sumatriptan Pharmacokinetics During Drug Development. I: Interspecies Allometric Scaling J Pharmacokin Biopharm 25:149-167 1997

[2]Martin-Jimenez T, et al., Mixed-Effects Modeling of the Interspecies Pharmacokinetic Scaling of Oxytetracycline.J Pharm Sci 91:331-341 2002

Acute Coronary Syndrome Study Results



High Sensitivity CRP vs. Time



Time	pre PCI	24h Post PCI	48h Post PCI	3-5d F/U	day 6Fu
P value	<0.05	<0.001	<0.001	0.057	<0.05

Jonckheere-Terpstra test of dose-response

Conclusions

-An integrated exposure-response analysis based on pharmacometric principles optimized a FIH study

-Real-time PK and PD data analysis would have permitted changes in later components of FIH study

-Population modeling of healthy subject data characterized human PK/PD and facilitated the design of and optimal dose selection for a Phase IIa Proof-of-Concept study in ACS

-Additionally, population PK/PD models were developed for other endpoints (not shown) that supported the design and doses selection for other Phase I (e.g. Thorough QTc Study) and Phase II studies. Thus, application of pharmacometrically-informed exposure-response methods in early clinical development can enhance decision-making and optimize outcomes.

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