PK/PD Model of Pegylated Thrombopoietin Mimetic Peptide in Healthy Subjects: Comparison of Verification Procedures for Assessing Model Predictability.

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Background & Objectives

✓ Thrombocytopenia is a common medical problem in patients undergoing chemotherapy. Recombinant thrombopoietins have failed to meet clinical end points, and one form of thrombopoietin (PEG-rHuMGDF) was observed to generate auto-antibodies leading to paradoxical thrombocytopenia.[1,2,3]

✓ Clinical development of these molecules has therefore been stopped.[3] Thus, platelet growth factors that do not generate antibodies represent an area of unmet medical need.

✓ Pegylated Thrombopoietin Mimetic (PEG-TPOm) peptide has shown potent in vitro activity with promising results for the treatment of thrombocytopenia. The synthetic compound bears no homology with TPO, thus reducing the potential for generation of anti-thrombopoietic antibodies.

✓ PEG-TPOm is active in a cellular assay of thrombopoietin receptor activation and has an EC_{50} of 5 pM indicating high affinity for the c-Mpl receptor. It also shows activity in vivo as evidenced by significant protection against chemotherapy-induced thrombocytopenia in mice.

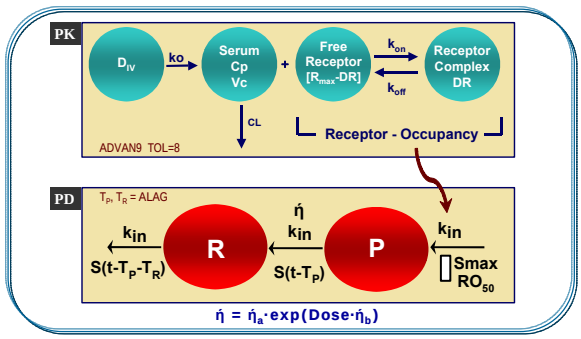
✓ The objective of this exercise was to model the pharmacokinetics (PK) and pharmacodynamics (PD) of a pegylated thrombopoietin mimetic peptide (PEG-TPOm) in healthy subjects and to compare verification procedures for assessing model predictability.

Methodology

✓ 30 healthy subjects were randomized to receive single intravenous doses (0.375, 0.75, 1.5, 2.25 or 3 ug/kg) of PEG-TPOm. Plasma concentrations and platelet counts were analyzed using a target mediated drug disposition model and a precursor pool life span system. Nonlinear mixed effects modeling using the first order conditional estimation was employed to characterize PK-PD using NONMEM® V. Estimation was performed using a sequential approach.[4] Individual Bayesian estimates of the target-mediated PK model[5] were used to predict the PEG-TPOm plasma concentrations, which in turn drove the life-span precursor pool PD model. [6,7]

✓ To verify the precision, stability, and predictability of the models, the final parameter estimates were subjected to internal model verification, which consisted of a non-parametric bootstrap (BS)[8], a visual predictive check (VPC)[9], and posterior predictive assessment (PPC).[10] VPC assesses the influence of variability (between subject [BSV]; residual [RV]) in parameters while PPC adds another level of complexity by incorporating the uncertainty in parameter estimates.

✓ PPC was performed using parameter uncertainty and variability, which were incorporated using 1000 different values of fixed and random effect parameters that were randomly sampled from the BS replicates. VPC was performed using the original parameter estimates. The 5th, 50th and 95th percentiles were calculated from the simulated PPC and VPC profiles. The prediction intervals were superimposed on the raw data to allow assessment of model predictability.



Population PK and PD Model

Results

✓ The terminal PK half-life ranged between 18-36 hours and the volume of distribution (5 L) suggested that PEG-TPOm was primarily restricted to the blood compartment.

✓ The estimated K_D (154 pM) indicated that PEG-TPOm has high affinity for TPO receptors.

✓ The megakaryocyte production rate displayed a maximal stimulatory increase of 52%. 22% receptor occupancy was necessary to achieve half maximal stimulatory effect.

✓ The increase in platelet counts was observed after a delay of 4 days and maximum platelets counts were achieved on day 9, which is reflective of the megakaryocyte and platelet life spans.

✓ BS analysis was used to validate parameter estimates. The original estimates were similar to the median values from the BS analysis and fell within the 90% confidence intervals (CI).

✓ An overlay of the observed data, the VPC, and the PPC confirmed that the models are able to capture the majority of PK/PD observations, which fell within the 90% prediction intervals.

✓ The concordance of the two verification procedures indicated that model uncertainty does not significantly affect model predictability.

✓ K_D, V_c, $Baseline_{PD}$, T_p, and T_r estimates were in agreement with physiological limits. However, the estimated R_{TOT} exceeded the circulating receptor levels because c-Mpl receptors reside not only on circulating platelets but also on thrombopoietic lineage cells in the bone marrow.

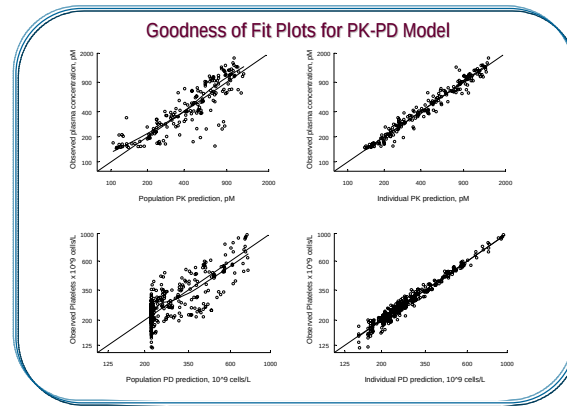
PK Parameters	Original Estimates	Bootstrap (n = 896) Median	90% CI	
Central Tendency				
R_{TOT} (pM)	1130	1240	674	4465
CL ($L \cdot h^{-1}$)	0.089	0.088	0.067	0.11
V_c (L)	4.97	4.92	4.29	5.66
k_{off} ($h^{-1} \cdot 10^{-2}$)	2.53	2.63	0.0001	20.8
k_{on} ($pM^{-1} \cdot h^{-1} \cdot 10^{-3}$)	0.164	0.158	0.0340	0.556
K_D (pM)*	154	153	0.006	2292
BSV (%)				
ω_{Rtot}	80.4	78.3	0.09	141.8
ω_{Cl}	20.8	18.7	0.003	32.3
ω_{Vc}	41.0	39.2	23.6	53.1
Residual Variability (%)	16.2	15.8	13.4	18.2

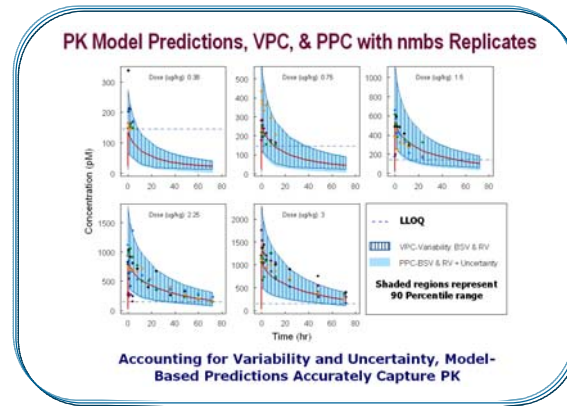
*Secondary Parameter

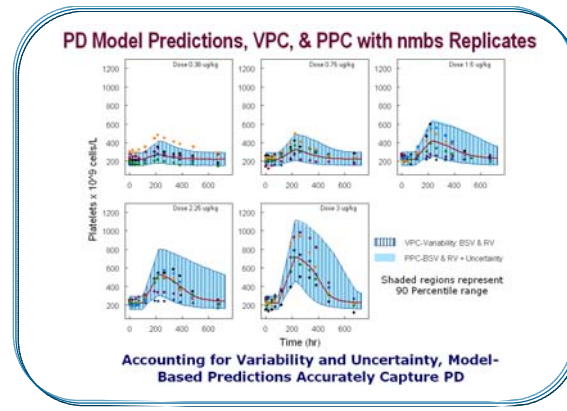
Parameter Estimates for the PK model

PD Parameters	Original Estimates	Bootstrap (N=996) Median	90% CI	
Central Tendency				
S_{Max}	0.518	0.519	0.442	0.628
Baseline (10^9 cells/L)	218	218	206	230
T_P (h)	96.3	96.3	90.4	99.7
T_R (h)	125	125	120	132
γ	3.40	3.39	2.80	4.14
RO_{50}	0.222	0.222	0.173	0.300
$ή_b$=3000 (fixed) & $ή_b$	0.528	0.529	0.431	0.614
BSV (%)				
ω_{Smax}	24.3	23.0	16.9	29.1
$\omega_{Baseline}$	16.6	16.2	12.5	19.7
ω_{RO50}	22.0	21.6	19.2	23.9
Residual Variability (SD)	17.4	16.9	10.0	27.7

Parameter Estimates for the PD Model







Physiological Relevance of Estimated Parameters

PK Parameter	Estimated Value	Physiologic Value
R_{TOT}	1130 pMoles = 227 pM	TPO receptors on platelets 14 - 42 pM
K_D	154 pM	Endogenous TPO-Receptor K_D 100 - 200 pM
Vc	4.97 L	Human Blood Volume 5 L

PD Parameter	Estimated Value	Physiologic Value
Baseline	218 x 10^9 cells/L	Normal adult platelet counts 150 - 450 x 10^9 cells/L
Tp	96.3 h = 4 day	Megakaryocyte life-span 3.5 - 5 day
Tr	125 h = 5.2 day	Platelet life-span 5 - 10 day

Conclusion

✓ A suitable mechanistic model was validated for describing the complex PK/PD of PEG-TPOm in humans, including target-mediated disposition, platelet stimulation and mean life spans of thrombopoietic cell populations.

✓ The two model verification procedures involving PPC and VPC gave similar results indicating that for this PK/PD dataset both methods are suitable for model validation since the predictions are primarily driven by BSV.

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