Semi-physiologic Population PKPD Model Characterizing the Effect of Bitopertin (RG1678) Glycine Reuptake Inhibitor on Hemoglobin Turnover in Humans

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Background

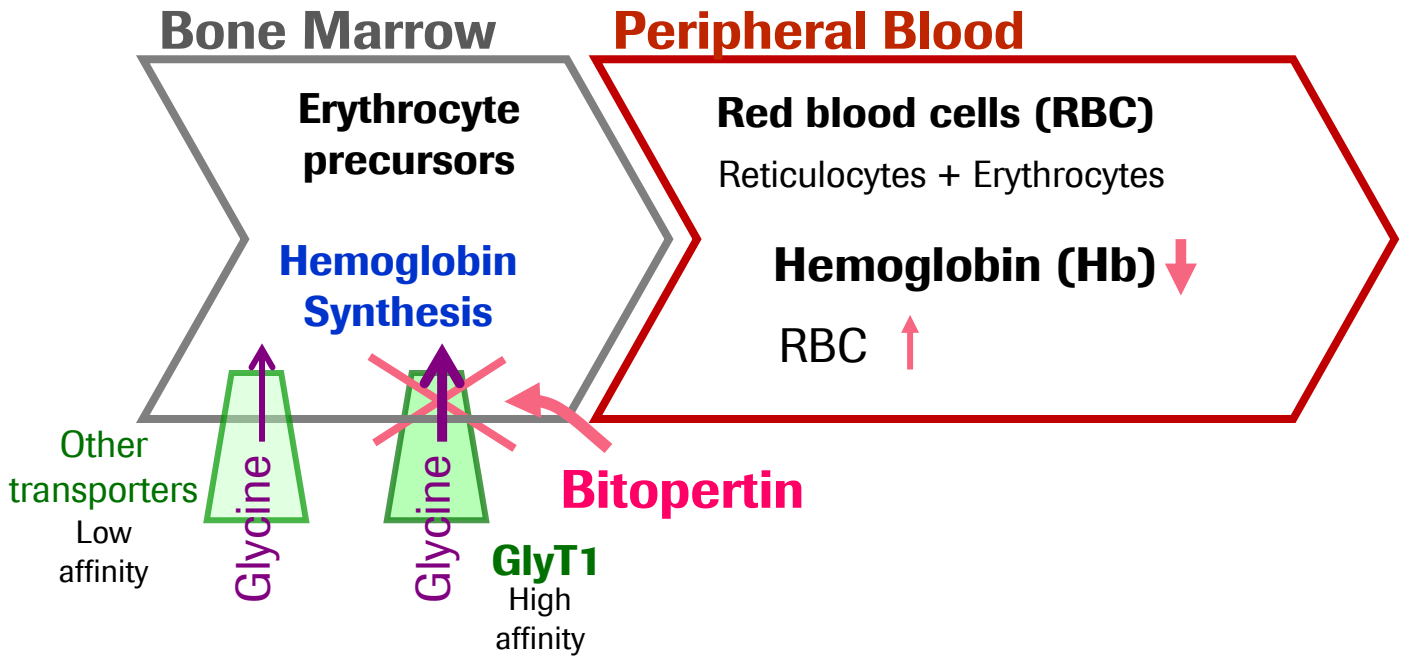
- Bitopertin is a selective glycine reuptake inhibitor targeting the **glycine type 1 transporter (GlyT1)**
  - Ø Currently in late stage development as a potential novel therapeutic approach in schizophrenia
  - Ø In the brain, inhibition of GlyT1 results in increased synaptic glycine levels leading to improved NMDA* receptor function
- Outside the brain, GlyT1 is also localized on **erythrocyte precursors** in the bone marrow and on circulating reticulocytes
  - Ø Glycine is required for hemoglobin (Hb) synthesis
  - Ø Complete ablation of GlyT1 in knock-out mice results in a 26 % Hb decrease [1]
- The **hematological effect of bitopertin** was studied in a 4 month phase 1 study in healthy subjects

[1]Schranzhofer et al., ASH meeting 2011, abstract #345

*NMDA = N-methyl-D-aspartate

Bitopertin Effect on Hemoglobin Synthesis

Proposed mechanism: reduced Hb synthesis is due to reduced glycine uptake in erythrocyte precursors



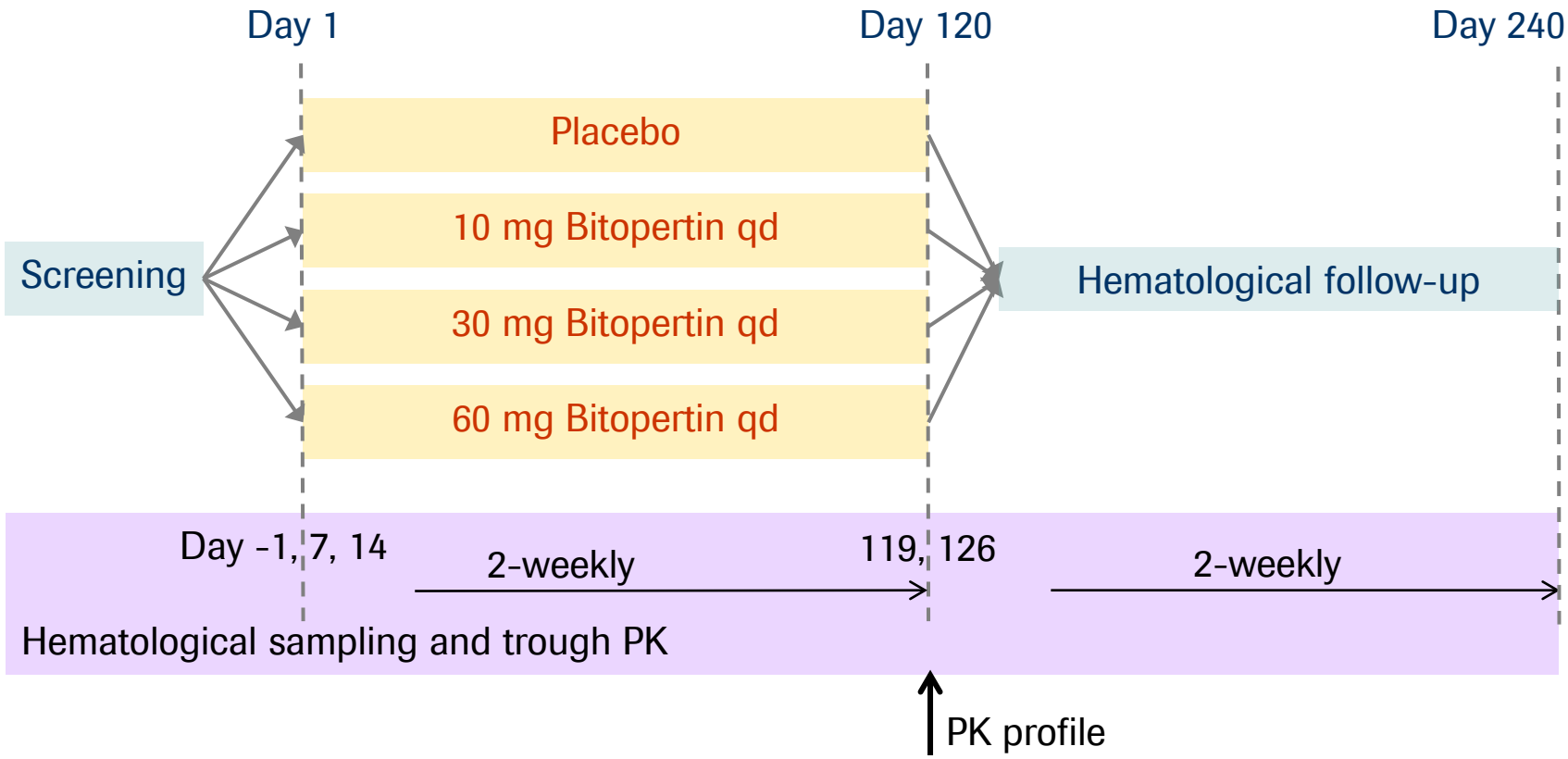
Objectives

A semi-mechanistic PKPD model for bitopertin was developed in order to

- Characterize the proposed effect of GlyT1 inhibition on the hematological system, taking into account hemoglobin synthesis and red blood cell turnover
- Support drug development with respect to the effect of bitopertin on hemoglobin concentrations as an important clinical parameter

Phase 1 Study in Healthy Subjects

To assess the hematological effects of 4 month treatment



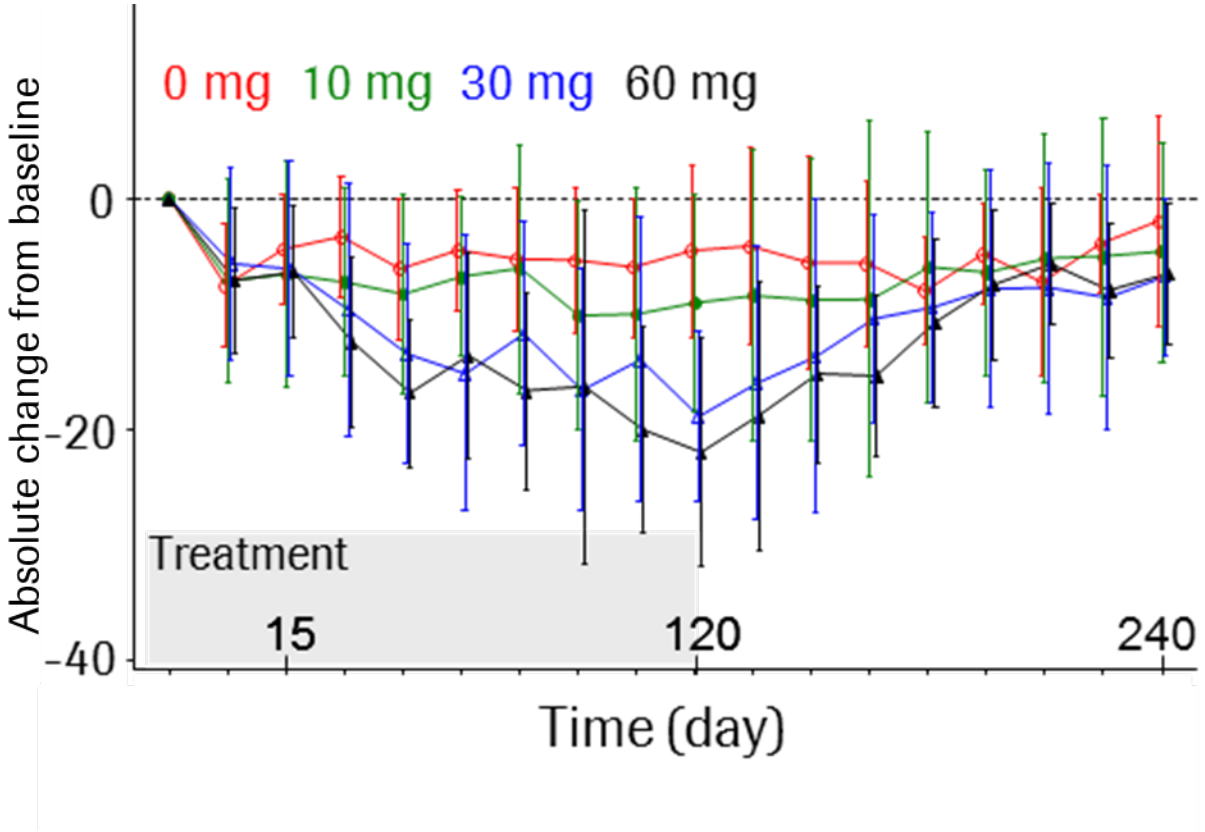
Population:

- 67 healthy male and female subjects enrolled
- Aged 18 to 45 years; baseline Hb within normal lab range

Hematological Data Observed in Healthy Subjects

Hemoglobin blood concentration

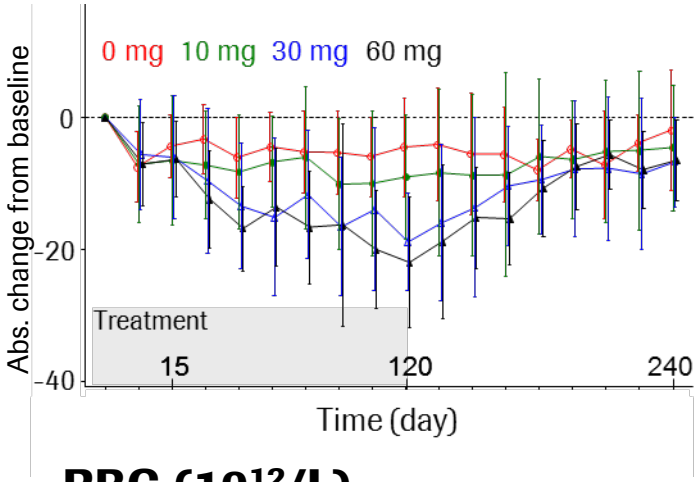
Hb (g/L)



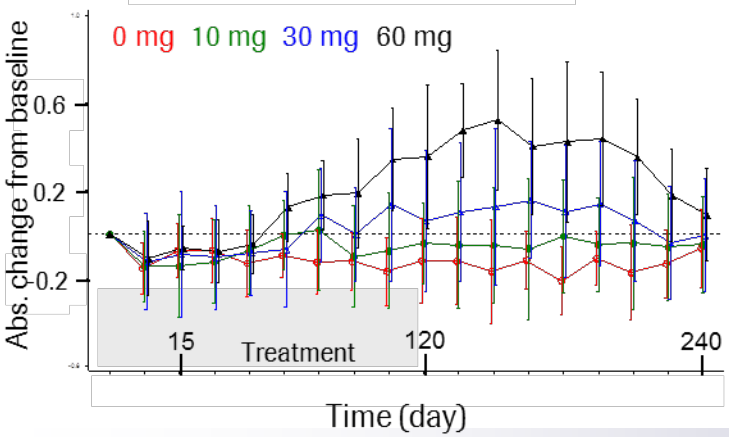
- Dose dependent decrease of Hb
- Reversible effect
- Plateau of effect delayed due to RBC lifespan
- No subject reached Hb discontinuation threshold (100 g/L in females, 110 g/L in males)
- About one week to PK steady-state

Hematological Data Observed in Healthy Subjects

Hb (g/L)

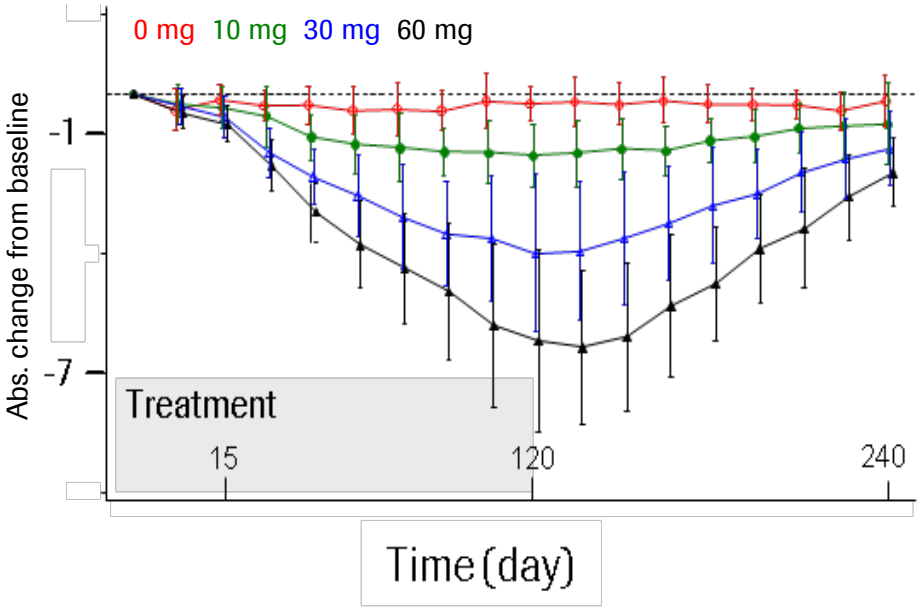


RBC (10^{12}/L)



Hb / RBC

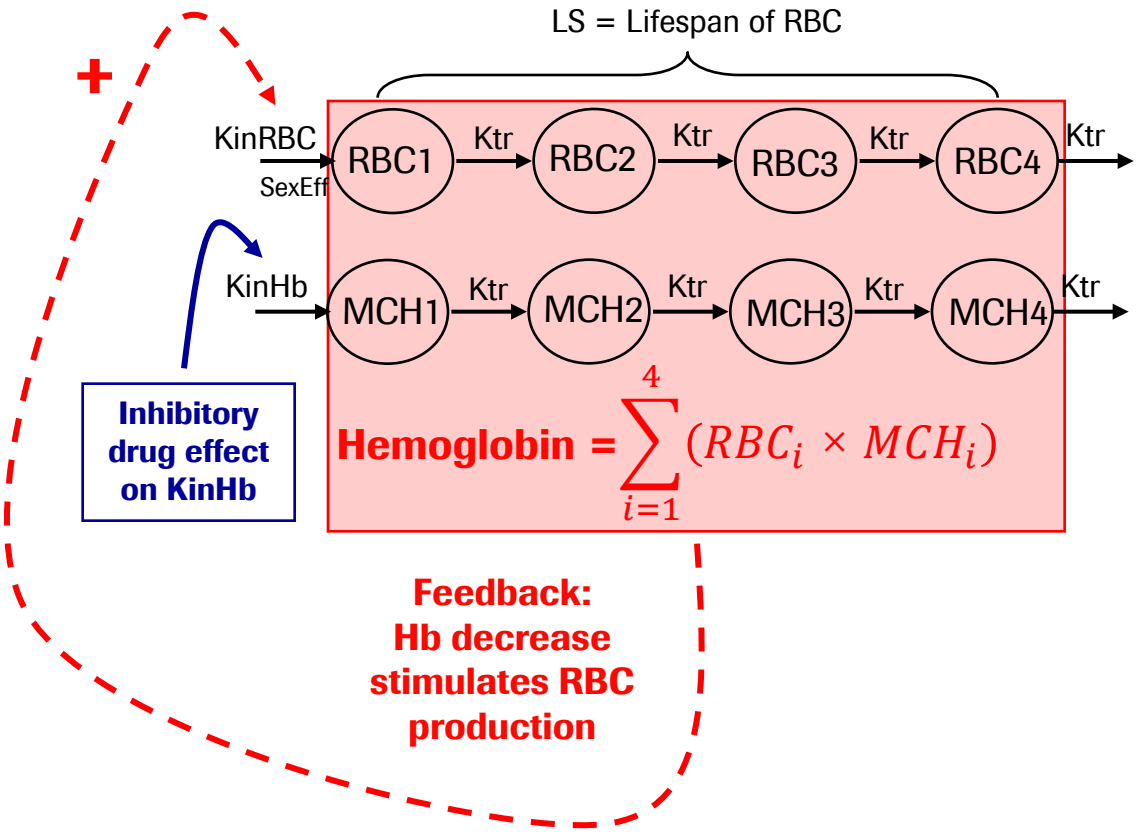
Mean Corpuscular Hemoglobin
MCH = Hb/RBC (pg/RBC)



- Decreased amount of Hb per red blood cell due to decreased Hb synthesis
- Plateau of effect delayed due to RBC lifespan

MCH best reflects drug effect on Hb synthesis

Semi-physiologic PKPD Model for GlyT1 Inhibitory Effect on Hemoglobin



Estimated Parameters:

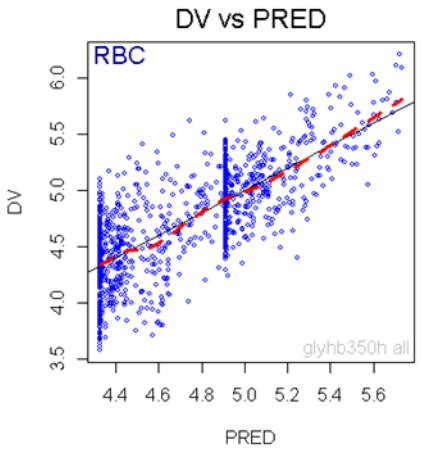
KinRBC, KinHb, LS, Emax, AUC50, Feedback, SexEff

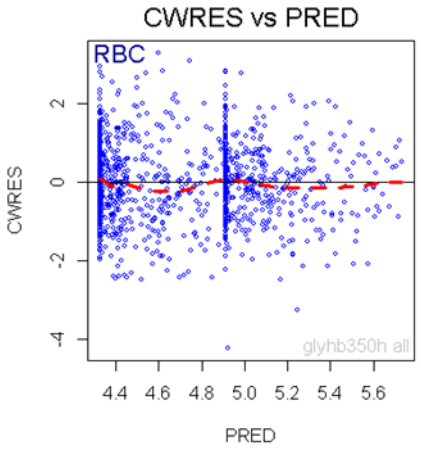
- Two parallel chains of transit compartments[1] represent the **production, senescence and elimination of RBC, with their respective MCH**
- AUCss is driving the inhibitory drug effect
- Model fit to **MCH and RBC** data simultaneously in NONMEM 7

[1]Hamrén et al., Clin Pharm Ther 84:228-35, 2008

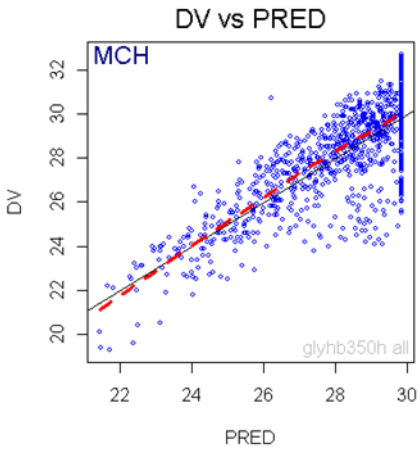
Model Diagnostics: GoF Plots

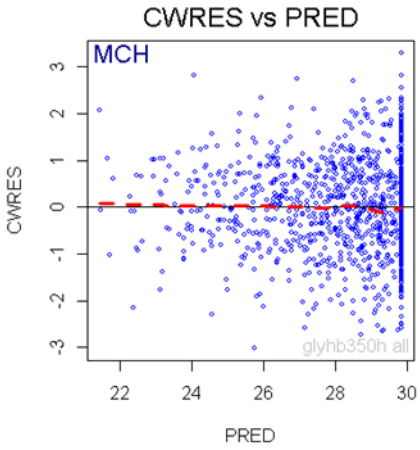
RBC



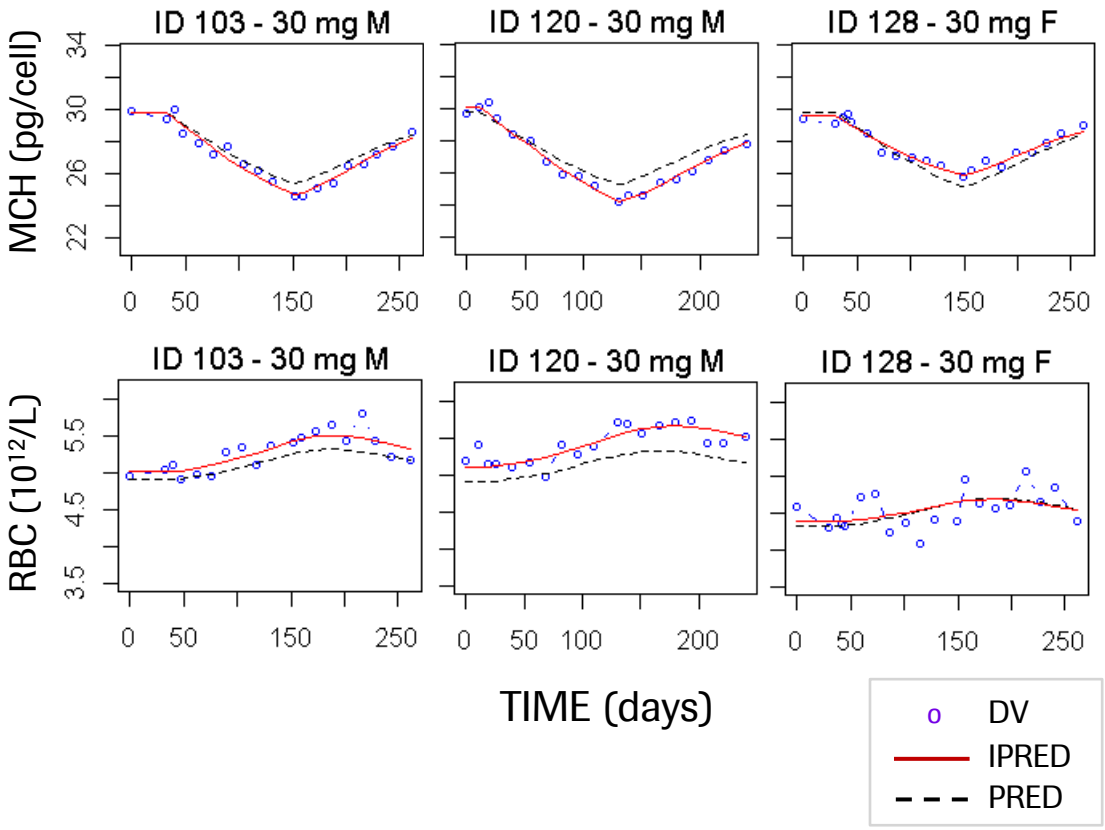


MCH



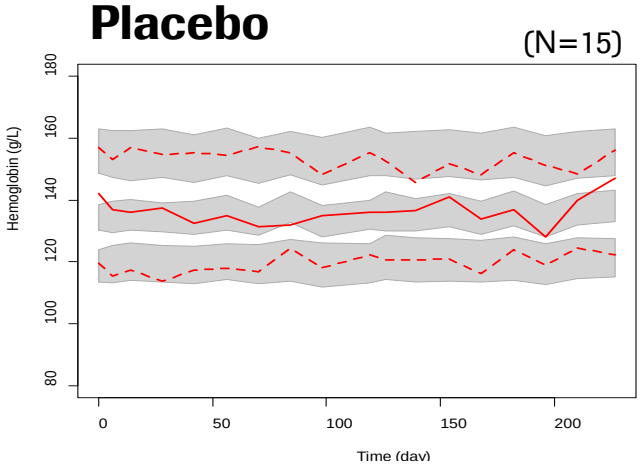


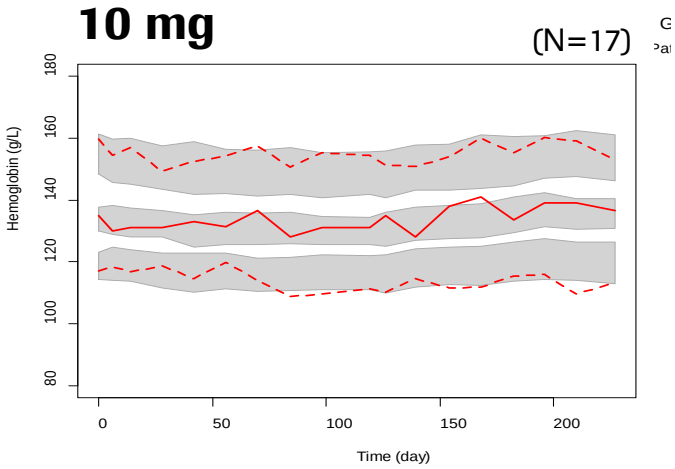
Individual Fits: MCH and RBC vs. TIME

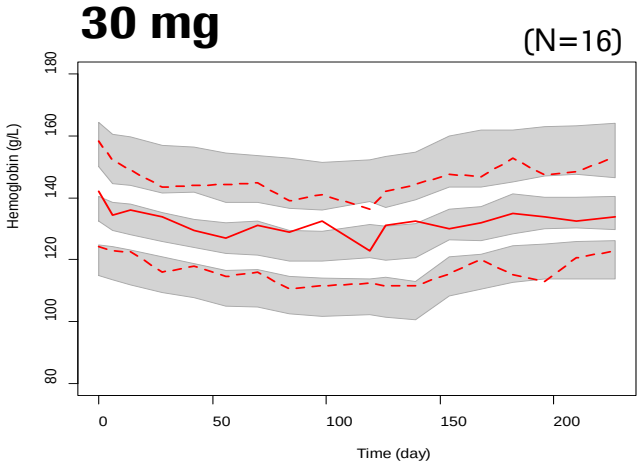


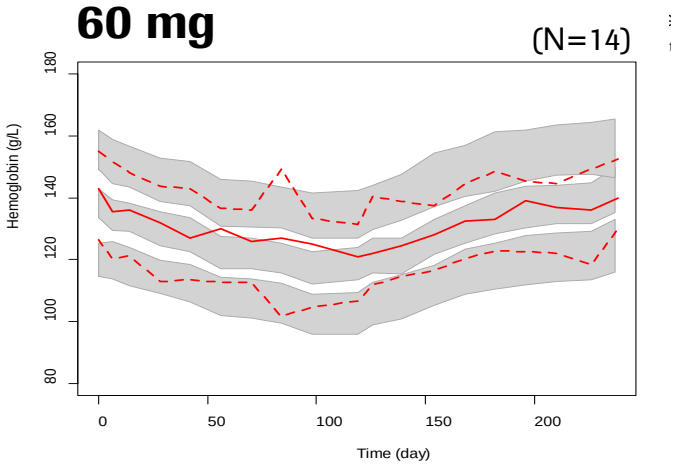
Model Predictive Performance for Hemoglobin

VPC for hemoglobin, predicted as cumulative RBC x MCH









$$Hb = \sum_{i=1}^{4} (RBC_i \times MCH_i)$$

Simulated Hb

Median, 5th, 95th

Observed Hb

Median

5th, 95th

Results

PKPD parameter estimates

	Unit	Estimate	% RSE	IIV (% CV)
LS	days	126	4.5	24.9
KinHB	pg/cell/day	0.949	4.8	28.0
KinRBC	10^12/L/day	0.039	4.3	24.3
Feedback		1.38	12.4	
Emax	fraction	*	13.2	
AUC50	mg/L*h	*	23.2	49.2
SexEff		-0.119	8.0	
ERR_RBC	10^12/L	0.183	3.0	
ERR_MCH	pg/cell	0.346	2.7	

Physiological parameters estimates generally in line with values in the literature

Baseline values (derived)

	Unit	males	females
MCH_0	pg/cell	29.8	29.8
RBC_0	10^12/L	4.9	4.3
HB_0	g/L	147	129

% RSE: Relative Standard Error

Feedback mechanism (FDB):

Scaling parameter to describe the stimulation on RBC production rate as a feedback to Hb reduction

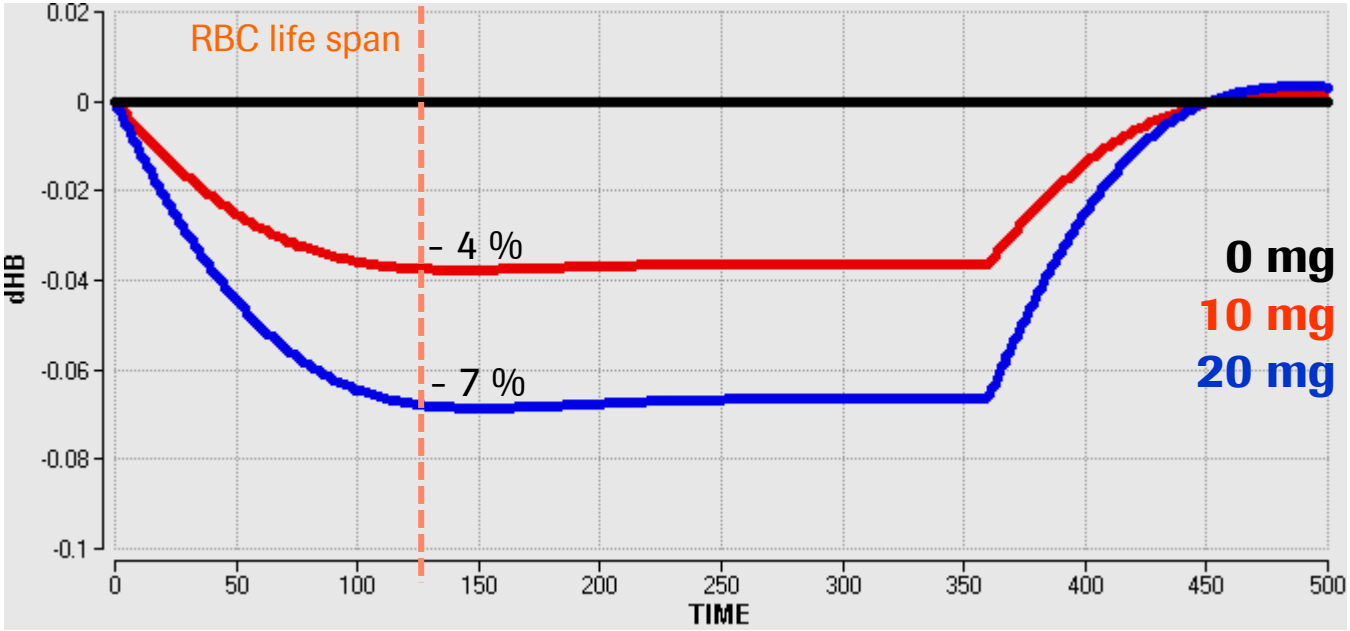
$KinRBC = KinRBC_0*[1+(HB_0-HB)/HB_0*FDB]$

SexEff: Female patients have 11.9 percent lower KinRBC

What is the predicted long term effect on Hb?

Doses up to 20 mg tested in phase 3

Predicted Hb change from baseline (%) for 360 days of treatment



Maximum Hb change from baseline (nadir) expected shortly after one RBC life span

Less than 10 % Hb drop expected at projected therapeutic doses

Conclusions

- The physiology of the hematopoietic system together with the inhibitory effect of bitopertin on Hb synthesis were integrated in the semi-physiologic PKPD model to successfully fit the data from healthy subjects
- The effect on hemoglobin, as the key clinical parameter, is best predicted by fitting MCH and RBC data simultaneously
- The model is a useful tool to support bitopertin drug development, and phase 3 trials will provide further information