Population pharmacokinetics and pharmacodynamics analysis of hydroxyurea, in adult patients with sickle cell anemia (SCA), and evaluation of disease markers.

Lezzar S.[1], Evene E.[1], Duguet C.[2], Habibi A.[3], Gellen-Dautremer J.[3], Galactéros F.[3], Legrand T.[3] and Hulin A.[3]

[1]PhinC Development, Massy, France.

[2]AddMedica, Paris, France.

[3]Hôpital Henri Mondor, Créteil, France.

Background

Hydroxyurea (hydroxycarbamide) (HU) is an antineoplastic agent, it was approved for indication of sickle cell anemia (SCA).
The efficacy of HU in SCA is generally attributed to its ability to boost the levels of fetal hemoglobin (HbF), and reducing the abnormal hemoglobin (HbS), hence reducing the frequency of painful crises in patients with SCA.

Objectives

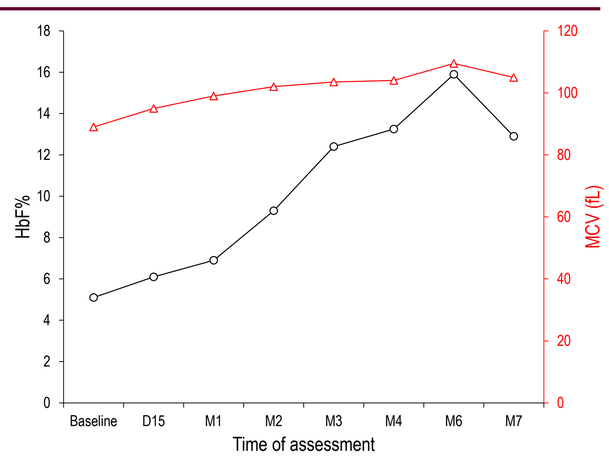
The aim of this study was to develop PK-PD models using HU PK parameters to characterize the exposure-efficacy relationships between HU and the two disease markers: HbF% and mean corpuscular volume (MCV).

Methods

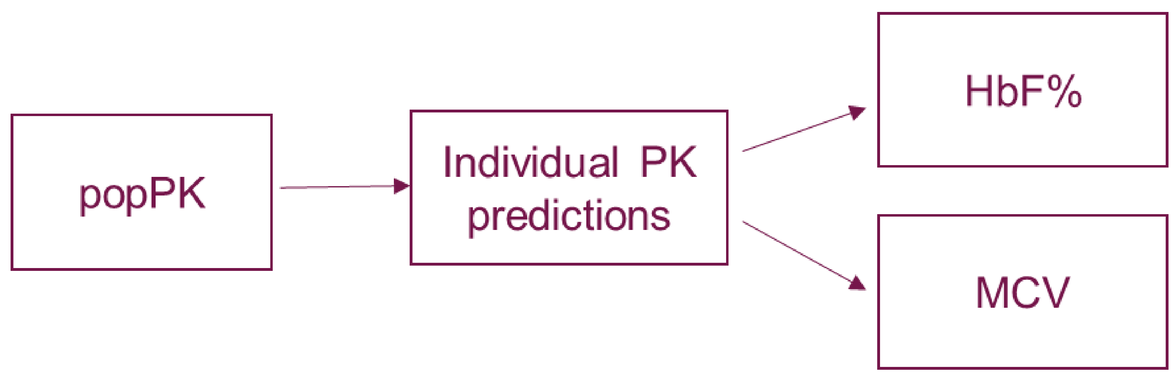
Data:
Data combined two datasets with different designs

Study part	SCA patients	Doses (mg)	Regimen	PK samples times	HU analyzed concentrations
Sparse data	115	500 - 2500	*MD - q.d*	each months up to 6 months	232
Rich data	15	1000 - 2000	*SD*	Over 24 h	130

PD parameters collected at the same time than the PK blood samples only on sparse data.



Modeling strategy:
Nonlinear mixed effects modeling was conducted using NONMEM® 7.2. The FOCE method was applied.
A sequential PKPD approach was used as schematized below:

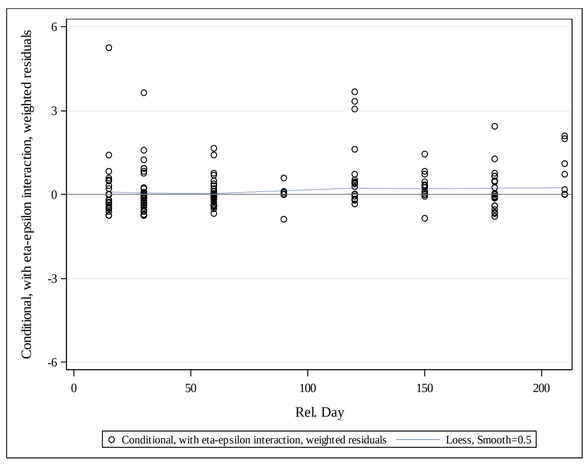


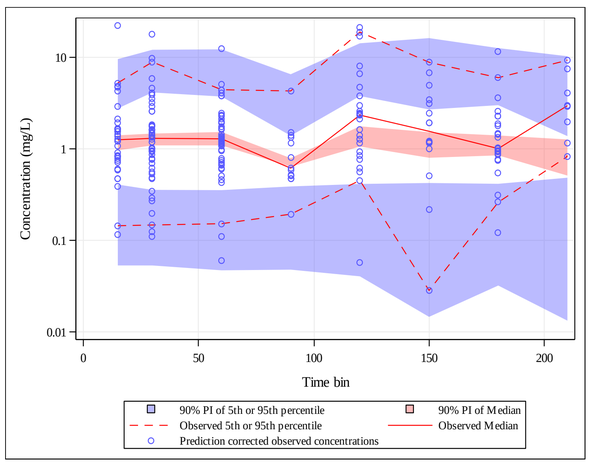
Results

HU popPK model

The popPK model was a 2-compartment model with first-order absorption and elimination from the central compartment.

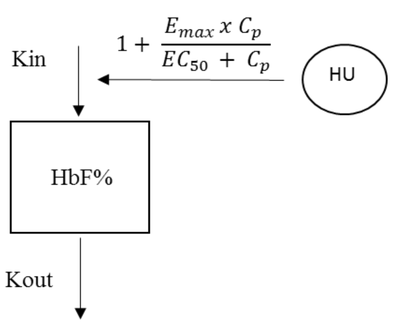
Parameter	Estimate (%RSE)	IIV (%CV)	%Shrinkage
CL/F (L/h)	9.87 (3.93%)	0.10 (32.3%)	17%
V_2/F (L)	31.7 (10.6%)	0.64 (79.7%)	20%
Q/F (L/h)	2.29 (8.95%)		
V_3/F (L)	73.4 (27.1%)		
Ka (h^{-1})	5.54 (15.6%)		





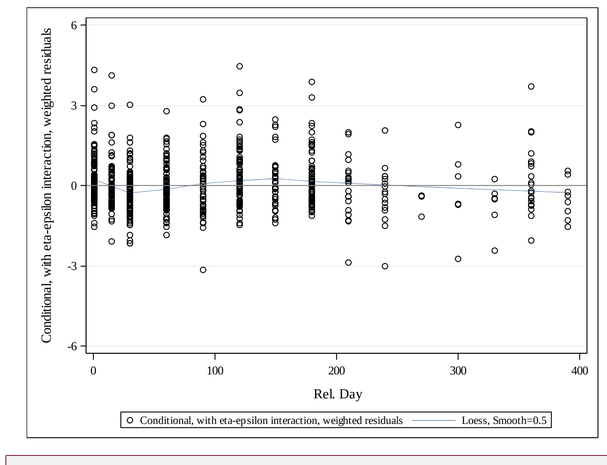
PKPD modeling

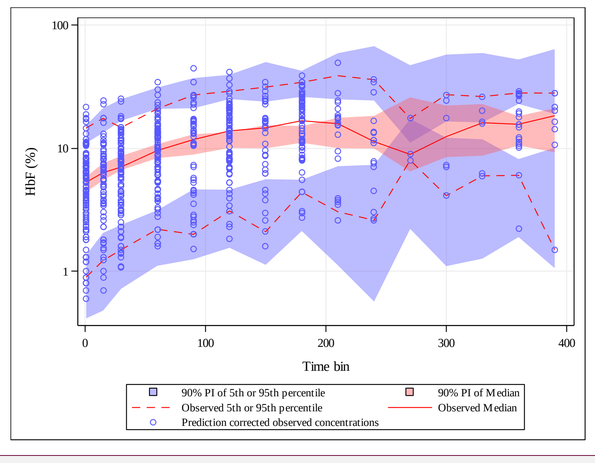
HbF% model



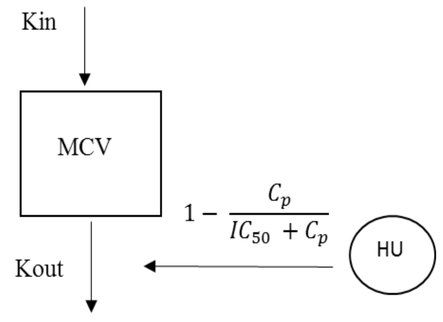
Parameter	Estimate (%RSE)	IIV (%CV)
E_{max} (HbF%)	17.3 (32.0%)	
EC_{50} (mg/L)	22.1 (46.2%)	
K_{in} (HbF%/day)	0.002 (7.4%)	0.365 (60.4%)
K_{out} (day^{-1})	0.00047 (5%)	

HbF% model validation



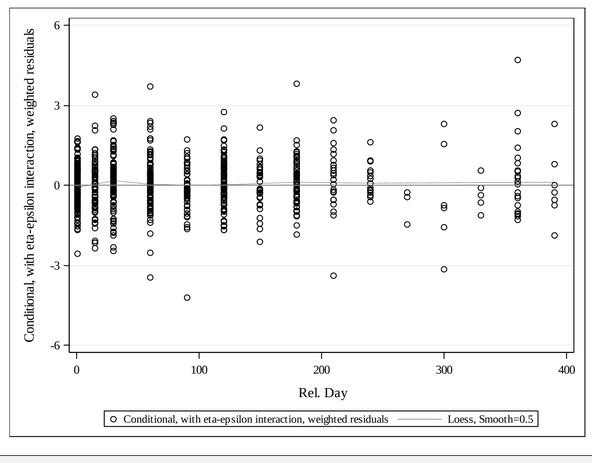


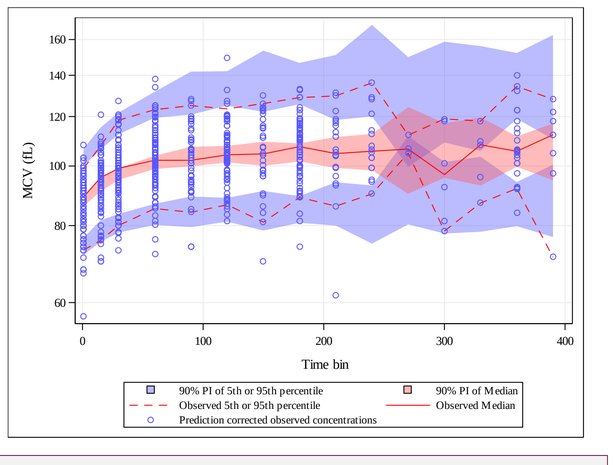
MCV model



Parameter	Estimate (%RSE)	IIV (%CV)
IC_{50} (mg/L)	16.8 (7.44%)	0.507 (71.2%)
K_{in} (MCV (fL)/day)	0.112 (3.21%)	0.0092 (9.57%)
K_{out} (day^{-1})	0.0013 (3.30%)	

MCV model validation





Conclusion

- The observed delay between the blood concentrations and the effect was due to the mechanism of action of hydroxyurea, which acts by stimulating HbF% production but also by inhibiting MCV decrease.
- As perspective, the model will be used for simulations to investigate the optimization of dosing schedule to reduce the time of occurrence of maximum drug effect.