Integrated Population PK and PBPK Modelling Approaches of IAMA-6 Plasma Concentrations following Oral, Intraperitoneal and Intravenous Administrations in Three Preclinical Species for First in Human Dose Prediction

Chiara Roversi[1], Simone Zannoni[1], Annalisa Mercuri[2], Marco Borgogno[4], Annalisa Savardi[4], Marco De Vivo[4], Laura Cancedda[4], Valentina Cenacchi[3], Alessia Tagliavini[1]

[1]*Department of Clinical Development & Translational Medicine, Aptuit an Evotec Company, Verona, Italy*
[2]*Department of Discovery DMPK, Aptuit an Evotec Company, Verona, Italy*
[3]*Department of Integrated Development Programmes, Aptuit an Evotec Company, Verona, Italy*
[4]*IAMA Therapeutics, Genoa, Italy*

III-101

Background and Aim

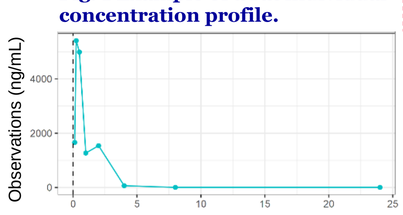
The sodium-potassium chloride cotransporter (NKCC1) has been implicated in the control of neuronal excitability with evidence for increased transporter activity in several pathological conditions. In particular, it plays a crucial role in regulating Cl^- homeostasis and GABAergic transmission in neurons. IAMA-6 is a small molecule, selective inhibitor of the NKCC1, showing encouraging both *in vitro* and *in vivo* proof-of-concept results in idiopathic autism and Down syndrome.

In this work, a stepwise methodology was applied to extrapolate IAMA-6 human expected exposure levels to support starting dose selection for First In Human (FIH) trial, integrating population (popPK) and physiologically-based (PBPK) pharmacokinetic modelling strategies.

Dataset

Data coming from 13 *in vivo* studies of three preclinical species (i.e. rat, mouse, and dog) treated with single or repeat dose of IAMA-6 given either orally (PO) with solutions, suspension or nanosuspension formulation, intravenously (IV) or intraperitoneally (IP) were considered. Different doses were tested, ranging from 1 to 300 mg/kg. Brain concentration data were also collected for mouse species.

Fig. 1 Example of a rat individual concentration profile.



Multiple peaks were observed in the individual concentration time curves of different species (Fig.1), potentially due to compound precipitation or the presence of enterohepatic circulation (EHC).

Methods

PopPK models

For each preclinical species, PO, IV and IP raw data collected in the different studies were pooled together to build up the popPK models to characterize subjects PK profile and assess the bioavailability of the administration routes. PopPK models were developed by using nonlinear mixed effects (MonolixSuite™), including the interindividual variability term on some parameters to explain inter-subject differences. Competing models were compared using the Bayesian Information Criterion Corrected (BICc).

PBPK model

A mechanistic PBPK model was built with GastroPlus® combining *in silico* predicted data (ADMET Predictor) with *in vitro* and *in vivo* measured data. Renal clearance (CL) was predicted by multiplying plasma fraction unbound for glomerular filtration. Hepatic CL was estimated by subtracting renal CL to the experimental total CL. All other parameters were set as default. Tissue distribution (Kp) was defined using the Lukacova (RodgersSingle) model.

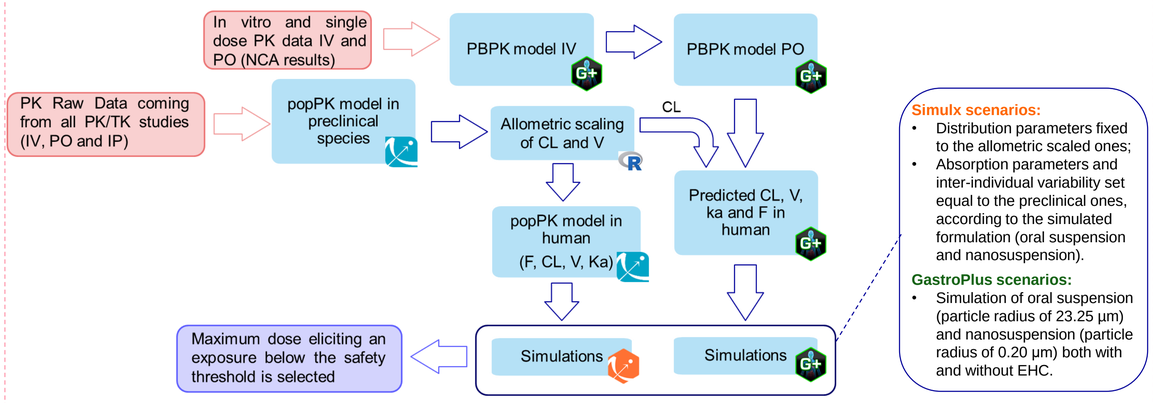
Human dose prediction

A multispecies allometric scaling was applied to the PK parameters derived from popPK models to predict human drug distribution and elimination, by correcting for the protein binding difference across species and assuming a human body weight of 70 kg [1].

Two different human PK models were implemented via either **GastroPlus®** (PBPK model) and **Simulx** (popPK model) to properly characterize the absorption process and to simulate different scenarios in humans at different doses to support FIH dose selection. For the PBPK model, human predictions were made by using the same assumptions used for the preclinical species and the allometrically scaled CL.

The predicted total exposure, i.e. the Area Under the Curve between 0 and 24 hours after dosing (AUC24), of the simulated population were compared to the safety threshold derived applying a 20-fold safety margin to rats' No Observed Adverse Effect Level (NOAEL) exposure [2]; the maximum dose for which at least 75% of the simulated population has the exposure below the threshold was selected as the human recommended starting dose.

Fig. 2 Human PK prediction Workflow

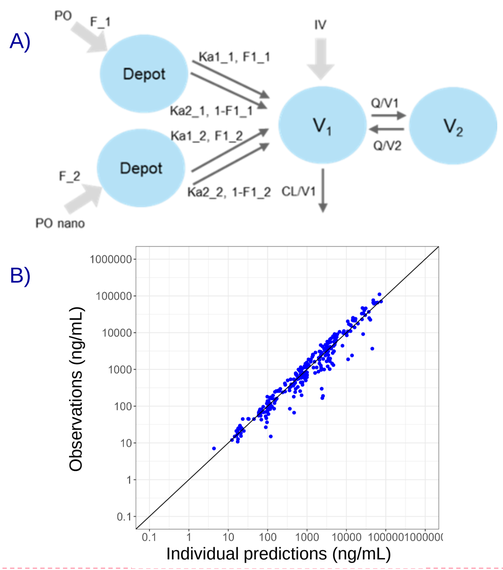


Results

PopPK models

Developed popPK models considered various absorption models to account for the observed heterogeneous absorption process across species (Fig.3, Fig.4, Fig.5 and Tab.1, Tab.2, Tab.3, respectively). A simple first order process well captures mouse data, while for rat and dog models a double first order absorption model with a lag time in the onset of the second process was adopted to describe the individual PK curves, where multiple peaks appear. With regards to the distribution and disposition processes, a two compartmental model with linear elimination was adequate in each species. Overall, popPK models shown good capability in describing the PK profiles and precise estimated parameters (Relative Standard Error <50%) were obtained.

Fig. 3 Rat model results. A: schematic representation of the structural model; B: Goodness of Fit (GoF) plot of plasma individual predictions (Log scale).

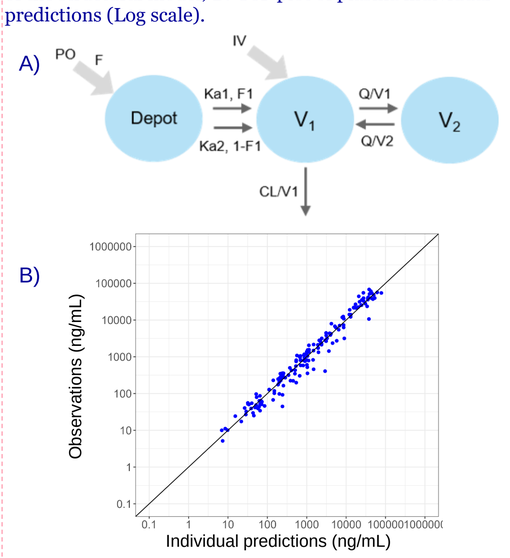


Tab. 1 Parameters estimates of the rat model.

Parameter	Estimate (CV%)	SE	RSE (%)
Fixed Effects			
F_1 (-)	0.52	0.098	18.9
F1_1 (-)	0.39	0.023	5.92
k_{a1_1} (1/h)	0.78	0.081	10.3
k_{a2_1} (1/h)	0.09	0.013	14.3
T_{lag2_1} (h)	3.92	0.026	0.660
F_2 (-)	0.27	0.051	19.0
F1_2 (-)	0.24	0.025	10.4
k_{a1_2} (1/h)	2.2	0.3	13.6
k_{a2_2} (1/h)	0.11	0.011	10.7
T_{lag2_2} (h)	1.91	0.036	1.86
Cl (L/h)	0.31	0.036	11.9
V_1 (L)	0.032	0.0057	17.5
Q (L/h)	0.013	0.0042	33.0
V_2 (L)	0.0081	0.0022	26.7
Standard Deviation of the Random Effects (ω)			
F_1	1.29 (48.21%)	0.27	21.4
k_{a1_1}	0.35 (35.84%)	0.13	36.5
k_{a2_1}	0.5 (53.09%)	0.17	35.0
F_2	0.49 (34.05%)	0.17	34.2
Error Model Parameters			
b	0.46	0.027	5.83

RSE: Percentage of relative standard error (100%·SE/Estimate).
ω Represents the standard deviation of the interindividual variability parameter.
The parameter b is the proportional component of the residual error of the model.

Fig. 4 Dog model results. A: schematic representation of the structural model; B: GoF plot of plasma individual predictions (Log scale).

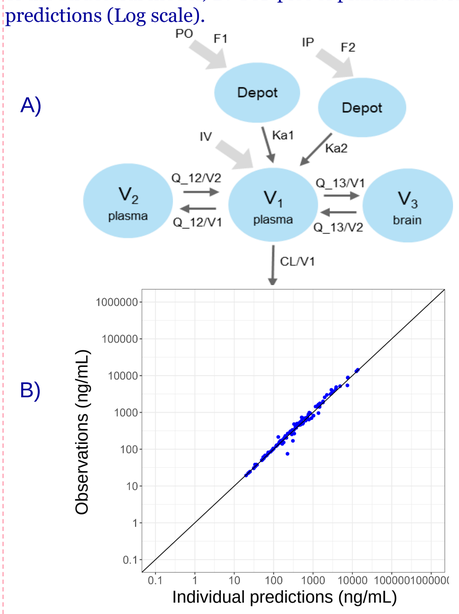


Tab. 2 Parameters estimates of the dog model.

Parameter	Estimate (CV%)	SE	RSE (%)
Fixed Effects			
ka1 (1/h)	2.11	0.46	21.8
ka2 (1/h)	0.17	0.024	14.1
F (-)	0.74	0.14	19.5
F1 (-)	0.83	0.028	3.42
Tlag2 (h)	5.56	1.23	22.0
Cl (L/h)	5.78	0.96	16.6
V1 (L)	2.78	0.53	19.0
Q (L/h)	4.15	1.01	24.3
V2 (L)	15.85	6.02	38.0
Standard Deviation of the Random Effects (ω)			
ka1	0.66 (73.92%)	0.15	23.2
F	1.22 (30.41%)	0.58	48.1
Cl	0.39 (40.50%)	0.09	23.0
Q	0.53 (56.47%)	0.24	46.3
V2	1.3 (209.65%)	0.36	27.4
Error Model Parameters			
b	0.46	0.034	7.48

RSE: Percentage of relative standard error (100%·SE/Estimate).
ω Represents the standard deviation of the interindividual variability parameter.
The parameter b is the proportional component of the residual error of the model.

Fig. 5 Mouse model results. A: schematic representation of the structural model; B: GoF plot of plasma individual predictions (Log scale).



Tab. 3 Parameters estimates of the mouse model.

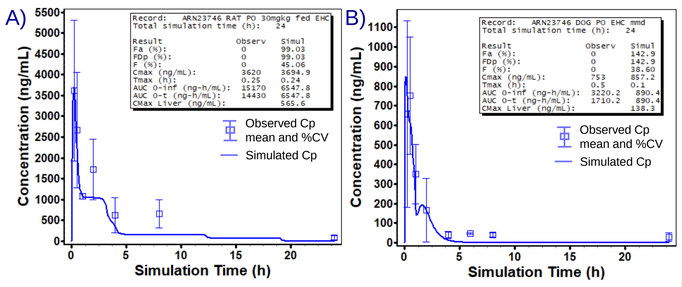
Parameter	Estimate (CV%)	SE	RSE (%)
Fixed Effects			
F1 (-)	0.95	0.073	7.77
ka1 (1/h)	6.79	1.38	20.3
F2 (-)	0.64	0.08	12.5
ka2 (1/h)	6.05	1.18	19.4
Cl (L/h)	0.02	0.0028	14.4
V1 (L)	0.0011	0.0015	138
V3 (L)	0.19	0.061	32.5
Q_13 (L/h)	0.00094	0.00015	15.7
V2 (L)	0.089	0.022	24.2
Q_12 (L/h)	0.047	0.0079	16.9
Standard Deviation of the Random Effects (ω)			
Cl	0.71 (81.02%)	0.11	15.9
V1	5.4 (>1000%)	1.33	24.6
V3	2.03 (785.64%)	0.24	11.9
Q_13	0.75 (86.83%)	0.14	18.4
V2	0.91 (113.67%)	0.18	19.7
Q_12	0.68 (76.2%)	0.15	22.2
Error Model Parameters			
b1	0.34	0.047	14.0
b3	0.17	0.055	32.0

RSE: Percentage of relative standard error (100%·SE/Estimate).
ω Represents the standard deviation of the interindividual variability parameter.
The parameters b1, b3 are the proportional components of the residual error of the model.

PBPK model

The PBPK model well predicted all preclinical species investigated, especially when enterohepatic circulation was considered (Fig.6). In addition, the model predicted rapid precipitation of the compound in the stomach, following redissolution and absorption along the intestinal tract. Indeed, the model correctly predicted the in vivo data, well capturing the multiple peaks observed following IAMA-6 oral administration.

Fig. 6 PBPK model results considering EHC contribution as simulated (continuous line) and observed (empty squares and bars) Cp profiles. Fig 6A reports rat PO; Fig 6.B reports dog PO.



Human dose prediction

Tab. 4 Human predicted parameters through allometric scaling

Parameter	CL (L/h)	V1 (L)	V2 (L)	Q (L/h)	T½ (h)
Human value	32.95	31.89	18.24	5.53	2.79

Fig. 7 Human Population PBPK model results. Simulation of 500 individuals administered with 200 mg of drug given as suspension (A) and as nanosuspension (B), both without and with EHC.

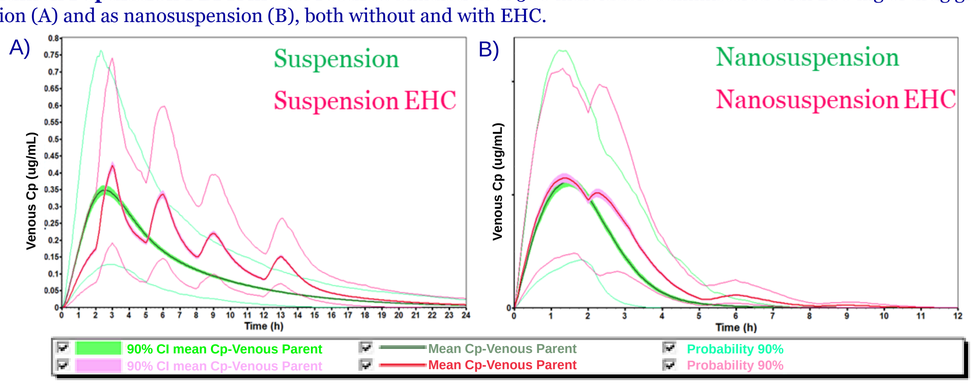
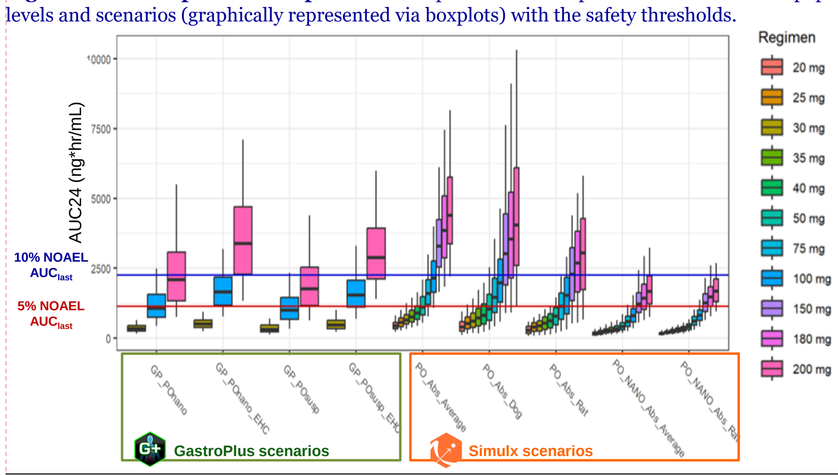


Fig. 8 Human PK predicted exposures. Comparison of the exposures of the simulated population obtained for different dose levels and scenarios (graphically represented via boxplots) with the safety thresholds.



The integrated PopPK-PBPK approach provided a human recommended starting dose of 30 mg/day, corresponding to median [25th-75th percentiles] predicted AUC24 following five Quaque Die (QD) administrations of 465 [223-893] ng·h/mL (looking at 5% exposure at NOAEL).

Conclusions

An integrated approach based on popPK and PBPK modelling has been proposed to predict IAMA-6 human exposure at different doses to support FIH dose selection to be tested for upcoming clinical trials. The popPK-PBPK modelling integration results in a robust approach to predict human PK considering both human physiology and information derived from preclinical species.

[1] Patel D, Dierks E. Single species Allometric Scaling: A Strategic Approach to Support Drug Discovery. Journal of Pharmaceutical Research International. 2018 May;22(3):1 7.
[2] EMA. Guideline on the Strategies to Identify and Mitigate Risks for First in human Clinical Trials with Investigational Medicinal Products. Committee for Medicinal Products for Human Use (CHMP). 2017 Jul.

Evotec SE, *Manfred Eigen Campus, Essener Bogen 7, 22419 Hamburg, Germany (Corporate Headquarters)*

CONTACTS:
chiara.roversi@evotec.com
alessia.tagliavini@evotec.com

info@evotec.com | www.evotec.com