Translational PBPK modeling of IDH305, an Inhibitor and Inducer of CYP3A4

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Background

IDH305 is a novel isocitrate dehydrogenase 1 (IDH1) inhibitor with antitumor activity in patient-derived xenograft (PDX) models of IDH1^{R132C} melanoma. It is a BCS/BDDCS II drug with low solubility, high permeability and metabolism mediated mainly by cytochrome P450 (CYP) 3A4. IDH305 modulated CYP3A4 as both a time-dependent inhibitor (TDI) and inducer *in vitro*. To support clinical development, physiology-based pharmacokinetic (PBPK) models were developed to predict human pharmacokinetics (PK). IDH305 has progressed into human clinical trials for the treatment of cancers with IDH1 mutation (1).

IDH305 is a weak base with a solubility in physiological gastrointestinal media between 0.1 to 0.4 mg/mL, and a high permeability in Caco-2 and PAMPA assays with no apparent significant efflux or influx transporter involvements.

IDH305 exhibited moderate-to-high clearance in rats and in monkey, while high clearance was observed in dog (with 62, 37 and 78% of hepatic blood flow, respectively). The steady-state volume of distribution was moderate (1.4- 7.2 L/kg). Estimated human CL (8 mL/min/kg) and Vd (3.6 L/kg) were obtained using recommended PK scaling methods (2), predicting an oral T1/2 near 6 h and possibility of BID dosing.

Absorption was complete in a rat radiolabeled study after PO dosing. Bioavailability was moderate in rat and monkey (25 - 63%) and high in dogs (~100%).

IDH305 showed time-dependent inhibition of CYP3A4/5 (*KI* and kinact were 13.6 µM and 0.0259 min-1, respectively). Notably, IDH305 induced CYP3A4 mRNA in human hepatocytes (EC_{50} and E_{max} values 3.61 µM and 22.2-fold, respectively).

With TDI and induction IDH305 could impact its own metabolism, leading to potential increased (time-dependent inhibition) or decreased IDH305 exposure (induction) after multiple dosing.

To support clinical development, two physiology-based pharmacokinetic (PBPK) models were developed to predict human pharmacokinetics (PK). Questions were: a) will light meal alter exposure and b) Will there be accumulation or lower exposure at steady state.

Methods

A PBPK absorption (GastroPlus) model describing IDH305 absorption dosing was developed to evaluate the food effect on PK. Gut physiologies in fasted and light-meal condition were used. An early "bottom-up" model had identified no food effects.

A PBPK (Simcyp) model was developed to predict counteracting interplays of TDI and induction following single and multiple dosing. PK in humanized tADMET CYP3A4 mice was studied (8 mg/kg, po) to investigate steady state.

Clinical IDH305 plasma pharmacokinetics data after a light meal (Fed LM , ~ 500 kcal) were available using an immediate release tablet. Doses of 75-900 mg BID in a Phase I trial in patients with advanced malignancies that harbor IDH1^{R132} mutations were tested.

Following single oral administration IDH305 exhibited absorption with median Tmax ranging from 1 to 3 h (Table 2). Minimal accumulation was observed (mean accumulation ratio (Racc) 1.1-2.4 fold)

Results (GastroPlus)

The "middle out" food-effect PBPK model prediction agreed with observed data (Table 1, Fig 1 and 2). The model predicted rapid absorption and that a light meal had little impact on systemic exposure, consistent with clinical data

Table 1: IDH305 300 mg (Day 1, Single Dose) predicted and observed Human PK parameters in light meal (LM) and fasted state (Mean Profile Data)

	Fed LM Pred	Fed LM Obs	Rsq	Fasted Pred	Fasted Obs	Rsq	Pred FE	Obs FE
Cmax (ng/mL)	768	850	0.91	809	800	0.94	0.96	1.06
Tmax (h)	2.6	3		2.4	2.0		--	
AUC_{0-12h} (ng/mLh)	5520	5710		5564	5318		0.99	1.0

FE Ratio = FED (LM) value/Fasted Value

Fig 1: Light Meal IDH305 Obs. vs. Pred. Human Pharmacokinetics, PBPK Virtual Trial (GastroPlus)

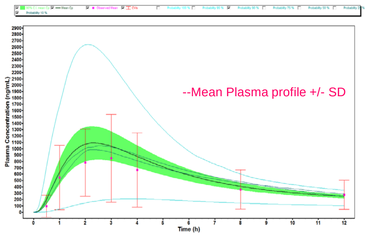
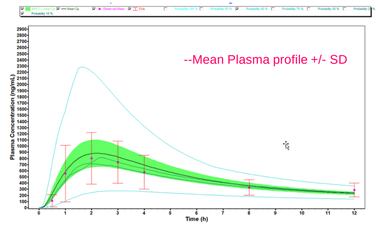


Figure 2: Fasted IDH305 Obs. Vs. Pred. Human Pharmacokinetics, PBPK Virtual Trial (GastroPlus)



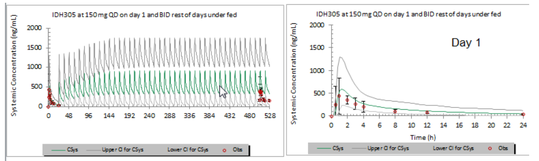
Results (Simcyp)

Predicted exposures on Day 1 and Day 21 were in agreement with observed clinical data i.e. 150 mg BID (< 1.7 fold prediction error). Predicted accumulation ratios (Racc) were 1.5-1.7 following multiple BID dosing (Fig 3), in agreement with patient data (Racc 1.1-2.4). Humanized mice (Racc 1.8-2.2) showed a similar trend Fig. 4.

Table 2: IDH305 observed clinical data on Day 1 and steady state in fed (light-meal) patients, selected dose groups (data cut-off date: November 30, 2016**)**

	Geometric Mean (Geometric CV%)														
	Cycle 1 Day 1								Cycle 2 Day 1 Day 21						
BID Dose (mg)	N[a]	Cmax (ng/mL)	Tmax (h)[b]	AUCtau (h*ng /mL)	AUCinf (h*ng/mL)	T1/2 (h)	CL/F (L/h)	Vz/F (L)	N[a]	Cmax (ng/mL)	Tmax (h)[b]	AUCtau (h*ng /mL)[c]	T1/2eff (h)	CLss/F (L/h)	Racc
75	6	328 (69.8)	1.96 (1.03 - 4)	1590 (49.7)	2690 (44.3) (N=2)	6.47 (38.4) (N=2)	27.9 (44.3) (N=2)	261 (93.7) (N=2)	3	458 (62.8)	2.00 (2-2.05)	3140 (62.0)	15.1 (36.0)	23.9 (62.0)	2.38 (26.7)
150	11	568 (49.0)	1.08 (0.58 - 3.12)	2350 (46.3)	3170 (66.8) (N=4)	8.7 (22.3) (N=4)	47.4 (66.8) (N=4)	595 (46.1) (N=4)	9	631 (51.5)	1.07 (0.5-3.17)	3400 (54.3)	7.53 (52.5)	44.2 (54.3)	1.55 (29.1)
300	17	923 (69.6)	2.17 (1 – 7.83)	4810 (61.6)	5270 (33.4) (N=3)	9.54 (36.3) (N=3)	56.9 (33.4) (N=3)	783 (68.1) (N=3)	13	1040 (59.1)	2.00 (0.67-3.12)	5960 (51.6) (N=11)	6.64 (44.5) (N=10)	50.3 (51.6) (N=11)	1.36 (30.1) (N=11)

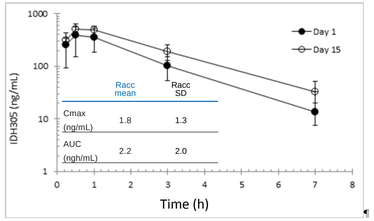
Fig. 3: IDH305 Obs vs. Pred Data between Day 1 and Steady State, Day 21, for 150 mg (PBPK, Simcyp)



Predicted, 150 mg

	Cmax (ng/mL)	AUC0-12 (ngh/mL)
Day 1	612 ± 312	3655 ± 1880
Steady State	945 ± 571	6178 ± 5559
[46]Racc	1.5	1.7

Fig. 4: IDH305 Mean profiles after 8 mg/kg/day for 15 days in humanized mice (N = 4)



Conclusions

Custom Human PBPK gut absorption and metabolism models were developed for IDH305, a time-dependent inhibitor and inducer of CYP3A4, to describe its metabolism and predict food effect on PK. Predicted IDH305 profile data were in good agreement with observed clinical data.

Based on the predicted lack of a food effect, light meal consumption was allowed in patients in the first-in-human study.

References

(1) Young Shin Cho, et.al. *ACS Medicinal Chemistry Letters* **2017** *8* (10), 1116-1121

(2) Ring B Et al. J Pharm Sci. 2011 Oct;100(10):4090-110. doi: 10.1002/jps.22552. Epub 2011 May 3.

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