Supplementary Information

Clinical Pharmacokinetics

Impact of Preclinical Verification in Physiologically Based Pharmacokinetic Modelling for First-In-Human Predictions – Application of a Published Model Building Strategy for Five Compounds

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Appendix

Table S 1 - ADMET Predictor predicted properties used for PBPK modelling approach 1 for the 5 compounds.

Compound	**1**	**2**	**3**	**4**	**5**
Distribution					
LogP	3.45	4.08	4.13	2.05	3.14
pKa	11.09 (A); 10.69 (A); 8.69 (A); 7.21 (B)	6.91 (A); 1.90 (B)	8.14 (A); 2.64 (B); 1.87 (B); -3.74 (B)	7.17 (B)	3.79 (B); 1.88 (B); -0.94 (B)
Human Fu_p (%)	7.75	4.11	3.23	21.80	8.78
Human RBP	1.08	0.59	0.61	0.91	0.83
Elimination					
Clearance *HLM CLp (L/h)*	7.94	7.59	4.12	14.66	6.68
Absorption					
Reference solubility mg/mL (pH)	0.006 (7.86)	0.009 (5.87)	0.015 (6.32)	1.57 (9.39)	0.28 (7.34)
BSSR (number)[a]	3923	15200	4460	0	0
Peff ($x10^{-4}$ cm/s)	0.91	0.96	3.36	1.10	2.74

pKa acid (A) and base (B); Fu_p, fraction unbound in plasma; RBP, blood to plasma ratio; HLM, human liver microsomes; CLp, plasma clearance; BSSR, bile salt solubilisation ratio; Peff, effective jejunal permeability.

[a] Calculated from predicted FaSSIF and FeSSIF (Fed Simulated Small Intestinal Fluid) solubility [17]

Table S 2 – Measured properties for the 5 compounds

Compound	1	2	3	4	5
Distribution Inputs					
LogP	3.84	3.46	3.83	2.63	2.39
pKa	4.88 (A), 8.43 (B)	6.3 (A)	7.92 (A)	NA	3.28 (B)
Fu_p (%)	3.92(m),9.25(r), 5.96(d), 2.18(h)	0.6(r), 0.8(d), 1(h)	0.098(h) 0.184(r, Fub)	24(m)[a], 58(r)[a], 11(d), 10(h)	8.2(r), 21(d), 13(h)
RBP	1.1(m),0.92(r), 1.07(d), 0.61(h)	0.65(r), 0.61(d), 0.58(h)	NA	0.92(m), 0.48(r), 0.74(d), 0.75(h)	NA
Elimination					
Clearance *in vitro* (mL/min/g)	Hepatocytes; 0.315h). All others BLQ.	Hepatocytes; 1.72(r), BLQ (d, h). Microsomes; 2.11(r), 2.03(h), BLQ(d)	Hepatocytes; 0.74(r), 7.29(d), 2.52(h). Microsomes; 0.48(r), 4.16(h).	Hepatocytes; 7.0(m), 2.5(r), 1.5(d), 0.81(h). Microsomes; 0.96(m), 3.1(r), 0.95(d), 1.4(h).	Microsomes; 0.53(r), 1.04(d), 0.65(h).
CL_{blood} *in vivo* (mL/min/kg)	32(m), 12(r), 1(d)	15(r), 9(d).	13(r), 5(d), 12(c)	105(m), 111(r), 27(d).	6.9(r), 2.0(d)
CLr (mL/min/kg)	NA	NA	NA	NA	0.12(r), 0.15(d)
Absorption Inputs					
Reference solubility mg/mL (pH)	0.006 (8)	0.002 (4)	0.0021 (6)	0.35 (8)	0.0014 (8)
FaSSIF Solubility mg/mL (pH)	0.01 (6.5)	0.01 (6.5)	0.010 (6.5)	1.03 (6.5)	0.0039 (6.5)
FeSSIF Solubility mg/mL (pH)	0.08 (5.0)	0.023 (6.5)	0.091 (5)	3.9 (5)	0.0166 (6.5)
Peff ($x10^{-4}$ cm/s)[b]	NA	1.986	2.62	2.37	NA
Particle radius (µm)	0.9	0.107	7.5	NA	NA

NA, not applicable/available; Mouse (m), Rat (r), Dog (d), Cynomolgus monkey (cy) and Human (h); pKa acid (A) and base (B); Fu_p, fraction unbound in plasma; Fub, blood to plasma ratio; RBP, blood to plasma ratio; CL_{blood}, total blood clearance; CLr, renal clearance; Peff, effective jejunal permeability.

[a] Fu_p data unreliable due to instability

[b] Peff values were converted from MDCK-hMDR1 Pexact [30] using an internally derived correlation equation

BLQ = Below Lower limit of Quantification

NA – not available.

Table S 3 - Classification of the 5 compounds based on preclinical species in vivo pharmacokinetic characteristics.

	Blood Clearance				Vss				Bioavailability			
	Mouse	Rat	Dog	Monkey	Mouse	Rat	Dog	Monkey	Mouse	Rat	Dog	Monkey
Compound 1	low	low	low	na	moderate	moderate	moderate	na	low	moderate-high[a]	low-high[b]	na
Compound 2	na	low	low	na	na	moderate	high	na	na	moderate - high[b]	moderate-high	na
Compound 3	na	low (SD), moderate (WH)	low	low	na	moderate (SD), high (WH)	moderate	moderate	na	moderate (SD), high (WH)	moderate	low
Compound 4	high	high	moderate	na	moderate	high	moderate	na	low	low	low	na
Compound 5	na	low	low	na	na	moderate	high	na	na	moderate (sl), low (c-sn), high (SDD-sn)	high (sl), moderate-high (SDD-sn)	na

SD = Sprague-Dawley, WH = Wistar Han, sl = solution, c-sn = crystalline suspension, SDD-sn spray-dried dispersion suspension.

Blood clearance categorised by percentage of liver blood flow where low is 0-33%, moderate is 34-66% and high is >66%.

Vss is categorised as compared to total body water, where low is <0.6 L/kg, moderate is 0.6 – 2 L/kg and high is >2 L/kg.

Bioavailability categorised where low is 0-33%, moderate is 34-66% and high is >66%. Combined categories denote study variability.

[a] variability identified as formulation dependent.

[b] variability identified as dose dependent.