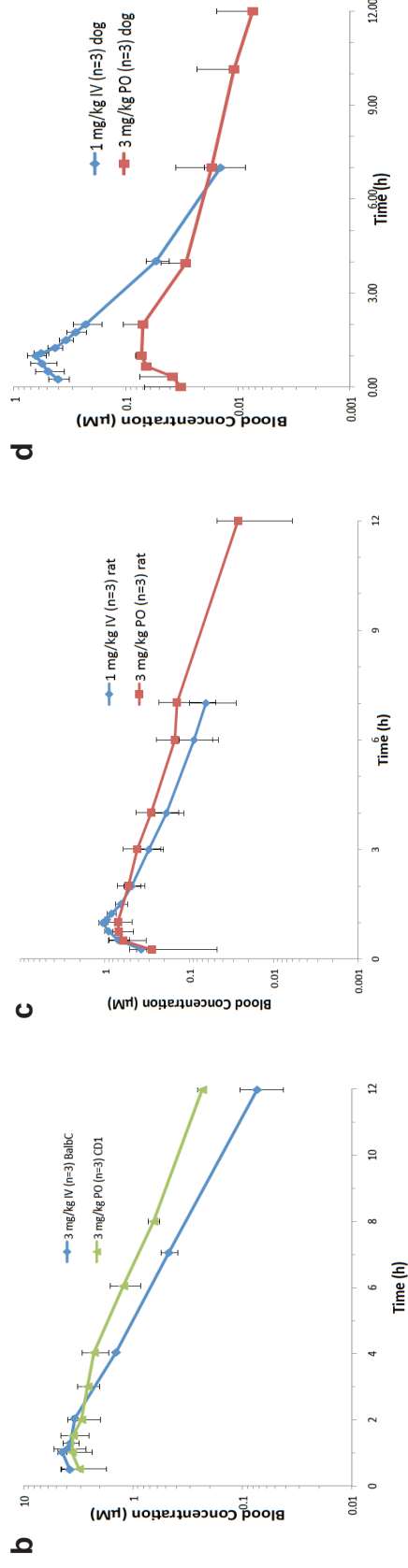


Supplementary Figure 20

a

	Mouse (n=3)	Rat (n = 3)	Dog (n=3)
IV dose (mg/kg)	3	1	1
CLb (mL/min/kg)	8 ± 1	18 ± 5	38 ± 10
Vss (L/kg)	1.2 ± 0.1	2.1 ± 0.1	3.0 ± 0.6
t _{1/2} (h)	1.8 ± 0.3	1.7 ± 0.3	1.2 ± 0.1
MRT (h)	2.5 ± 0.2	2.1 ± 0.5	1.3 ± 0.1
AUC _{last} (uM/h)	15.0 ± 1.5	2.3 ± 0.5	1.1 ± 0.3
AUC _∞ (uM/h)	15.3 ± 2.3	2.4 ± 0.6	1.2 ± 0.3
Oral dose (mg/kg)	3	2	3
C _{max} (uM)	3.87 ± 1.03	0.72 ± 0.24	0.09 ± <0.1
T _{max} (h)	1.02 (1.0 – 1.5)	0.75 (0.5 – 1)	2 (0.7 – 3.9)
t _{1/2} (h)	2.6 ± 0.3	2.1 ± 0.3	4.7 and 2.2 (n = 2)
AUC _{last} (uM/h)	18.2 ± 4.9	2.8 ± 1.1	0.5 ± 0.2
AUC _∞ (uM/h)	19.1 ± 4.8	2.9 ± 1.2	0.8, 0.3 (n=2)
F (%)	ca. 100%	66 ± 26	16 ± 3

(based on AUC_{last} data)



Supplementary Figure 20: (a) The preclinical pharmacokinetics of I-BET151 determined in mouse, rat and dog. All intravenous doses were infused over 1h. For mouse studies male Balb/C mice were used for the intravenous experiments and male CD1 mice were used for the oral experiments. Male Sprague Dawley rats and male beagle dogs were used in a crossover manner with an appropriate washout period between doses (3 days for rat, 7 days for dog). For intravenous doses I-BET151 was dissolved in normal saline containing 2% (v/v) DMSO and 10% (w/v) Kletopse HPB. For oral dose I-BET151 was suspended in 1%(w/v) methylcellulose (CP400). Serial blood samples were taken and analysed as described previously. Pharmacokinetic data analysis was performed using non-compartmental analysis and WinNonlin Phoenix v6.1 software. Mean ± SD data (except T_{max} [mean and range]) are shown below. Calculated pharmacokinetic parameters show low clearance (CLb) with high oral bioavailability (F_{po}) in mouse and rat, with higher clearance and lower oral bioavailability in the dog. Volume of distribution at steady state (V_{ss}) varied from 1 to 3 L/kg indicative of tissue distribution. Terminal half-lives (t_{1/2}) were between 1.2 and 1.8 h with corresponding mean residence times (MRT) of 1.3 to 2.5 h. C_{max} is the maximum blood concentration determined at time T_{max}. AUC_{last} and AUC_∞ are the area's under the curve to the last data point and extrapolated to infinity, respectively. Data are expressed graphically as follows: (b) Mean ± SD (n = 3) blood concentration-time profiles of I-BET151 after intravenous (1 h infusion) and oral administration to the mouse. (c) Mean ± SD (n = 3) blood concentration-time profiles of I-BET151 after intravenous (1 h infusion) and oral administration to the rat. (d) Mean ± SD (n = 3) blood concentration-time profiles of I-BET151 after intravenous (1 h infusion) and oral administration to the dog.