Table 1 Patch clamp assay data available for modelling. Data included in the current analysis are marked with an asterix (*). ** For the sake of completeness, IC_{50} values derived from the original experimental protocols are also presented along with the experimental protocol details. These estimates may differ from the values obtained by nonlinear mixed effects modelling, which was used to analyse the data in the current investigation.

Compound	Dataset ID	# of cells tested	Cell line	Temperature	$[K^+]$ (mM)	Voltage protocol steps	Concentration range tested (nM)	IC_{50} observed**
Cisapride	225*	11	HEK293	RT	4	-80mV +20mV 5sec -50mV 5sec 80mV	1,3,10,30,100	6.8
	248	9	HEK293	RT	10	-80mV +30mV 1sec -80mV	0.0195, 0.0391, 0.156, 0.313, 0.625, 1.25, 2.5, 5, 10, 20	938
	249	4	HEK293	RT	5.3	-80mV +30mV 1sec -80mV	3,10,30,100	18
	254	7	HEK293	RT	4	-80mV -60mV 0.5sec +60mV 2sec -40mV 6sec	10, 100, 1000	65
	256	3	HEK293	RT	4	-80mV +20mV 4sec -50mV 3sec -80mV 8sec	1,10,100	19
moxifloxacin	240*	17	HEK293	RT	5.4	0mV -80mV 20ms +40mV 80ms	1000, 10000, 100000,300000, 1000000	353600
	252*	5	HEK293	RT	5.3	-80mV +30mV 1sec -80mV	10000, 30000, 100000, 300000	141000
	254*	6	HEK293	RT	4	-80mV -60mV 0.5sec +40mV 2 sec -40mv 6sec	30000, 100000, 300000	122000
Sotalol	217*	4	HEK293	RT	4	-80mV +20mV 0.5sec -50mV 5 sec -80mV	10000,30000, 100000,300000	163000
	222*	4	HEK293	RT	4	-80mV +20mV 0.5sec -50mV 5 sec -80mV	10000,30000, 100000,300000	117000

Table 2a: Mean parameter estimates (90% confidence intervals) and derived pharmacokinetic-pharmacodynamic indices IC_{20}, IC_{70} and IC_{80}, i.e., the inhibitory concentrations associated with 20, 70 and 80% binding, respectively. Data (n=3 for each experimental point) from the equilibrium [^{3}H] dofetilide binding displacement assay were analysed using an Imax model. I_0 represents the percentage [^{3}H] dofetilide binding in the absence of a competing molecule.

	Cisapride	**Moxifloxacin**	**Sotalol**
I0 (%)	98.1 (96.5-99.7)	94.0 (90.9-97.2)	99.7 (97.9-101.6)
Imax (%)	99.5 (96.0-103.0)	104 (94.0-114.5)	103 (100.3-106.3)
IC_{50} (μM)	0.1 (0.086-0.12)	1030 (752-1466)	56.4 (50.4-63.2)
IC_{20} (μM)	0.02	160.68	13.32
IC_{70} (μM)	0.22	1649.88	117.18
IC_{80} (μM)	0.36	2543.77	190.81

Table 2b: Population parameter estimates for cisapride (n=11), moxifloxacin (n=28) and sotalol (n=8) in the hERG patch clamp assay. Experimental data obtained with the different compounds were analysed concomitantly. System-specific parameters (I_0, Imax and Hill coefficient (γ)) were unique to the experimental setting. Only IC_{50} varied for each compound. A separate additive error term was estimated for cisapride due to the higher residual variability in those experiments.

Parameter	**Cisapride (n=11)**	**Moxifloxacin (n=28)**	**Sotalol (n=8)**
I_0 (%)	6.43%		
I_{max} (%)	95.7%		
IC_{50} (nM)	3.57	227000	103000
γ	*0.887*		
Interindividual variability	60%		
Additive error	57.7%	23.3%	

Table 2c: Population pharmacokinetic-pharmacodynamic parameter estimates along with 90% credible intervals describing the probability of QT interval prolongation $\geq$ 10 ms, as reported by Chain and Dubois et al., 2013. Data analysis was performed using a Bayesian hierarchical model, which comprises three components, namely: an individual correction factor for RR interval (heart rate), an oscillatory component describing the circadian variation and a truncated Emax model, which is parameterised in terms of a slope.

Primary and derived model parameters	Cisapride		moxifloxacin		Sotalol	
	dogs (n=8)	healthy subjects (n=24)	dogs (n=8)	healthy subjects (n=137)	dogs (n=6)	healthy subjects (n=30)
Slope [ms nM^{-1}]	0.0045 (0.00096 - 0.0098)	0.09 (0.087 - 0.12)	0.00056 (0.00002 - 0.0014)	0.0039 (0.0033 - 0.0044)	0.002 (0.0006 - 0.008)	0.021 (0.017 - 0.026)
Prob. of $\geq$ 10 ms increase at Cmax	0.75	1.0	1.0	1.0	0.9	1.0
Cmax [nM]	2808	936	112930	10300	22310	5605
CP50 [nM]	2200	140	6400	2644	4600	470

Table 3 Summary table for the comparison between *in vitro* (dofetilide displacement, functional assay) and *in vivo* (probabilities of QT prolongation *in vivo* in dogs and humans) data, where CP50D and CP50H is the concentration associated with a 50% probability of reaching ≥ 10msec increase of the QT interval in dogs and humans respectively. The onset of inhibition (Oinh) was obtained by log-linear regression using mean IC20, IC_{50} and IC70 estimates from the displacement assays. IC_{50} values are population parameter estimates of the nonlinear mixed effect modelling of patch clamp assays.

	Cisapride	**Moxifloxacin**	**Sotalol**
CP50 dogs (CP50D) [µM]	2.23	6.39	4.62
CP50 healthy subjects (CP50H) [µM]	0.14	2.64	0.47
Onset of inhibition (Oinh) [µM]	0.09992	62.62	5.69
Ratio Oinh/CP50D	0.004	9.8	1.2
Ratio Oinh/CP50H	0.07	23.7	12.1
IC_{50} **(**IC_{50}**) [µM]**	0.00357	227	103
Ratio IC_{50}**/CP50D**	0.0016	35.53	22.3
Ratio IC_{50}**/CP50H**	0.026	86.0	219.1