Supplementary material

Rat telemetry study design

AZ1 was dosed at 10 (single dose), 100 (daily dosing for three days) and 450 mg/kg (single dose). Regorafenib was dosed at 8 and 16 mg/kg (daily dosing for three days). The study design is outlined in Table 1. In Speed *et al.*, rat PK was performed at 15 mg/kg sunitinib (single dose) and in Engle *et al.*, rat telemetry was performed at 5 and 50 mg/kg (daily dosing for three days) (Engle & Watson, 2016; Speed et al., 2012).

Supplementary Table 1: Study design for rat telemetry study with AZ1 and regorafenib.

Compound	**AZ1**	**Regorafenib**
n size	6	6
Test occasion 1: **Day, test item and dose**	Day 0: control (vehicle) Day 1: AZ1 (450 mg/kg)	Day 0: control (vehicle) Day 1: Regorafenib 8 mg/kg Day 2: Regorafenib 8 mg/kg Day 3: Regorafenib 8 mg/kg
Test occasion 2: **Day, test item and dose**	Day 0: control (vehicle) Day 1: AZ1 (10 mg/kg)	Day 0: control (vehicle) Day 1: Regorafenib 16 mg/kg Day 2: Regorafenib 16 mg/kg Day 3: Regorafenib 16 mg/kg
Test occasion 3: **Day, test item and dose**	Day 0: control (vehicle) Day 1: AZ1 (100 mg/kg) Day 2: AZ1 (100 mg/kg) Day 3: AZ1 (100 mg/kg)	-
Dose volume	10 ml/kg	5 mL/kg

Plasma concentrations in rat telemetry study

Supplementary table 2 shows the observed mean concentrations at 2 hour post dose of AZ1 and regorafenib. Concentrations were below the limit of quantification on vehicle dosed days.

Supplementary Table 2: Concentrations obtained at 2 hours post dose in the rat telemetry study.

Compound	**Dose level (mg/kg)**	**Test occasion**	**Day**	**Mean concentration 2 hours post dose (SD) (µM)**
AZ1	450	1	1	112 (9.32)
	10	2	1	8.7 (0.949)
	100	3	1	54.0 (6.79)
	100	3	2	56.7 (10.9)
	100	3	3	64.6 (5.15)
Regorafenib	8	1	1	0.246 (0.118)

8	1	2	0.413 (0.184)
8	1	3	0.461 (0.237)
16	2	1	0.347 (0.168)
16	2	2	0.555 (0.272)
16	2	3	0.663 (0.271)

Literature reports of clinical BP exposure-response at steady state

The literature PKPD reports used in the analysis for BP elevation are shown in supplementary table 3.

Supplementary Table 3 Overview of Clinical PKPD models of BP changes with VEGFR-2 inhibitors used in analysis.

Compound	**Axitinib**	**Sunitinib**	**Sunitinib**	**Sunitinib**
Report	(Chen *et al*., 2015)	(Houk *et al*., 2010)	(Khosravan *et al*., 2016)	(Lindauer et al., 2010)
Dose schedule	2-10 mg BD for 15 days	25-150 mg QD or QOD	25-75mg QD: continuous, 4weeks on 2 off, or 2 weeks on 1 off	50 mg QD for 4 weeks
Patient population	Metastatic renal cell carcinoma (RCC)	Advanced solid tumours, including gastrointestinal stromal tumour (GIST) and RCC	GIST and RCC	Healthy subjects
DBP/SBP simulated	DBP	DBP	DBP	DBP
PK model	Linear 2 compartment with first order absorption	Not reported	2 compartment with first order absorption and elimination for sunitinib and its metabolite SU12662	2 compartment model for sunitinib with pre-systemic and systemic metabolism to metabolite SU12662 and transit compartment for delayed absorption.
PD model	Type 3 indirect response model (IDR) with Emax function	Emax function	Type 2 IDR with linear drug function	Proportional function with immediate and slow (transducing) functions

Results of PKPD modelling analysis in rat

The parameter estimates derived from the PKPD analysis of the in house telemetry studies (AZ1 and regorafenib) are shown in supplementary tables 4 and 5 respectively. The PKPD model fits versus observations for AZ1 and regorafenib are shown in supplementary figures 1 and 2. Supplementary table 6 shows the parameter estimates obtained using the literature mean BP data for sunitinib in the rat, and the model fit versus observations is shown in supplementary figure 3.

Supplementary Table 4: Final parameter estimates for PKPD model estimated from rat telemetry study with AZ1 (PK was fixed). A handling effect was included as described in Equation 1

Parameter	Estimate (dose in mg/kg)	%RSE	%BSV (%RSE)	%IOV (%RSE)
k_a (h^{-1})	0.26 (10) 0.1357 (100) 0.0226 (450)	-	-	-
V (L/kg)	0.701 (10) 0.247 (100) 0.0477 (450)	-	-	-
k_e (h^{-1})	0.66 (10) 1.87 (100) 5.49 (450)	-	-	-
P_{BP}	15.1	8.0	22.4 (27)	-
k_{HD} (h^{-1})	0.028	14.2	-	-
slope (μM) $^{-1}$	0.45	8.7	-	-
E_0 (mm Hg)	137.0	1.2	-	3.1 (28)
k_{e0} (h^{-1})	0.013	14.1	66 (12)	-

Supplementary Table 5: Final parameter estimates for PKPD model estimated from rat telemetry study with regorafenib (PK was fixed). No handling effect was required.

Parameter	Estimate	%RSE	%BSV (%RSE)	%IOV (%RSE)
k_a (h^{-1})	0.071	-	-	-
V (L/kg)	7.24	-	-	-
k_e (h^{-1})	0.213	-	-	-

slope (µM) $^{-1}$	12.1	15.7	41.3	-
E_0 (mm Hg)	130.5	4.0	32.9 (58)	216.6 (158)
k_{e0} (h^{-1})	0.047	14.5	3.0 (37)	-

Supplementary Table 6: Sunitinib Rat telemetry parameter estimates (PK was fixed during PD estimation) using PK model estimated from data in Speed *et al* and average rat BP from Engle *et al*. No mixed effects (i.e. IIV or IOV) or handling effect was included in the final model fit.

Parameter	Estimate	%CV
k_a (h^{-1})	0.115	-
V (L/kg)	14.8	-
CL (L/h/kg)	1.72	-
slope (µM) $^{-1}$	22.62	36.7
E_{BL} (mm Hg)	99.43	1.4
k_{e0} (h^{-1})	0.0057	51
Amp	2.80	17.3
Tshift	17.45	10.1
Freq	22.7	1.7

PKPD model parameters used in simulations for human PKPD reports

Supplementary table 7 contains the parameter estimates and equations used in the simulation of PK metric versus BP elevation. The time course of effects could not be replicated for Lindauer et al. since the data was converted to a ratio of BP increase rather than raw BP effect, where the model was driven by concentrations of sunitinib and its active metabolite SU12662, which are at similar concentrations following dosing with the parent drug. In the model these are assumed to be equipotent so rather than simulate the time course which included an immediate and slow transducing effect, the underlying steady state relationship accounting for both effects was used.

This dual drug effect function at steady state which predicted ~11 mm Hg change at 100 ng/mL which was in line with the observed level of effect. The resulting PK metrics were converted into µM units for comparison to VEGFR-2 potency.

Supplementary Table 7: Overview of approach to simulate exposure-response relationship for clinical PKPD reports.

Compound	**Axitinib**	**Sunitinib**	**Sunitinib**	**Sunitinib**
Report	(Chen, *et al*., 2015)	(Houk *et al*., 2010)	(Khosravan *et al*., 2016)	(Lindauer et al., 2010)
Dose range simulated	0.2 to 20 mg	C_{trough} 0.0001 to 0.1 ug/mL	1-75mg	Total Concentrations up to 100 ng/mL
PK parameter estimates	k_a=0.482 h^{-1} V_c/F=47.3 L V_p/F=393 L Cl/F=14.6 L/h Q/F=4L/h Tlag=0.454 h	-	k_a=0.126 h^{-1} V_c/F=2700 L V_p/F=774 L Cl/F=34.1 L/h Q/F=0.688 L/h	-
PD model equations	$dDBP/dt=k_{in}\cdot(1+E_{max}.C)/(EC_{50}.C))-k_{out}.BP$ BP change=DBP(t)-E_0	$DBP(t)=E0+E_{max}.C_{trough}/C_{trough}+EC_{50}$ BP change=DBP(t)-E_0	$dDBP/dt=k_{in}.(k_{PD}.C)-k_{out}.BP$ $k_{in}=k_{out}.E_0$ BP change=DBP(t)-E_0	$DBP(t)=E_0.(1+\alpha_{dia}(2.INH))$ $INH=C.f_u/(kd+ C.f_u)$ BP change=DBP(t)-E_0
PD Parameter estimates	E_0=72.4 mm Hg k_{out}=0.254 h^{-1} E_{max}=0.208 EC_{50}=12.4 ng/mL	E_0=74 mm Hg E_{max}=17 EC_{50}=0.084 µg/mL	k_{PD}=0.00184 $(mg/L)^{-1}$ E_0=74.6 mm Hg k_{out}=0.0288 h^{-1}	E_0=67.6 mmHg k_d=4 ng/mL α_{dia}=0.145 f_u=0.05

VEGFR-2 potency

The IC_{50} values obtained in the different assays together with relevant species' f_u are summarised in supplementary table 8 and table 9.

Supplementary Table 8 VEGFR-2 IC_{50} values from HUVEC, PAE and SPR assays, and rat and human f_u where relevant. *was obtained from Wilhelm *et al*., 2011.

Compound	***HUVEC, IC_{50}* (µM)**	***PAE, IC_{50}* (µM)**	***SPR, IC_{50}* (µM)**	**rat PPB f_u**
AZ1	0.341	0.836	0.439	0.065

rat PPB fu = fraction unbound based on rat plasma protein binding

Reported incidence of clinical hypertension

The patient population and references for each reported incidence of clinical hypertension used in the analysis is detailed in supplementary table 9. The PK metrics were converted into μM units for comparison to VEGFR-2 potency.

Supplementary Table 9: References for studies used to determine the incidence of hypertension for tyrosine kinase inhibitors

Drug	MW	Dose (mg/day)	Free Cmax (μM)	Free AUC (μM.hr)	Free Cav (μM)	HT Grade 1-4 (%)	HT Grade 3-4 (%)	PPB f_u	HUVEC IC_{50} (μM)	SPR IC_{50} (μM)	PAE IC_{50} (μM)	Cmax/HUVEC (μM)	Cmax/SPR (μM)	Cmax/PAE (μM)	AUC/HUVEC (μM)	AUC/SPR (μM)	AUC/PAE (μM)	Cav/HUVEC (μM)	Cav/SPR (μM)	Cav/PAE (μM)	References
Axitinib	386	4	0.000673	0.005	0.0004	0		0.01	5.28E-05	0.00008	0.0006	12.7	8.9	1.1	89.7	62.6	7.8	7.5	5.2	0.6	(Rugo et al., 2005)
		10	0.000699	0.007	0.0006	0						13.2	9.2	1.1	126.4	88.3	10.9	10.5	7.4	0.9	(Locati et al., 2014)
		10	0.00163	0.012	0.0010	0						30.9	21.6	2.7	221.0	154.4	19.1	18.4	12.9	1.6	
		15	0.002122	0.019	0.0008	17						40.2	28.1	3.5	351.4	245.4	30.4	14.6	10.2	1.3	
		40	0.004192	0.056	0.0047	50						79.4	55.4	6.9	1063.9	743.1	92.0	88.7	61.9	7.7	
		10		0.008	0.0007	54									154.9	108.2	13.4	12.9	9.0	1.1	
Brivanib	370	800	0.23	2.2	0.1	41	13	0.013	0.0118	0.0308	0.0375	19.6	7.5	6.2	186.2	71.6	58.8	7.8	3.0	2.4	(Jonker et al., 2011)
Crenolanib	444	100	0.06	0.42	0.02	0	0	0.0796	1.258	>2	>5	0.05	0.03	0.01	0.33	0.21	0.08	0.02	0.01	0.00	(Lewis et al., 2009)
		200	0.14	0.93	0.04	0	0					0.11	0.07	0.03	0.74	0.46	0.19	0.03	0.02	0.01	
		280	0.22	2.06	0.10	0	0					0.17	0.11	0.04	1.64	1.03	0.41	0.08	0.05	0.02	
		340	0.31	2.75	0.13	0	0					0.25	0.16	0.06	2.18	1.37	0.55	0.10	0.06	0.03	
		120	0.09	0.58	0.05	0	0					0.07	0.05	0.02	0.46	0.29	0.12	0.04	0.03	0.01	
Dasatinib	488	50	0.00	0.019	0.001	0	0	0.0425	>0.771	>5	>10	0.0062	0.001	0.0005	0.02485	0.004	0.002	0.0010	0.0002	0.0001	(Aplenc et al., 2011)
		65	0.01	0.031	0.001	0	0					0.0168	0.003	0.0013	0.03987	0.006	0.003	0.0017	0.0003	0.0001	(Demetri et al., 2009)
		85	0.01	0.042	0.002	0	0					0.0155	0.002	0.0012	0.05467	0.008	0.004	0.0023	0.0004	0.0002	
		110	0.02	0.057	0.002	0	0					0.0234	0.004	0.0018	0.07331	0.011	0.006	0.0031	0.0005	0.0002	
		35	0.00	0.007	0.000	0	0					0.0021	0.000	0.0002	0.00949	0.001	0.001	0.0004	0.0001	0.0000	
		50	0.00	0.014	0.001	0	0					0.0049	0.001	0.0004	0.01785	0.003	0.001	0.0007	0.0001	0.0001	
		70	0.00	0.014	0.001	0	0					0.0028	0.000	0.0002	0.01819	0.003	0.001	0.0008	0.0001	0.0001	
		70	0.00	0.028	0.002	0	0					0.0056	0.001	0.0004	0.03671	0.006	0.003	0.0031	0.0005	0.0002	
		90	0.01	0.043	0.002	0	0					0.0094	0.001	0.0007	0.05557	0.009	0.004	0.0023	0.0004	0.0002	
		90	0.01	0.024	0.002	0	0					0.0081	0.001	0.0006	0.03095	0.005	0.002	0.0026	0.0004	0.0002	
		100	0.00	0.018	0.002	0	0					0.0059	0.001	0.0005	0.02338	0.004	0.002	0.0019	0.0003	0.0002	
		120	0.01	0.034	0.001	0	0					0.0111	0.002	0.0009	0.04473	0.007	0.003	0.0019	0.0003	0.0001	

Drug	MW	Dose (mg/day)	Free Cmax (μM)	Free AUC (μM.hr)	Free Cav (μM)	HT Grade 1-4 (%)	HT Grade 3-4 (%)	PPB f_u	HUVEC IC_{50} (μM)	SPR IC_{50} (μM)	PAE IC_{50} (μM)	Cmax/HUVEC (μM)	Cmax/SPR (μM)	Cmax/PAE (μM)	AUC/HUVEC (μM)	AUC/SPR (μM)	AUC/PAE (μM)	Cav/HUVEC (μM)	Cav/SPR (μM)	Cav/PAE (μM)	References
		120	0.01	0.018	0.002	0	0					0.0068	0.001	0.0005	0.02338	0.004	0.002	0.0019	0.0003	0.0002	
		160	0.02	0.044	0.002	0	0					0.0201	0.003	0.0016	0.05670	0.009	0.004	0.0024	0.0004	0.0002	
Dovitinib	392	25	0.001	0.01	0.000	0	0	0.0285	0.022467	>0.5	0.0292	0.032	0.001	0.025	0.3	0.012	0.2	0.01	0.0005	0.01	(Sarker et al., 2008) (Angevin et al., 2013)
		50	0.002	0.04	0.002	0	0					0.097	0.004	0.075	1.6	0.073	1.2	0.07	0.003	0.05	
		75	0.004	0.06	0.002	0	0					0.162	0.007	0.125	2.6	0.116	2.0	0.11	0.0048	0.08	
		100	0.004	0.07	0.003	0	0					0.194	0.009	0.149	3.2	0.145	2.5	0.13	0.0061	0.10	
		100	0.004	0.07	0.003	6	0					0.194	0.009	0.149	3.2	0.145	2.5	0.13	0.0061	0.10	
		125	0.007	0.09	0.004	0	0					0.291	0.013	0.224	4.0	0.182	3.1	0.17	0.0076	0.13	
		175	0.007	0.11	0.005	0	0					0.323	0.015	0.249	4.8	0.218	3.7	0.20	0.0091	0.16	
		500	0.022	0.32	0.013	27	0					0.981	0.044	0.756	14.3	0.641	11.0	0.59	0.027	0.46	
		600	0.023	0.32	0.013	20	20					1.013	0.046	0.781	14.4	0.646	11.1	0.60	0.0269	0.46	
Erlotinib	393	100	0.14	0.082	0.0034	0	0	0.059	>0.5	>2	>10	0.28	0.071	0.014	0.16466	0.041	0.008	0.0069	0.0017	0.00034	(Herbst et al., 2005)
		150	0.17	0.103	0.0043	0	0					0.34	0.085	0.017	0.20635	0.052	0.010	0.0086	0.0021	0.00043	
Foretinib	633	252	0.00034	0.006	0.0003	36	0	0.001	0.00457	0.0449	0.03	0.074	0.008	0.011	1.4	0.14	0.21	0.06	0.0059	0.0086	(Eder et al., 2010)
		80	0.00007	0.001	0.00005	75	17					0.016	0.002	0.002	0.3	0.028	0.041	0.01	0.0012	0.0017	(Shapiro et al., 2013)
Imatinib	494	400	0.31	5.0	0.4	0	0	0.05	49.86	>5	>10	0.0062	0.062	0.031	0.100	1.001	0.500	0.008	0.083	0.042	(Reardon et al., 2008)
		600	0.36	5.7	0.5	0	0					0.0072	0.071	0.036	0.115	1.149	0.574	0.010	0.096	0.048	
		800	0.33	4.1	0.3	0	0					0.0065	0.065	0.033	0.082	0.820	0.410	0.007	0.068	0.034	
		1000	0.31	4.3	0.4	0	0					0.0062	0.062	0.031	0.086	0.857	0.428	0.007	0.071	0.036	
		1200	0.22	3.5	0.3	0	0					0.0043	0.043	0.022	0.071	0.705	0.353	0.006	0.059	0.029	
Lapatinib	581	750	0.0008	0.006	0.0003	0	0	0.0001	1.49	>2	>10	0.00050	0.0004	0.000075	0.00427	0.003	0.0006	0.00018	0.0001	0.00003	(Thiessen et al., 2010) (Nakagawa et al., 2009)
		1000	0.0001	0.001	0.0000	0	0					0.00009	0.0001	0.000014	0.00057	0.000	0.0001	0.00002	0.0000	0.00000	
		1500	0.0004	0.004	0.0002	0	0					0.00030	0.0002	0.000045	0.00293	0.002	0.0004	0.00012	0.0001	0.00002	
		900	0.0003	0.005	0.0002	0	0					0.00022	0.0002	0.000033	0.00338	0.003	0.0005	0.00014	0.0001	0.00002	
		1200	0.0003	0.004	0.0002	0	0					0.00020	0.0001	0.000030	0.00297	0.002	0.0004	0.00012	0.0001	0.00002	

Drug	MW	Dose (mg/day)	Free Cmax (μM)	Free AUC (μM.hr)	Free Cav (μM)	HT Grade 1-4 (%)	HT Grade 3-4 (%)	PPB f_u	HUVEC IC_{50} (μM)	SPR IC_{50} (μM)	PAE IC_{50} (μM)	Cmax/HUVEC (μM)	Cmax/SPR (μM)	Cmax/PAE (μM)	AUC/HUVEC (μM)	AUC/SPR (μM)	AUC/PAE (μM)	Cav/HUVEC (μM)	Cav/SPR (μM)	Cav/PAE (μM)	References
		1600	0.0005	0.009	0.0004	0	0					0.00036	0.0003	0.000054	0.00590	0.004	0.0009	0.00025	0.0002	0.00004	
		1800	0.0004	0.007	0.0003	0	0					0.00027	0.0002	0.000040	0.00456	0.003	0.0007	0.00019	0.0001	0.00003	
Linifanib	375	7	0.002	0.058	0.0024	33	0	0.007	0.000358	0.02	0.000937	6.3	0.12	2.4	161.5	3.2	61.7	6.7	0.13	2.57	(Wong et al., 2009)
		700	0.004	0.076	0.0032	66	0					10.9	0.21	4.2	213.6	4.2	81.6	8.9	0.17	3.40	
		18	0.005	0.108	0.0045	58	0					13.0	0.25	5.0	302.1	5.9	115.4	12.6	0.25	4.81	
		21	0.006	0.147	0.0061	100	0					17.7	0.35	6.8	411.5	8.0	157.2	17.1	0.34	6.55	
Motesanib	373	125	0.13	0.39	0.02	47	23	0.0577	0.002775	0.016	0.0069	46.8	8.1	18.9	140.9	24.4	56.9	5.9	1.0	2.4	(Benjamin et al., 2011)
		125	0.09	0.33	0.01	27	10					32.8	5.7	13.2	120.3	20.9	48.5	5.0	0.9	2.0	
		125	0.12	0.62	0.03	56	25					43.8	7.6	17.7	222.2	38.5	89.7	9.3	1.6	3.7	(Schlumberger et al., 2009)
		50	0.09	0.20	0.01	0	0					31.2	5.4	12.6	73.0	12.7	29.4	3.0	0.5	1.2	
		100	0.06	0.36	0.02	100	0					21.7	3.8	8.8	128.1	22.2	51.7	5.5	0.9	2.2	
		125	0.10	0.31	0.01	67	0					35.6	6.2	14.4	110.8	19.2	44.7	4.6	0.8	1.9	(Sherman et al., 2008)
		50	0.03	0.15	0.01	42	20					11.9	2.1	4.8	54.1	9.4	21.8	2.3	0.4	0.9	
		125	0.05	0.30	0.01	63	14					19.7	3.4	8.0	107.5	18.6		4.5	0.8	1.8	(Fujisaka et al., 2010) (Rosen et al., 2007) (Sawaki et al., 2010)
Nilotinib	530	50-200		0.2	0.006	0	0	0.016	>3.518	>2	>10	0.019411	0.034144	0.006829	0.043	0.076	0.015	0.002	0.003	0.001	(Kantarjian et al., 2006)
		400		0.2	0.010	0	0								0.069	0.121	0.024	0.003	0.005	0.001	
		600-1200	0.068289	0.6	0.025	0	0								0.172	0.302	0.060	0.007	0.013	0.003	
		800		0.9	0.038	0	0								0.258	0.453	0.091	0.011	0.019	0.004	
		1200		1.2	0.050	0	0								0.344	0.604	0.121	0.014	0.025	0.005	

Drug	MW	Dose (mg/day)	Free Cmax (μM)	Free AUC (μM.hr)	Free Cav (μM)	HT Grade 1-4 (%)	HT Grade 3-4 (%)	PPB f_u	HUVEC IC_{50} (μM)	SPR IC_{50} (μM)	PAE IC_{50} (μM)	Cmax/HUVEC (μM)	Cmax/SPR (μM)	Cmax/PAE (μM)	AUC/HUVEC (μM)	AUC/SPR (μM)	AUC/PAE (μM)	Cav/HUVEC (μM)	Cav/SPR (μM)	Cav/PAE (μM)	References
		50	0.002	0.036	0.0015	0						1.1	ND	0.7	19.9	-	12	0.8	-	0.5	(Hurwitz et al., 2009)
		100	0.003	0.037	0.0015	0						1.4	ND	0.9	20.4	-	13	0.9	-	0.5	
		200	0.005	0.088	0.0037	0						3.0	ND	1.9	48.9	-	30	2.0	-	1.3	(Shibata et al., 2013)
		600	0.008			0						4.7	ND	2.9	0.0	-			-		
		400	0.005	0.102	0.0043	0						2.8	ND	1.7	56.8	-	35	2.4	-	1.5	(Yau et al., 2011)
		800	0.008			0						4.6	ND	2.8	0.0	-			-		
		600	0.004	0.076	0.0032	0						2.3	ND	1.4	42.4	-	26	1.8	-	1.1	
		800	0.010	0.170	0.0071	33						5.7	ND	3.5	94.4	-	58	3.9	-	2.4	
		1000	0.012	0.182	0.0076	33						6.8	ND	4.2	101.1	-	63	4.2	-	2.6	
		1400	0.007	0.123	0.0051	33						4.2	ND	2.6	68.1	-	42	2.8	-	1.8	
		2000	0.012	0.197	0.0082	33						6.7	ND	4.1	109.2	-	68	4.6	-	2.8	
		50	0.002	0.024	0.0010	33	25					1.0	ND	0.6	13.3	-	8	0.6	-	0.3	
		100	0.002	0.027	0.0011							1.1	ND	0.7	15.3	-	9	0.6	-	0.4	
Pazopanib	438	200	0.002	0.033	0.0014			0.0001	0.0018	ND	0.00291	1.3	ND	0.8	18.1	-	11	0.8	-	0.5	
		600	0.001	0.022	0.0018							0.8	ND	0.5	12.2	-	8	1.0	-	0.6	
		400	0.003	0.036	0.0015							1.4	ND	0.9	20.0	-	12	0.8	-	0.5	
		800	0.004	0.063	0.0052							2.5	ND	1.5	34.9	-	22	2.9	-	1.8	
		600	0.008	0.091	0.0038							4.6	ND	2.8	50.8	-	31	2.1	-	1.3	
		800	0.012	0.060	0.0099		4					6.6	ND	4.1	33.1	-	20	5.5	-	3.4	
		400	0.005	0.029	0.0048		11					2.9	ND	1.8	15.9	-	10	2.6	-	1.6	
		800	0.008	0.040	0.0067		7					4.3	ND	2.6	22.4	-	14	3.7	-	2.3	
		200	0.005	0.028	0.0047		15					2.8	ND	1.7	15.5	-	10	2.6	-	1.6	
		400	0.004	0.022	0.0036		0					2.2	ND	1.4	11.9	-	7	2.0	-	1.2	
		100	0.001	0.003	0.0005		0					0.3	ND	0.2	1.6	-	1	0.3	-	0.2	
		200	0.002	0.011	0.0019		0					1.2	ND	0.7	6.2	-	4	1.0	-	0.6	
		200	0.007	0.035	0.0058	50						3.8	ND	2.3	19.2	-	12	3.2	-	2.0	
		400	0.007	0.038	0.0063	82						4.0	ND	2.5	21.0	-	13	3.5	-	2.2	

Drug	MW	Dose (mg/day)	Free Cmax (μM)	Free AUC (μM.hr)	Free Cav (μM)	HT Grade 1-4 (%)	HT Grade 3-4 (%)	PPB f_u	HUVEC IC_{50} (μM)	SPR IC_{50} (μM)	PAE IC_{50} (μM)	Cmax/HUVEC (μM)	Cmax/SPR (μM)	Cmax/PAE (μM)	AUC/HUVEC (μM)	AUC/SPR (μM)	AUC/PAE (μM)	Cav/HUVEC (μM)	Cav/SPR (μM)	Cav/PAE (μM)	References
		600	0.007	0.029	0.0049	50						3.7	ND	2.3	16.4	-	10	2.7	-	1.7	
		800	0.009	0.049	0.0082	40						5.0	ND	3.1	27.2	-	17	4.5	-	2.8	
Regorafenib	483	10	0.005379	0.06	0.002	33		0.0049	0.0026	0.00219	0.0117	2.1	2.5	0.5	21.9	26.0	4.9	0.9	1.1	0.2	(Mross et al., 2012)
		30	0.015984	0.19	0.008	20						6.1	7.3	1.4	72.8	86.4	16.2	3.0	3.6	0.7	
		60	0.041965	0.49	0.020	17	17					16.1	19.2	3.6	188.7	224.0	41.9	7.9	9.3	1.7	(Eisen et al., 2012)
		120	0.043883	0.47	0.019	25						16.9	20.0	3.8	179.4	213.0	39.9	7.5	8.9	1.7	
		120	0.044857	0.52	0.022							17.3	20.5	3.8	198.8	236.0	44.2	8.3	9.8	1.8	
		160	0.03958	0.59	0.025	50	17					15.2	18.1	3.4	227.4	270.0	50.5	9.5	11.3	2.1	
		220	0.045263	0.65	0.027							17.4	20.7	3.9	248.6	295.2	55.3	10.4	12.3	2.3	
		160	0.045568	0.59	0.025	49						17.5	20.8	3.9	227.6	270.2	50.6	9.5	11.3	2.1	
Saracatinib	542	50	0.04	0.6	0.02	0	0	0.2	>1	ND	>10	0.035	ND	0.0035	0.5893	-	0.29	0.025	-	0.002	(Hannon et al., 2010)
		125	0.09	1.4	0.06	0	0					0.091	ND	0.0091	1.3619	-	0.68	0.057	-	0.006	
		175	0.16	2.8	0.12	0	0					0.164	ND	0.0164	2.7999	-	1.40	0.117	-	0.012	
Semaxanib	238	136	0.574943	0.457	0.0191	0	0	0.05	0.05	0.015	0.0970	11.49886	38.330	5.925715	9.14873	30.496	4.7146	0.38120	1.2707	0.19644	(Lockhart et al., 2006)
		232	0.721826	0.993	0.0414	16	0					14.43653	48.122	7.439584	19.85022	66.167	10.2294	0.82709	2.7570	0.42623	
Sorafenib	465	800	0.05	0.001	0.0177	43	29	0.005	0.002923	0.015	0.0136	15.86	3.09	3.41	0.31	0.061	0.067	6.1	1.2	1.3	(Fukudo et al., 2014)
		200	0.04	0.001	0.0219	0	0					12.88	2.51	2.77	0.19	0.038	0.042	7.5	1.5	1.6	
		400	0.03	0.000	0.0171	0	0					9.57	1.86	2.06	0.15	0.029	0.033	5.9	1.1	1.3	(Clark, Eder, Ryan, Lathia & Lenz, 2005)
		800	0.07	0.001	0.0507	0	0					22.82	4.45	4.90	0.45	0.087	0.096	17.4	3.4	3.7	
		1200	0.07	0.001	0.0581	0	0					24.29	4.73	5.22	0.51	0.100	0.110 0.158	19.9	3.9	4.3	
		1600	0.13	0.002	0.0832	33	33					45.27	8.82	9.73	0.73	0.143		28.5	5.5	6.1	(Strumberg et al., 2007)
Sunitinib	398	50	0.0089	0.16	0.0066	0	0	0.049	0.0194	0.0012	0.0039	0.46	7.34	2.27	8.21	131.71	40.73	0.34	5.49	1.70	(Faivre et al., 2006)
		75	0.0509	0.30	0.0126	9	9					2.62	42.07	13.01	15.58	249.80	77.26	0.65	10.41	3.22	
		100	0.0221	0.36	0.0150	50	50					1.14	18.29	5.66	18.61	298.38	92.28	0.78	12.43	3.85	

Drug	MW	Dose (mg/day)	Free Cmax (μM)	Free AUC (μM.hr)	Free Cav (μM)	HT Grade 1-4 (%)	HT Grade 3-4 (%)	PPB f_u	HUVEC IC_{50} (μM)	SPR IC_{50} (μM)	PAE IC_{50} (μM)	Cmax/HUVEC (μM)	Cmax/SPR (μM)	Cmax/PAE (μM)	AUC/HUVEC (μM)	AUC/SPR (μM)	AUC/PAE (μM)	Cav/HUVEC (μM)	Cav/SPR (μM)	Cav/PAE (μM)	References
Telatinib	410	20	0.011	0.09	0.007	0	0	0.034	0.00702	ND	0.0137	1.6	ND	0.8	12.8	-	6.5	1.1	-	0.5	(Eskens et al., 2009)
		75	0.015	0.13	0.011	17	0					2.2	ND	1.1	18.4	-	9.4	1.5	-	0.8	
		300	0.016	0.10	0.008	33	0					2.2	ND	1.1	14.0	-	7.2	1.2	-	0.6	
		600	0.066	0.41	0.034	33	0					9.4	ND	4.8	57.8	-	29.5	4.8	-	2.5	
		1200	0.068	0.42	0.035	17	0					9.7	ND	5.0	59.8	-	30.6	5.0	-	2.5	
		900	0.094	0.54	0.045	0	0					13.4	ND	6.9	77.1	-	39.4	6.4	-	3.3	
		3000	0.133	1.01	0.085	33	0					19.0	ND	9.7	144.5	-	73.8	12.0	-	6.2	
Tivozanib	455	1	0.00012	0.002	0.0001	33	0	0.005	0.000185	0.00016	0.0011	0.7	0.8	0.1	9.5	10.8	1.5	0.4	0.4	0.1	(Niwakawa et al., 2013)
		1	0.00016	0.011	0.0001	0	0					0.8	1.0	0.1	60.2	68.6	9.8	0.6	0.6	0.1	
		1.5	0.00053	0.003	0.0005	50	0					2.8	3.3	0.5	13.6	15.6	2.2	2.5	2.9	0.4	
		1.5	0.00105	0.020	0.0009	44	22					5.6	6.4	0.9	108.6	125.3	17.9	4.5	5.2	0.7	
		1	0.00055	0.009	0.0004	39	28					2.9	3.4	0.5	49.8	57.7	8.3	2.1	2.4	0.3	
		1.5	0.00074	0.013	0.0005	62	62					3.9	4.5	0.7	68.3	79.6	11.4	2.8	3.3	0.5	
		2	0.00121	0.022	0.0009	100	71					6.3	7.4	1.1	114.9	134.7	19.3	4.8	5.6	0.8	
		1.5	0.00104	0.018	0.0008	45	0					5.4	6.4	0.9	93.9	110.7	15.8	3.9	4.6	0.7	
Vandetanib	475	100	0.05	1.7	0.1	8	0	0.07	ND	0.05	ND	-	0.9	-	-	32.2	-	-	1.3	-	(Zhang et al., 2011)
		100	0.08	1.6	0.1	0	0					-	1.4	-	-	29.6	-	-	1.2	-	
		300	0.30	5.7	0.2	17	0					-	5.5	-	-	105.7	-	-	4.4	-	

HT Grade = Grade of hypertension observed. PPB fu = fraction unbound based on human plasma protein binding. ND, not determined.

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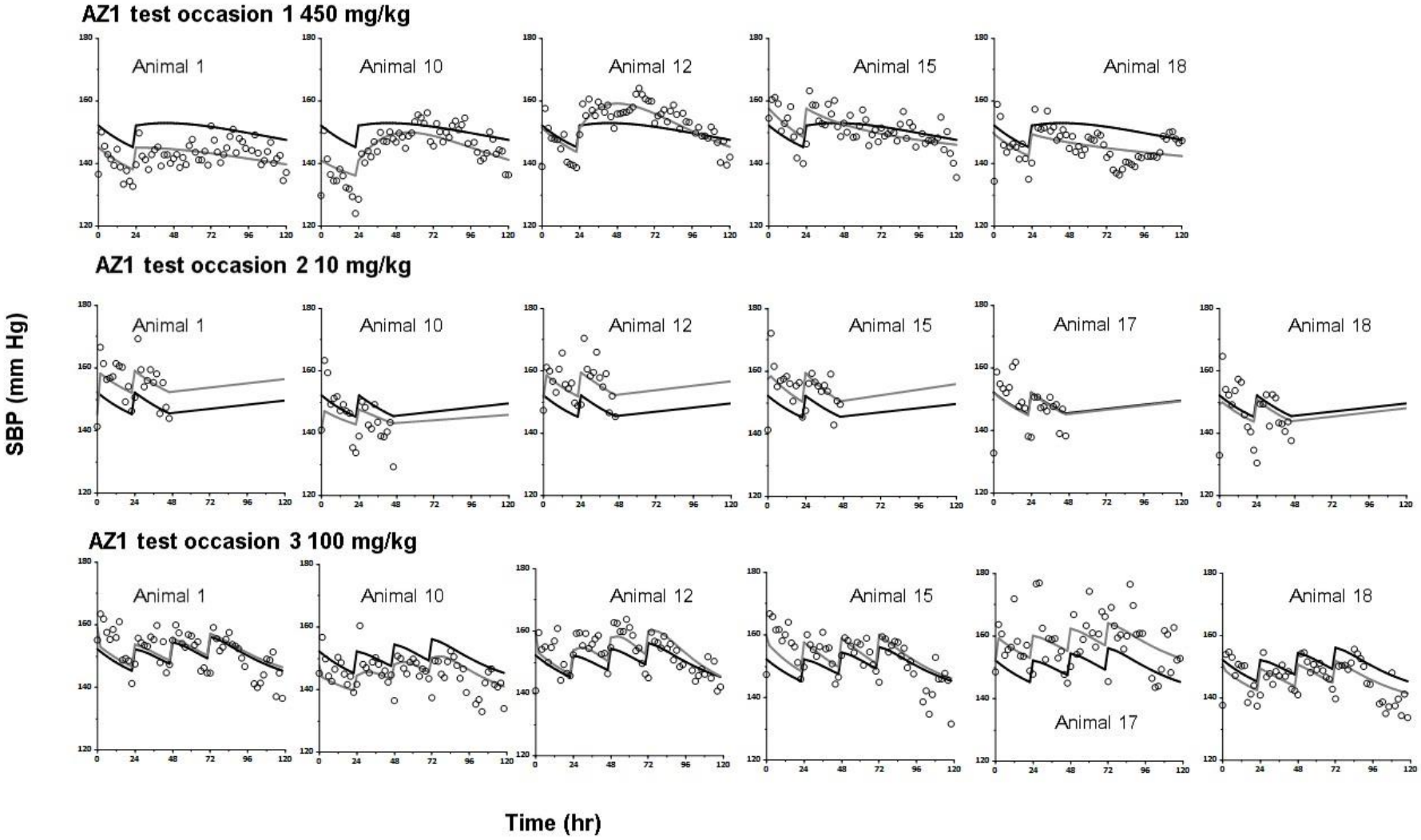
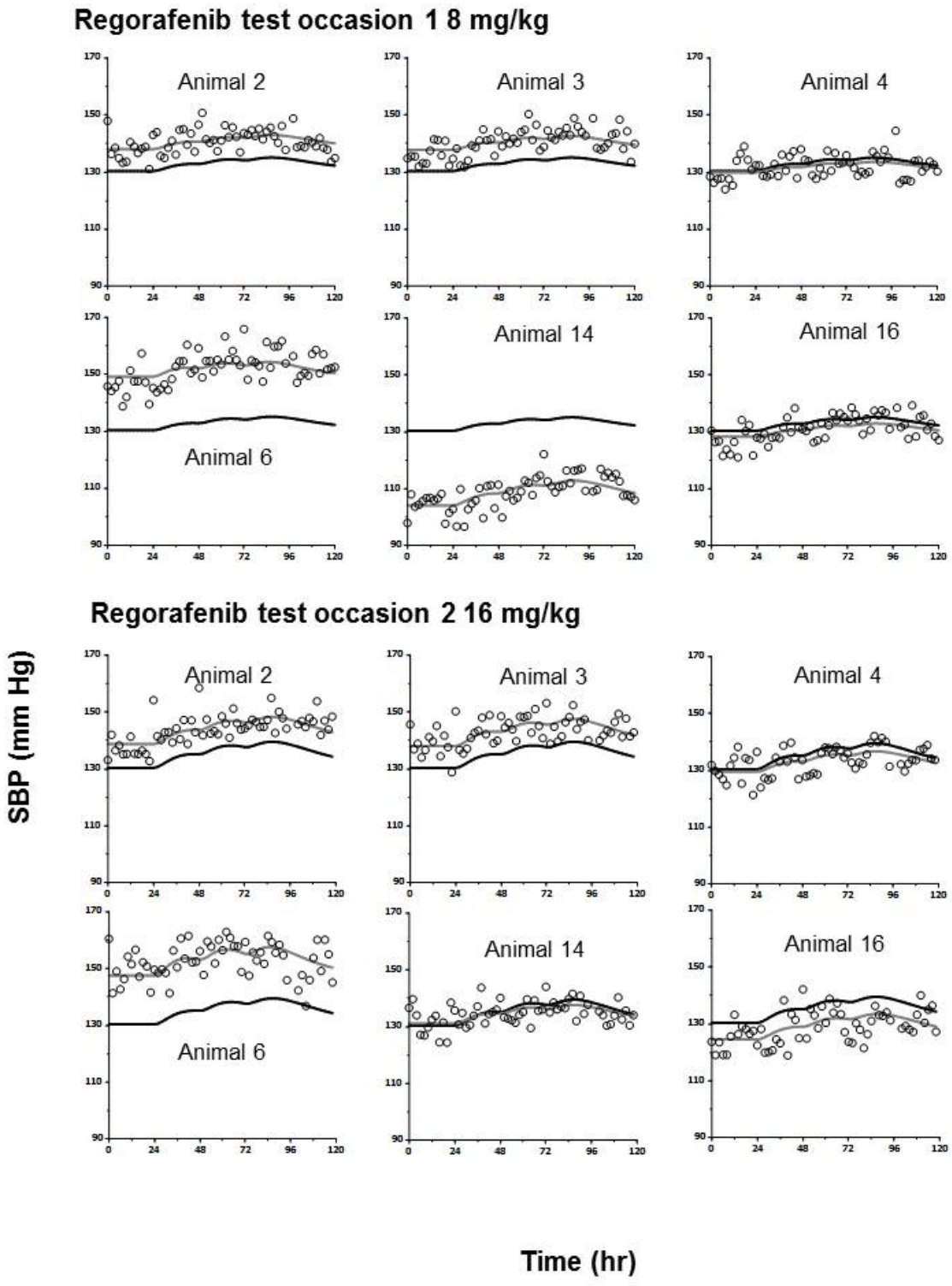
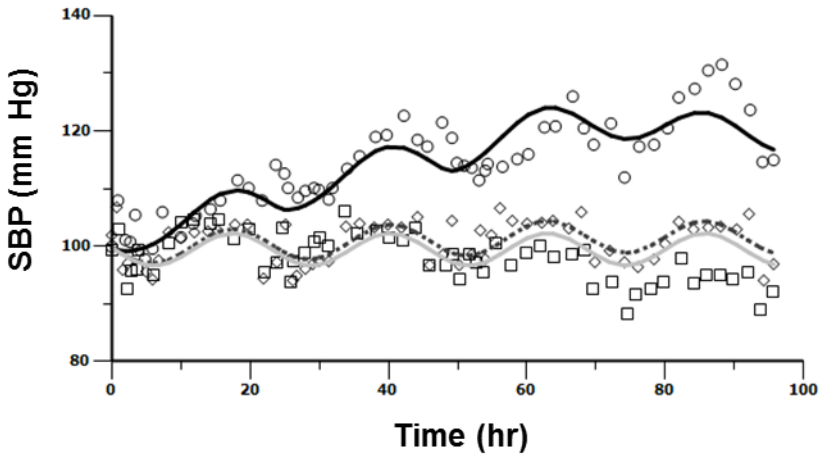

AZ1 test occasion 1 450 mg/kg
Animal 1
Animal 10
Animal 12
Animal 15
Animal 18
AZ1 test occasion 2 10 mg/kg
Animal 1
Animal 10
Animal 12
Animal 15
Animal 17
Animal 18
AZ1 test occasion 3 100 mg/kg
Animal 1
Animal 10
Animal 12
Animal 15
Animal 17
Animal 18
SBP (mm Hg)
Time (hr)

Supplementary Figure 1. Observed systolic blood pressure (SBP) over time following dosing of vehicle and AZ1 to male Han Wistar rats, versus the individual and population PKPD model fit for each animal. The black circles indicate the observations the population model fit is represented as the black line, the individual model fit as the grey line. Top row for test occasion 1 high dose (450 mg/kg), middle row for test occasion 2 low dose (10 mg/kg) and bottom row for test occasion 3 mid dose (100 mg/kg).



Supplementary Figure 2. Observed systolic blood pressure (SBP) over time following dosing of vehicle and regorafenib to male Han Wistar rats, versus the individual and population PKPD model fit for each animal. The black circles indicate the observations the population model fit is represented as the black line, the individual model fit as the grey line. Top panel for test occasion 1 low dose (8 mg/kg) and bottom panel for test occasion 2 high dose (16 mg/kg) as indicated.



Supplementary Figure 3. Observed mean aortic blood pressure (MBP) over time following repeated daily dosing of vehicle, 5 and 50 mg/kg of sunitinib in male Sprague Dawley rats (n=4), versus the PKPD model fit. The dots indicate the observations after vehicle (diamonds), 5 mg/kg (squares) and 50 mg/kg, the model fit for vehicle represented as grey line, 5 mg/kg in dashed black line, 50 mg/kg as solid black line. Data-points extracted from (Engle & Watson, 2016; Speed et al., 2012).