Appendix from Frey et al., "Assessment of the effects of renal impairment and smoking on the pharmacokinetics of a single oral dose of the soluble guanylate cyclase stimulator riociguat (BAY 63-2521)"
(Pulm. Circ., vol. 6, no. S1, p. S15)

Supplementary table

Table S1. Pharmacokinetic parameters for riociguat and metabolite M1 in nonsmoking healthy individuals and patients with mild, moderate, or severe renal impairment, following a single oral dose of riociguat 1.0 mg

Parameter	Normal ($CL_{CR} > 80$ mL/min)	Mild ($CL_{CR} = 50–80$ mL/min)	Moderate ($CL_{CR} = 30–49$ mL/min)	Severe ($CL_{CR} < 30$ mL/min)[a]
Patients, no.	14	12	12	14
Riociguat				
AUC, μg·h/L	283 (32.3)	466 (73.2)	691 (80.7)	523 (70)[b]
AUC_{norm}, kg·h/L	24.0 (34.9)	36.7 (79.8)	57.4 (83.9)	37.0 (66.6)
C_{max}, μg/L	37.7 (16.3)	46.0 (21.1)	42.9 (37.0)	40.6 (38)[b]
$C_{max,norm}$, kg/L	3.20 (13.5)	3.62 (24.4)	3.57 (34.3)	3.13 (29.2)
t_{max}, hours	1.00 (0.500–2.00)	1.00 (0.750–3.00)	1.25 (0.750–3.00)	1.00 (0.500–4.00)
$t_{1/2}$, hours	7.00 (36.9)	12.2 (72.6)	15.8 (71.8)	11.1 (60.5)
CL/F, L/h	3.54 (32.3)	2.15 (73.2)	1.45 (80.7)	2.13 (65.0)
f_u, %	3.39 (19.4)	3.14 (22.5)	4.00 (22.8)	4.21 (27.0)
$AUC_{u,norm}$, kg·h/L	0.813 (32.6)	1.15 (80.6)	2.30 (80.4)	1.56 (63.7)
$C_{max,u,norm}$, kg/L	0.108 (24.5)	0.114 (36.4)	0.143 (35.5)	0.132 (22.6)
$A_{E,ur}$, %	9.63 ± 4.19	11.4 ± 7.28	7.65 ± 3.55	4.04 ± 2.93[c]
CL_R, L/h	0.312 (42.6)	0.208 (37.8)	0.105 (55.2)	0.0564 (92.1)[c]
Metabolite M1				
AUC, μg·h/L	256 (23.7)	285 (43.8)	407 (50.2)	547 (62)[b]
AUC_{norm}, kg·h/L	22.5 (21.5)	23.2 (44.0)	35.0 (44.8)	40.9 (48.9)
C_{max}, μg/L	8.92 (40.8)	7.09 (74.4)	6.85 (55.0)	8.73 (52)[b]
$C_{max,norm}$, kg/L	0.783 (37.8)	0.577 (69.7)	0.589 (46.0)	0.679 (45.5)
t_{max}, hours	8.00 (4.00–24.0)	11.0 (3.00–24.1)	24.0 (4.00–48.0)	24.0 (2.00–24.1)
$t_{1/2}$, hours	14.7 (24.3)	25.04 (44.3)	31.4 (60.0)	34.0 (74.7)
CL/F, L/h	3.77 (23.7)	3.39 (43.8)	2.38 (50.2)	1.93 (55.7)
f_u, %	2.86 (15.1)	2.65 (18.9)	3.47 (19.9)	3.96 (30.6)
$AUC_{u,norm}$, kg·h/L	0.643 (24.4)	0.619 (43.5)	1.21 (44.8)	1.62 (50.1)
$C_{max,u,norm}$, kg/L	0.0224 (40.9)	0.0153 (70.5)	0.0204 (47.4)	0.0269 (51.5)
$A_{E,ur}$, %	18.7 ± 7.29	11.0 ± 6.24	8.87 ± 2.98[d]	4.16 ± 3.64[e]
CL_R, L/h	0.688 (56.9)	0.367 (67.3)	0.256 (39.9)[d]	0.0670 (75.0)[e]

Note: Values are geometric means (percentage coefficient of variation), except for the number of patients; t_{max}, which is expressed as median (range); and $A_{E,ur}$, which is expressed as arithmetic mean ± standard deviation. $A_{E,ur}$: amount excreted into urine from time 0 to infinity; AUC: area under the plasma concentration–time curve from time 0 to infinity; AUC_{norm}: AUC divided by dose of riociguat per kilogram body weight for total riociguat/M1; $AUC_{u,norm}$: AUC divided by dose of riociguat per kilogram body weight for unbound riociguat/M1; CL_{CR}: creatinine clearance; CL/F: apparent oral clearance for total riociguat/M1; CL_R: renal clearance of riociguat/M1; C_{max}: maximum concentration in plasma; $C_{max,norm}$: C_{max} divided by dose of riociguat per kilogram body weight for total riociguat/M1; $C_{max,u,norm}$: C_{max} divided by dose of riociguat per kilogram body weight for unbound riociguat/M1; f_u: fraction unbound; t_{max}: time to C_{max} of total riociguat/M1; $t_{1/2}$: terminal elimination half-life for total riociguat/M1.

[a] In study I, individuals with severe renal impairment received riociguat 0.5 mg, and therefore pharmacokinetic concentrations recorded for these individuals were normalized to a 1.0-mg dose before analysis; all other participants in both studies received riociguat 1.0 mg.

[b] AUC and C_{max} values shown for individuals with severe renal impairment are taken from study II ($n = 8$), in which individuals with severe renal impairment received riociguat 1.0 mg.

[c] Data available from 11 patients.

[d] Data available from 8 patients.

[e] Data available from 7 patients.