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Pharmacokinetics of the soluble guanylate cyclase stimulator riociguat in individuals with renal impairment

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Background

Riociguat is the first oral, soluble guanylate cyclase stimulator under review for the treatment of pulmonary hypertension (PH), a progressive, ultimately fatal disease [1-7]. This pooled analysis of two studies evaluated the pharmacokinetics of riociguat and its metabolite M1 (BAY 60-4552) in individuals with and without renal impairment. The safety and tolerability of riociguat were also assessed.

Methods

Two non-randomized, non-blinded, observational studies with group stratification were conducted in a single centre in Germany, following Good Clinical Practice and relevant industry guidelines [8,9]. Participants were assigned to one of four renal function groups according to their creatinine clearance (CL_{CR}): group 1, CL_{CR} > 80 mL/min; group 2, CL_{CR} 50–80 mL/min; group 3, CL_{CR} 30–49 mL/min; group 4, CL_{CR} < 30 mL/min. In the first study, individuals in group 4 received riociguat 0.5 mg; all other participants in both studies received riociguat 1 mg (single tablet doses). Pharmacokinetic parameters were assessed using dense sampling.

Results

Sixty-three participants (40 men and 23 women; mean age, 61.3 years [range, 36–78 years]) completed the study and were eligible for pharmacokinetic analysis. Riociguat was

Table 1 Pharmacokinetic parameters of riociguat in healthy participants and in individuals with mild, moderate or severe renal impairment

Parameter	Group 1 (CR_{CL} > 80 mL/min) n = 16	Group 2 (CR_{CL} 50–80 mL/min) n = 15	Group 3 (CR_{CL} 30–49 mL/min) n = 16	Group 4[a] (CR_{CL} < 30 mL/min) n = 16
AUC, µg·h/L	245.7 (51)	347.5 (111)	499.0 (110)	523.0 (70.4)[b]
C_{max}, µg/L	36.6 (17)	44.2 (21)	42.0 (32)	40.56 (37.8)[b]
AUC_{norm}, kg·h/L	20.6 (56)	29.4 (126)	42.1 (109)	29.7 (102)
$C_{max,norm}$, kg/L	3.07 (17)	3.48 (25)	3.54 (30)	2.97 (40)
$t_{½}$, h	6.19 (50)	10.1 (116)	11.4 (103)	9.52 (75)

[a]In the first study, individuals with severe renal impairment (group 4) received riociguat 0.5 mg; all other participants in both studies received riociguat 1 mg.

[b]AUC and C_{max} values shown for individuals with severe renal impairment (group 4) are taken from the second study (n = 8), in which individuals with severe renal impairment received riociguat 1.0 mg.

Values are geometric means (percentage coefficient of variation). AUC, area under the plasma concentration–time curve from time 0 to infinity; AUC_{norm}, AUC divided by dose per kilogram of body weight for total riociguat; C_{max}, maximum concentration in plasma; $C_{max,norm}$, C_{max} divided by dose per kilogram of body weight for total riociguat; $t_{½}$, terminal elimination half-life for total riociguat.

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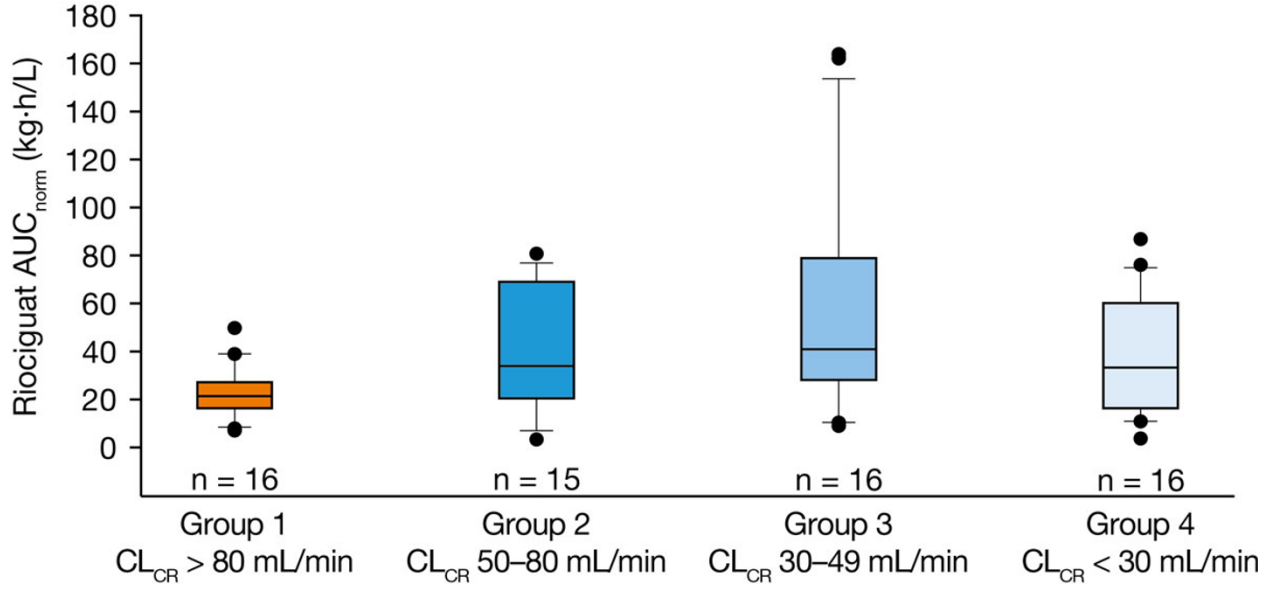

Figure 1 Box-and-whisker plot of riociguat AUC_{norm} (kg·h/L) after a single oral dose of riociguat. In the first study, individuals with severe renal impairment (group 4) received riociguat 0.5 mg; all other participants in both studies received riociguat 1 mg . Box, 25–75th percentile; vertical line, 10th–90th percentile; horizontal line, median; more extreme values are plotted as points; individuals eligible for pharmacokinetic analysis, n = 63; AUC_{norm}, area under the plasma concentration–time curve from time 0 to infinity divided by dose per kilogram of body weight for total riociguat.

rapidly absorbed; median time to reach maximum concentration in plasma (t_{max}) (C_{max}) was 1 hour in all four groups. Mean half-life of total riociguat was longer in groups 2–4 (9.5–11.4 hours) than in group 1 (6.2 hours) (Table 1), and renal clearance of riociguat decreased with decreasing renal function. Mean exposure to total riociguat (area under the concentration–time curve divided by dose per kilogram of body weight [AUC_{norm}]) was 42.7–104.3% higher in groups 2–4 than in group 1 (Table 1, Figure 1). However, exposure was highly variable in groups 2–4 and the exposure ranges in all groups overlapped (Figure 1). Exposure to riociguat did not increase strictly in parallel with decreasing CL_{CR}. Results for unbound riociguat and M1 were similar to those for total riociguat and M1. No serious or severe adverse events were reported. Headache was the most common drug-related adverse event. No changes in safety or tolerability were detected with decreasing CL_{CR}. Riociguat C_{max} and AUC ranges in patients with renal impairment overlapped those previously observed in healthy volunteers and patients with PH [2,3].

Conclusion

Exposure to riociguat was higher in individuals with renal impairment (CL_{CR} 15–80 mL/min) than in controls; particular care should be exercised during individual dose titration in patients with renal impairment.

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