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BAY 63–2521, an oral soluble guanylate cyclase stimulator, has a favourable safety profile and decreases peripheral vascular resistance in healthy male volunteers

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Background

BAY 63–2521 is an oral soluble guanylate cyclase (sGC) stimulator that acts independently of nitric oxide (NO). It targets the reduced form of sGC, and enhances the sensitivity of the enzyme to low levels of bioavailable NO. Preclinical data suggest that BAY 63–2521 has the potential to be effective in the treatment of pulmonary hypertension, with the advantage of having a different mode of action from currently available agents.

Materials and methods

This randomized, placebo-controlled, single-blinded study assessed the safety, tolerability, pharmacodynamics and pharmacokinetics of orally administered BAY 63–2521 in healthy male volunteers. Subjects received a single oral dose of BAY 63–2521 in solution (0.25 mg, n = 6; 0.5 mg n = 5; 1 mg, n = 12; 2.5 mg, n = 6; 5 mg, n = 10) or as an immediate-release tablet (2.5 mg, n = 6), or matching placebo solution (n = 11) or a placebo tablet (n = 2). Safety parameters (adverse events [AEs], electrocardiograms [ECGs] and standard laboratory values), pharmacodynamics (heart rate [HR], systolic blood pressure [SBP], diastolic blood pressure [DBP], cyclic guanosine monophosphate [cGMP] levels and plasma vasoactive hormone levels) and pharmacokinetics were assessed.

Results

Overall, 72 AEs (66 mild, 6 moderate) were reported in 29 of 58 subjects. Forty-eight AEs occurring in 20 (44%) of 45 individuals receiving BAY 63–2521 were attributed to the study compound. The rate of AEs was dose-dependent. No serious AEs occurred, and all except one (stretched ligament, left ankle joint – lost to follow up) were found to have resolved by study completion. BAY 63–2521 had no clinically relevant effects on ECGs or laboratory values. Pharmacodynamic evaluation showed that BAY 63–2521 increased HR in a dose-dependent manner ($P < 0.0001$; Table 1). In healthy young subjects, the cardiovascular system compensates for changes in blood pressure with changes in HR to keep the blood pressure constant as long as possible. Therefore, HR is considered the most sensitive non-invasive parameter for indirect estimation of the effect of a vasodilating agent on the cardiovascular system. Pharmacodynamic evaluation also showed that BAY 63–2521 reduced mean DBP in the 2.5 mg and 5.0 mg dose groups; SBP was not significantly affected. In terms of vasoactive hormones, BAY 63–2521 dose-dependently increased plasma renin activity ($P < 0.0001$) and noradrenalin levels ($P = 0.0099$), while having no significant effects on aldosterone or angiotensin II levels. Plasma levels of cGMP increased dose-dependently ($P < 0.0001$). The two 2.5 mg formulations of BAY 63–2521 (oral solution and immediate-release tablet) exhibited similar bio-

Table 1: Increase in heart rate after oral administration of BAY 63–2521 in solution, compared with placebo.

Dose	Increase in heart rate (beats/minute)	95% confidence interval	*P* value
0.25 mg	-1.35	(-5.10 to 2.40)	0.4726
0.5 mg	0.44	(-3.45 to 4.32)	0.8218
1.0 mg	4.09*	(1.10 to 7.08)	0.0084
2.5 mg	7.77*	(4.22 to 11.32)	<0.0001
5.0 mg	11.34*	(8.29 to 14.39)	<0.0001

*statistically significant

availability. BAY 63–2521 pharmacokinetics showed high inter-individual variability.

Conclusion

BAY 63–2521 had a favourable safety profile and was well-tolerated up to a single oral dose of 5 mg. In line with its mode of action as an sGC stimulator, BAY 63–2521 dose-dependently reduced DBP and increased HR. Further studies are warranted to assess the therapeutic potential of BAY 63–2521 in patients with pulmonary hypertension.