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Acute hemodynamic response to single oral doses of BAY 60-4552, a soluble guanylate cyclase stimulator, in patients with biventricular heart failure

Veselin Mitrovic*[1], B Swidnicki[1], Ardeschir Ghofrani[2], Wolfgang Mück[3], Nina Kirschbaum[4], Joachim Mittendorf[5], Johannes-Peter Stasch[6], Georg Wensing[3], Reiner Frey[3] and Silvia Lentini*[3]

Address: [1]Kerckhoff Heart Center, Department of Cardiology, 61231 Bad Nauheim, Germany, [2]Department of Internal Medicine, Medical Clinic II/V, University Hospital Giessen and Marburg GmbH, Klinikstrasse 36, 35392 Giessen, Germany, [3]Clinical Pharmacology, 42096 Wuppertal, Germany, [4]Global Biostatistics, 42096 Wuppertal, Germany, [5]Medicinal Chemistry, 42096 Wuppertal, Germany and [6]Cardiology Research, Bayer Schering Pharma AG, Pharma Research Centre, 42096 Wuppertal, Germany

Email: Veselin Mitrovic* - v.mitrovic@kerckhoff-klinik.de

* Corresponding authors

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Background

BAY 60-4552 is a direct soluble guanylate cyclase (sGC) stimulator that acts independently of nitric oxide (NO). In preclinical studies BAY 60-4552 exhibited potent vasorelaxing properties and end-organ protective effects. Secondary pulmonary hypertension is a determinant of morbidity and mortality in patients with biventricular heart failure (bivHF). Weassumed that BAY 60-4552 would improve cardiopulmonary hemodynamics by restoring functionality of the NO/sGC/cGMP pathway and be well tolerated in patients with bivHF.

Methods

This study evaluated safety, tolerability and invasive hemodynamics of 1, 2.5, 5, 7.5 and 10 mg oral BAY 60-4552 in patients with bivHF (LVEF ≤ 45%, mean pulmonary artery pressure (mPAP) ≥ 25 mmHg, pulmonary capillary wedge pressure [PCWP] ≥ 18 mmHg).

Results

31 male and 11 female patients (65 ± 11 years; BMI 27.4 ± 4.4) were included. Mean hemodynamic parameters at baseline were PCWP: 23.9 ± 4.5 mmHg; right atrial pressure (RAP): 10.6 ± 4.3 mmHg; mPAP: 35.7 ± 8 mmHg; systolic blood pressure (SBP): 119.2 ± 17.4 mmHg; systemic vascular resistance (SVR): 1721 ± 534 dyn•s•cm^{-5}; heart rate (HR): 70.6 ± 11.2 bpm; and cardiac index (CI): 1.99 ± 0.48 L/min/m^2. Table 1 summarizes peak changes in invasive hemodynamics aftersingle dosesof 2.5, 7.5 and 10 mg. No relevant HR increase was observed. BAY 60-4552 was safe and well tolerated with mild adverse events (asymptomatic hypotension, n = 1; transient facial flushing, n = 5; mild headache, n = 4). Pharmakokinetic parameters were linear and mean elimination half-life ranged between 14 – 20 h.

Conclusion

In patients with bivHF, oral administration of BAY 60-4552 was well tolerated and mediated a potent vasodilation. Biventricular pre- and afterload were improved, which resulted in a significant increase in cardiac index. These first clinical results with an oral sGC stimulator in patients with bivHF demonstrate the potential of this new therapeutic principle.

Table 1: Changes in hemodynamic parameters

	2.5 mg (n = 7)	7.5 mg (n = 12)	10 mg (n = 12)
PCWP [mmHg]	-7.3 ± 2.8 [-28 ± 10%]	-8.4 ± 3.1 [-36 ± 13%]	-9.3 ± 2.5 [-43 ± 11%]
MPAP [mmHg]	-8.9 ± 6.1 [-22 ± 12%]	-8.0 ± 3.3 [-24 ± 9%]	-7.3 ± 3.3 [-23 ± 8%]
RAP [mmHg]	-3.1 ± 3.5 [-26 ± 29%]	-4.3 ± 1.9 [-40 ± 15%]	-4.0 ± 2.3 [-39 ± 15%]
SVR [dyn•s•cm^{-5}]	-378 ± 550 [-15 ± 21%]	-523 ± 293 [-33 ± 15%]	-546 ± 267 [-31 ± 12%]
CI [L/min/m^2]	+0.3 ± 0.3 [+17 ± 22%]	+0.6 ± 0.4 [+31 ± 22%]	+0.7 ± 0.5 [+33 ± 25%]

Changes from baseline (absolute and [relative] mean ± SD) of invasive hemodynamics after oral administration of 2.5, 7.5 and 10 mg BAY60-4552, $p < 0.05$ (for each change from baseline).