

POSTER PRESENTATION

Open Access

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

Reiner Frey^{1*}, Corina Becker¹, Sigrun Unger², Anja Schmidt¹, Georg Wensing¹, Wolfgang Mueck¹

From 6th International Conference on cGMP: Generators, Effectors and Therapeutic Implications Erfurt, Germany. 28-30 June 2013

Background

Riociguat is the first oral, soluble guanylate cyclase stimulator currently under review for the treatment of pulmonary hypertension (PH), a progressive disease with high mortality [1-7]. The present pooled analysis assessed the pharmacokinetics of riociguat and its metabolite M1 (BAY 60-4552) in individuals with hepatic impairment (Child-Pugh A or B) and healthy controls. The safety and tolerability of riociguat were evaluated.

Methods

Two non-randomized, non-blinded, observational studies with group stratification were included in the analysis. The studies were conducted in a single centre in Germany, in accordance with Good Clinical Practice and industry guidelines [8,9]. Individuals with liver cirrhosis (Child-Pugh A, n = 16; Child-Pugh B, n = 16) and 32 healthy age-, weight- and sex-matched volunteers received a single

oral tablet dose of riociguat 1 mg. Dense sampling was performed for pharmacokinetic parameters.

Results

Sixty-four participants (42 men and 22 women; mean age, 55.1 years [range, 35–72 years]) received riociguat and completed the study according to protocol. Owing to the rapid absorption of riociguat (median time to reach maximum concentration in plasma [C_{max}], ≤ 1.5 hours in all groups), mean dose- and body-weight-normalized C_{max} values for total riociguat were similar in all groups (Table 1). Mean half-life of total riociguat was longer in the Child-Pugh B group than in the Child-Pugh A group and the controls (Table 1). Exposure (dose- and body-weight-normalized area under the plasma concentration-time curve [AUC_{norm}]) to total riociguat was elevated in Child-Pugh B but not Child-Pugh A individuals compared with controls (Table 1, Figure 1). Antagonizing

Table 1 Pharmacokinetic parameters of riociguat in plasma following a single oral dose of riociguat 1 mg

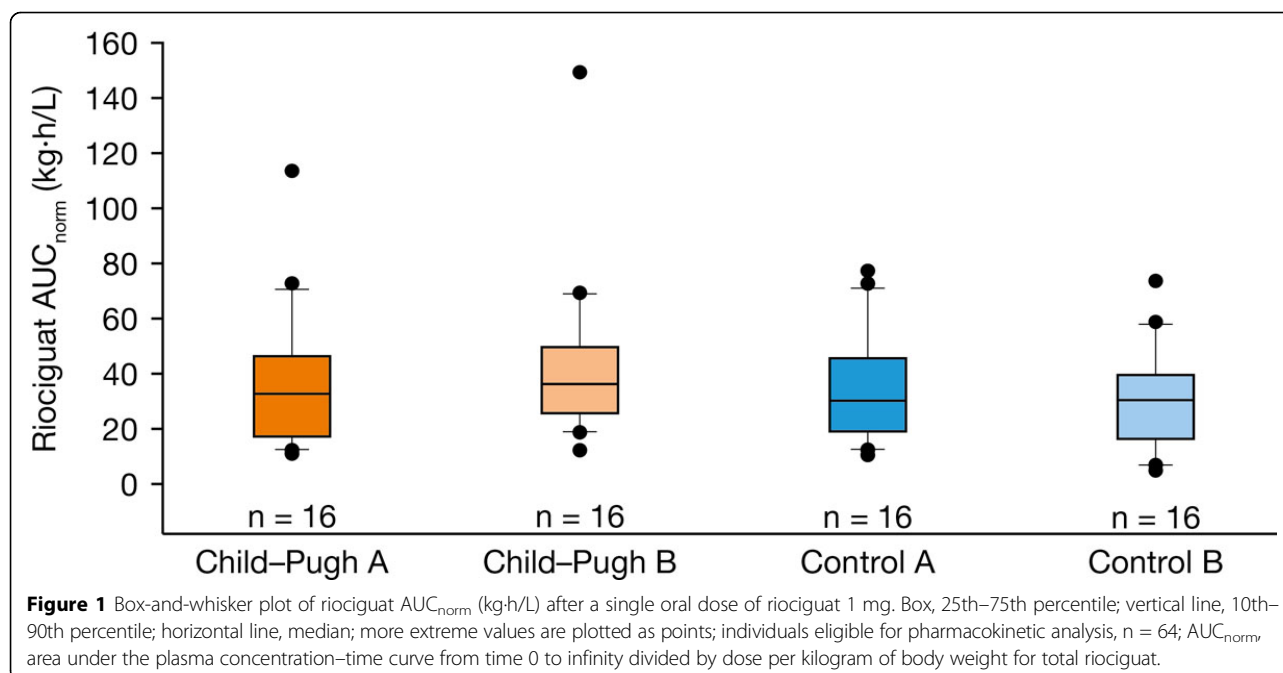
| Parameter | Child-Pugh A (n = 16) | Child-Pugh B (n = 16) | Control A (n = 16) | Control B (n = 16) |
|--|-----------------------|-----------------------|--------------------|--------------------|
| AUC, $\mu\text{g}\cdot\text{h}/\text{L}$ | 371.0 (74) | 458.9 (62) | 349.9 (67) | 300.9 (92) |
| C_{max} , $\mu\text{g}/\text{L}$ | 42.67 (37) | 43.27 (39) | 42.67 (23) | 38.68 (30) |
| AUC_{norm} , $\text{kg}\cdot\text{h}/\text{L}$ | 30.9 (75) | 36.6 (65) | 29.1 (67) | 23.9 (94) |
| $C_{max, norm}$, kg/L | 3.56 (33) | 3.45 (26) | 3.55 (20) | 3.07 (23) |
| $t_{1/2}$, h | 9.19 (53) | 13.7 (50) | 9.02 (63) | 7.54 (86) |

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; $t_{1/2}$, terminal elimination half-life for total riociguat.

* Correspondence: reiner.frey@bayer.com

¹Clinical Pharmacology, Bayer Pharma AG, Pharma Research Centre, Wuppertal, Germany

Full list of author information is available at the end of the article



effects – reduced rate of formation and impaired M1 elimination – led to relatively small differences in overall exposure to M1 in the Child–Pugh A and B groups and their controls. Results for unbound riociguat and M1 were similar to those for total riociguat and M1. No serious or severe adverse events were reported. The most common drug-related adverse event was headache. There was no difference in safety or tolerability between study groups. Riociguat AUC and C_{max} ranges in patients with hepatic impairment overlapped those previously observed in healthy volunteers and patients with PH [2,3].

Conclusion

Child–Pugh A individuals had similar plasma riociguat concentrations to controls. Child–Pugh B individuals had a higher exposure to riociguat than those in the other groups; particular care should be exercised during individual dose titration in patients with moderate hepatic impairment.

Acknowledgements

The studies were funded by Bayer Pharma AG, Wuppertal, Germany, and performed by Atef Halabi, Clinical Trial Director, CRS Clinical Research Services Kiel GmbH, Lornsenstrasse 7, 24105 Kiel, Germany.

Authors' details

¹Clinical Pharmacology, Bayer Pharma AG, Pharma Research Centre, Wuppertal, Germany. ²Global Biostatistics, Bayer Pharma AG, Pharma Research Centre, Wuppertal, Germany.

Published: 29 August 2013

References

1. Stasch JP, Pacher P, Evgenov OV: Soluble guanylate cyclase as an emerging therapeutic target in cardiopulmonary disease. *Circulation* 2011, **123**:2263-2273.
2. Frey R, Mück W, Unger S, Artmeier-Brandt U, Weimann G, Wensing G: Single-dose pharmacokinetics, tolerability and safety of the soluble guanylate cyclase stimulator BAY 63-2521; an ascending-dose study in healthy male volunteers. *J Clin Pharmacol* 2008, **48**:926-934.
3. Grimminger F, Weimann G, Frey R, Voswinckel R, Thamm M, Bölkow D, Weissmann N, Mück W, Unger S, Wensing G, et al: First acute haemodynamic study of soluble guanylate cyclase stimulator riociguat in pulmonary hypertension. *Eur Respir J* 2009, **33**:785-792.
4. Ghofrani HA, Hoepfer MM, Halank M, Meyer FJ, Staehler G, Behr J, Ewert R, Weimann G, Grimminger F: Riociguat for chronic thromboembolic pulmonary hypertension and pulmonary arterial hypertension: a phase II study. *Eur Respir J* 2010, **36**:792-799.
5. Ghofrani H, Galie N, Grimminger F, Humbert M, Keogh A, Langleben D, Kilama MO, Neuser D, Rubin L: Riociguat for the treatment of pulmonary arterial hypertension: a randomized, double-blind, placebo-controlled study (PATENT-1). *Chest* 2012, **142**:1027A.
6. Ghofrani H, Grimminger F, Hoepfer M, Kim N, Mayer E, Neuser D, Pena J, Simonneau G, Wilkins M: Riociguat for the treatment of inoperable chronic thromboembolic pulmonary hypertension: a randomized, double-blind, placebo-controlled study (CHEST-1). *Chest* 2012, **142**:1023A.
7. Hurdman J, Condliffe R, Elliot CA, Davies C, Hill C, Wild JM, Capener D, Sephton P, Hamilton N, Armstrong IJ, Billings C, Lawrie A, Sabroe I, Akil M, O'Toole L, Kiely DG: Aspire Registry: assessing the spectrum of pulmonary hypertension identified at a referral centre. *Eur Respir J* 2012, **39**:945-955.
8. Guidance for industry. Pharmacokinetics in patients with impaired hepatic function: study design, data analysis, & impact on dosing and labeling [<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072123.pdf>].
9. Guideline on the evaluation of the pharmacokinetics of medicinal products in patients with impaired hepatic function [http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003122.pdf].

doi:10.1186/2050-6511-14-S1-P21

Cite this article as: Frey et al: Pharmacokinetics of the soluble guanylate cyclase stimulator riociguat in individuals with hepatic impairment. *BMC Pharmacology and Toxicology* 2013 **14**(Suppl 1):P21.