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No pharmacodynamic (PD) and pharmacokinetic (PK) interaction of riociguat (BAY 63-2521) and aspirin

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Objectives

Riociguat, an oral soluble guanylate cyclase (sGC) stimulator, is a new candidate for treatment of pulmonary hypertension (PH). Riociguat increases cGMP production through a novel dual mode of action: direct NO-independent stimulation of sGC and increasing sensitivity of sGC to low levels of NO. Another sGC stimulator, BAY 41-2272, has shown anti-platelet activity in animal models, as have BAY 41-2272 and riociguat in washed human platelets, although bleeding has not been noted as an adverse event (AE) in riociguat clinical studies [1,2]. As riociguat and aspirin are likely to be used together in PH, it was of interest to investigate potential PD and PK interactions.

Methods

In this randomized, open-label, crossover study, participants took 2.5 mg/day riociguat, two morning doses of 500 mg aspirin, or both drugs concomitantly.

Results

Eighteen healthy men were enrolled. Six of 17 participants in the safety evaluation reported ≥1 treatment-emergent AE. All AEs were mild except 1 case of moderate headache following riociguat administration. Fifteen participants were valid for PD/PK analysis. Riociguat PK values were independent of aspirin coadministration. One hour after coadministration of riociguat and aspirin, the mean increase in fraction unbound was 19% for riociguat and 24% for its metabolite M-1 (BAY 60-4552) indicating mild displacement by salicylic acid, the main aspirin metabolite. Effects of aspirin on bleeding time, platelet aggregation and plasma thromboxane B_2 were not affected by concomitant riociguat. Riociguat alone had no effect on PD variables.

Conclusion

Riociguat demonstrated no clinically relevant PD or PK interaction with aspirin. Coadministration of riociguat and aspirin does not require dose adjustment. Phase 3 randomized controlled trials are investigating riociguat in chronic thromboembolic pulmonary hypertension or pulmonary arterial hypertension.

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