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Title: Absorption behavior of riociguat (BAY 63-2521): Bioavailability, food effects, and dose-proportionality

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Body: Introduction Riociguat, an oral soluble guanylate cyclase (sGC) stimulator, is currently investigated in the treatment of PH. Riociguat increases cGMP production through a novel dual mode of action: direct NO-independent sGC stimulation and increasing sGC sensitivity to low NO levels. Aim To characterize the biopharmaceutic properties of riociguat including absolute bioavailability (BA), interaction with food, and dose-proportionality. Methods Pharmacokinetics (PK) following IV and oral administration of immediate release tablets were characterized in 3 open-label, randomized, crossover studies in healthy male subjects: absolute BA (n=22), food effect at 2.5 mg (n=24), and dose-proportionality over 0.5–2.5 mg (n=24). Safety and tolerability were also assessed. Results Absolute BA was 94% (90% CI: 83–107). A high-fat breakfast delayed absorption with little effect on the extent of riociguat absorption (ratio AUC_{fed}/AUC_{fasted} 88% CI: 82–95). PK were dose-proportional over 0.5–2.5 mg (common slope of AUC 1.09 [90%CI: 1.04–1.14]; C_{max} 0.98 [90% CI: 0.93–1.04]). Intra-individual variability was low (G-CV AUC, C_{max} <20%); inter-individual variability was moderate-to-high (G-CV AUC 30%, C_{max} G-CV 65%). Riociguat was well tolerated in all studies. Adverse events were as expected from the mode of action. Conclusion Riociguat shows complete oral absorption, and no clinically relevant food effect. At 0.5–2.5 mg, riociguat systemic exposure increased dose-proportionately with moderate-to-high inter-individual and low intra-individual variability. Results support the suitability of the individualized dose titration concept investigated in Phase 3 PAH and CTEPH studies.