Randomized placebo-controlled crossover study to assess tolerability and pharmacodynamics of zagociguat, a soluble guanylyl cyclase stimulator, in healthy elderly.

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Abstract

Aim Dysfunction of nitric oxide (NO) – soluble guanylate cyclase (sGC) – cyclic guanosine monophosphate (cGMP) signalling is implicated in the pathophysiology of cognitive impairment and dementia. Zagociguat is a central nervous system-(CNS-) penetrant sGC stimulator designed to amplify NO-cGMP signalling in the CNS. This article reports on a phase 1b study evaluating the safety and pharmacodynamic effects of zagociguat. Methods In this randomized crossover study, 24 healthy participants [?]65 years of age were planned to receive 15 mg zagociguat or placebo once daily for two 15-day periods separated by a 27-day washout. Adverse events, vital signs, electrocardiograms, and laboratory tests to assess safety. Pharmacokinetics of zagociguat were evaluated in blood and CSF. Pharmacodynamic assessments included evaluation of cerebral blood flow, CNS tests, pharmaco-electroencephalography, passive leg movement, and biomarkers in blood, cerebrospinal fluid, and brain. Results Twenty-four participants were enrolled and 12 participants completed both treatment periods, while 12 participants completed only one treatment period. Zagociguat was well tolerated and penetrated the blood-brain barrier. Zagociguat induced modest decreases in blood pressure. No consistent effects of zagociguat on other pharmacodynamic parameters were detected. Conclusion Zagociguat was well tolerated and induced modest systemic blood pressure reductions consistent with other sGC stimulators. No clear pharmacodynamic effects of zagociguat were detected, perhaps due to optimal CNS function in healthy participants. Studies in participants with proven reduced cerebral blood flow or CNS function may be an avenue for further evaluation of the compound.

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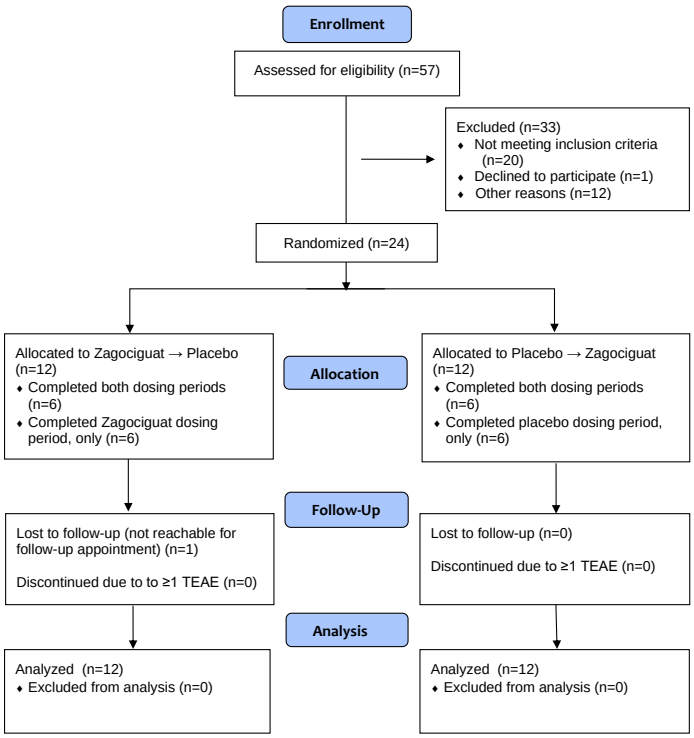

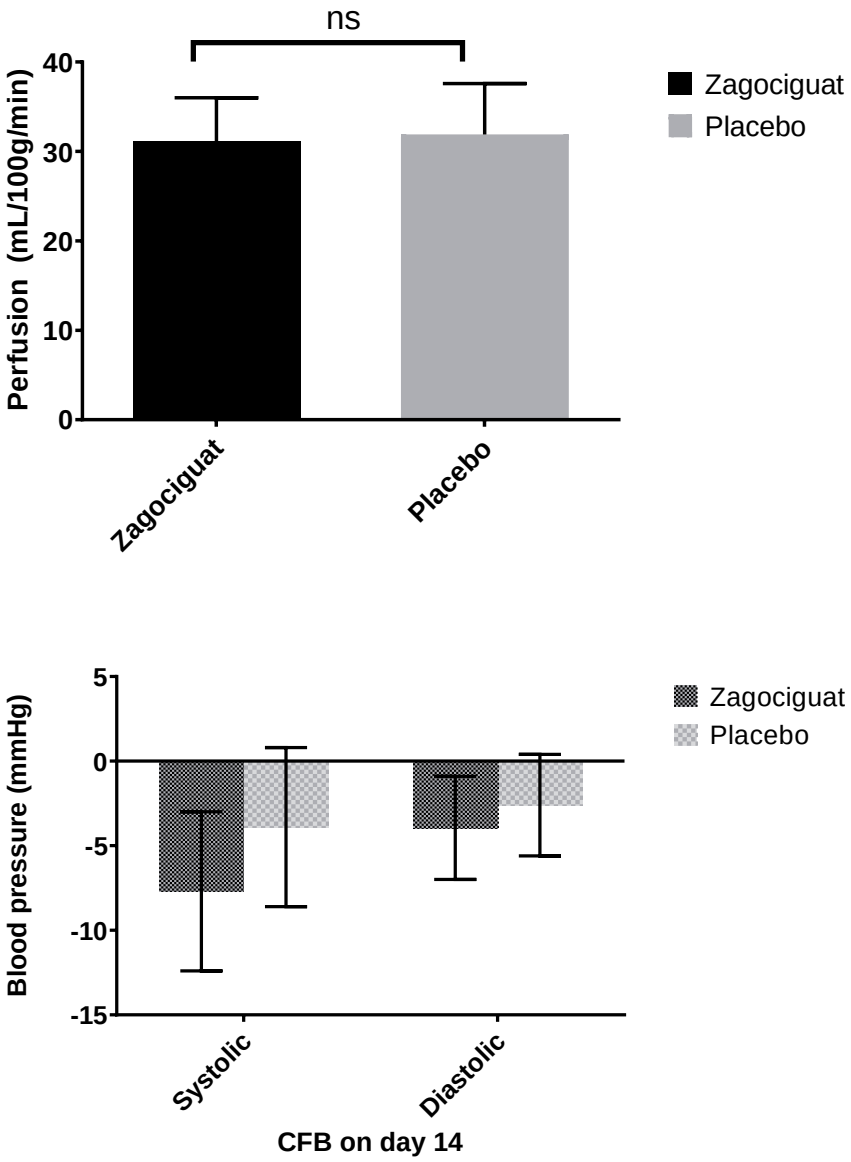

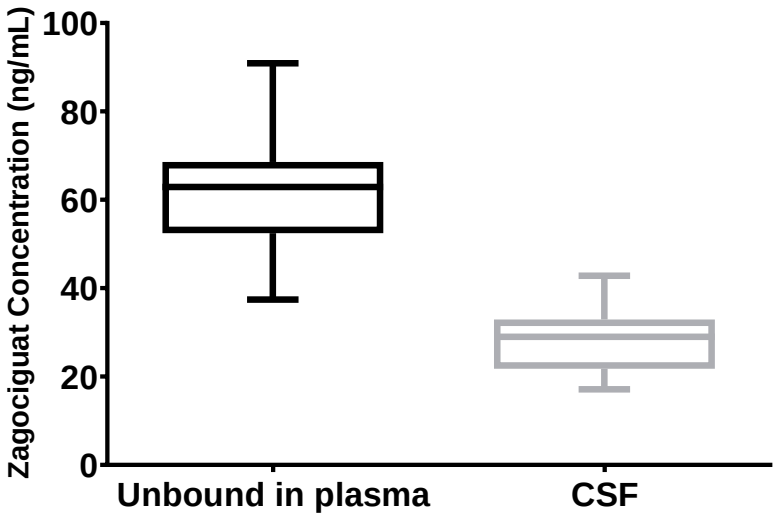

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