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LETTER TO THE EDITOR

Authors' Reply to Ganijee et al.: "Comment on: Evaluation of the Influence of Sildenafil on Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Vericiguat in Healthy Adults"

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Dear Editor,

We highly appreciated the comments of Ganijee et al. [1] on our publication [2]. We thank the authors for bringing to our attention their recent observation of an increase in concurrent use of sildenafil and vericiguat in patients with heart failure with erectile dysfunction.

We would like to provide some noteworthy background information prior to discussing their comments:

The physiological mechanism responsible for smooth-muscle relaxation involves the release of nitric oxide (NO). NO then activates the enzyme soluble guanylate cyclase (sGC), which results in increased levels of cyclic guanosine monophosphate (cGMP). Currently, two members of the drug class of direct sGC stimulators are approved: vericiguat and riociguat. Both act as direct sGC stimulators with a dual mode of action: they sensitize sGC to the body's own NO and can also increase sGC activity in the absence of NO, causing vasorelaxation, antiproliferative effects, and antifibrotic effects. Sildenafil is a potent and selective inhibitor of cGMP-specific phosphodiesterase type 5 (PDE-5), which is responsible for degradation of cGMP.

In summary, both drug classes act on the same pathway. Therefore, a mechanistic understanding on the magnitude of the mutual pharmacokinetic and pharmacodynamic interaction is critical for the assessment of combinability.

PDE-5 inhibitors, including sildenafil, are approved for the treatment of erectile dysfunction [3] and for treatment of pulmonary arterial hypertension (PAH) [4]. Two sGC stimulators are currently approved: riociguat for the treatment of pulmonary hypertension (PH; includes PAH and chronic thromboembolic PH) [5] and vericiguat for the treatment of heart failure with reduced ejection fraction [6].

Formerly, combinations of drug classes that act on the NO–sGC–PDE-5 pathway such as nitrates, PDE-5 inhibitors, or sGC stimulators have been contraindicated [3–5, 7–9]. However, more recent experience and literature have become available, highlighting the medical need and combinability of the drug classes [10–13].

Given these existing data and the general contraindication, the pharmacodynamic and pharmacokinetic interactions of vericiguat and the PDE-5 inhibitor sildenafil were first mechanistically investigated in healthy male adult volunteers. In the published study by the authors [2], the influence of single oral doses of sildenafil 25 mg, 50 mg, and 100 mg (doses approved for the treatment of erectile dysfunction) on top of vericiguat 10 mg at steady state (the target dose of vericiguat in the phase III VICTORIA trial [14]) or placebo tablets was studied. The study design was intended to mimic a potential use of sildenafil for the treatment of erectile dysfunction in patients with heart failure who were stable on the recommended vericiguat maintenance dose of 10 mg [6].

In line with the knowledge about the direct relationship between drug plasma levels and pharmacodynamic effects observed with sGC stimulators, combined treatment of vericiguat with single doses of sildenafil was generally well tolerated in healthy volunteers [2]. However, vericiguat co-administered with sildenafil resulted in an increased frequency of transient adverse events within the system organ class of nervous system disorders, most commonly headache and head discomfort, which were predominantly of mild intensity. In addition, co-administration of vericiguat with sildenafil resulted in decreases in seated systolic blood pressure and diastolic blood pressure of less than or equal to 5.4 mmHg when compared with co-administration of

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placebo with sildenafil. No trend for dose-dependency was observed across the different sildenafil doses. Overall, the observed blood pressure effects with vericiguat and sildenafil in our study were lower than those observed with sildenafil alone, as the reported mean maximum decrease in supine systolic blood pressure following oral dosing of sildenafil 100 mg was 8.4 mmHg [3].

As the vericiguat–sildenafil interaction study was conducted in parallel to the phase III VICTORIA trial, and absent of these data, the use of PDE-5 inhibitors was prohibited in VICTORIA. Unintentional co-administration was very rare (only two patients received vericiguat and a PDE-5 inhibitor). Thus, experience on the concomitant use of vericiguat and PDE-5 inhibitors, such as sildenafil, is limited and has not been systematically studied yet.

Patients with heart failure are treated with contemporary guideline-directed medical therapy (GDMT) [15, 16]. This includes medications such as beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin (II) receptor blockers, angiotensin receptor–neprilysin inhibitors, mineralocorticoid receptor antagonists, hydralazine–nitrate combinations, sodium–glucose cotransporter 2 inhibitors, ivabradine, and cardiac device therapies such as implantable cardioverter-defibrillators and biventricular pacemakers. Most of these drug classes possess blood pressure lowering effects as well; therefore, careful investigation of the concomitant use of vericiguat and PDE-5 inhibitors on top of current GDMT is required before drawing a conclusion on the safety of the co-administration of both drug classes in patients with heart failure.

In summary, in healthy volunteers, concomitant use of vericiguat and PDE-5 inhibitors, such as sildenafil, has been thoroughly investigated at the highest approved dose levels. Vericiguat in combination with sildenafil resulted in combined hemodynamic effects that were in the range of, or less than, the reported blood pressure effects observed with sildenafil alone. The combined treatment was generally well tolerated, with only a minor increased frequency of mainly mild transient adverse events.

Currently, experience with vericiguat and PDE-5 inhibitors in the vericiguat-indicated population (adults with symptomatic chronic heart failure with reduced ejection fraction who are stabilized after a recent decompensation event requiring intravenous therapy) is very limited and has not been systematically studied. Therefore, the concomitant use of vericiguat and PDE-5 inhibitors such as sildenafil is not recommended due to the potential increased risk for symptomatic hypotension [6].

We agree with Ganijee et al. that the available clinical data investigating the interaction potential between sildenafil and vericiguat is limited. However, the study published in *Clinical Pharmacokinetics* [2] intended to address this medical need by providing a foundation for further studies with the results on the mechanistic pharmacokinetic and pharmacodynamic interactions. Therefore, the authors acknowledge that generalizability (especially the safety results) is limited for a real-world patient population. An interaction study in patients with heart failure and erectile dysfunction is of interest and should address the proposed items (inclusive of a diverse range of patient demographics crossing ethnicity, age, and health status border) to support the concurrent use of these medications.

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Declarations

Conflict of interest Michael Boettcher is a former employee of Bayer AG and, within the last 36 months, has received salary, pension, and payment for writing and reviewing vericiguat manuscripts from Bayer AG and for lectures, exercises, and awarding and supporting bachelor and master theses at the Rheinische Fachhochschule Köln (RFH; University of Applied Science, Cologne, Germany). Corina Becker is an employee of Bayer AG.

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Authors' contributions Michael Boettcher and Corina Becker contributed equally to the reply.

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