Physiologically-based pharmacokinetic (PBPK) exploration of extrinsic factors influencing vericiguat pharmacokinetics

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Introduction: Vericiguat is a once daily, novel oral stimulator of soluble guanylate cyclase (sGC) that showed clinical benefit in the Phase III VICTORIA study in heart failure patients with reduced ejection fraction (HFrEF, NCT02861534). Nonclinical and clinical studies demonstrated that the primary route of elimination of vericiguat was glucuronidation to an inactive metabolite M-1 (N-glucuronide). This glucuronidation was catalyzed by uridine 5’-diphospho-glucuronosyltransferases (UGT)1A9 as well as UGT1A1, thus vericiguat may have a potential for victim drug-drug interaction (DDI) when co-administered with potent UGT inhibitors.

Purpose: In a clinical DDI study with mefenamic acid as an UGT1A9 inhibitor no clinically relevant increase in vericiguat exposure in healthy subjects was observed (EudraCT 2014-000764-17). This analysis aims to prospectively investigate as extrinsic factors the DDI potential with atazanavir as a selective UGT1A1 inhibitor via full dynamic physiologically-based pharmacokinetic (PBPK) modelling.

Methods: A PBPK model for vericiguat and M-1 in healthy adults was built with PK-Sim (PBPK platform as part of the Open Systems Pharmacology Suite) by integrating physicochemical, in vitro metabolism and transporter data as well as PK data from clinical pharmacology studies in order to assess the victim DDI potential of vericiguat when co-administered with UGT inhibitors. First, PBPK models for mefenamic acid and atazanavir were separately developed and verified using published literature data. The PBPK model for vericiguat was then verified with regard to its fraction of metabolism by UGTs by comparing simulated and observed data of the clinical mefenamic acid DDI study. Finally, the UGT1A1 DDI potential of vericiguat was prospectively predicted by simulating an in silico study between the UGT1A1 inhibitor atazanavir and vericiguat.

Results: In line with the results of the clinical DDI study with mefenamic acid, an increase in total vericiguat exposure by 14% (area under the concentration time curve ratio (AUCR) of 1.14 (geoCV 5.3%; 90% population interval: 1.06 to 1.25) and peak exposure increase by 6% (CmaxR of 1.06; geoCV 5.9%; 90% population interval: 1.01 to 1.20) was simulated using the PBPK model. A prospective prediction of a virtual DDI trial between the UGT1A1 inhibitor atazanavir yielded an AUCR of 1.12 (geoCV 2.9%; 90% population interval: 1.07 to 1.17) and a CmaxR of 1.04 (geoCV 1.1%; 90% population interval: 1.03 to 1.06). The proposed population intervals for AUCR and CmaxR for both DDI studies lie within the default no-effect boundary of 0.80 to 1.25 according to the to January 2020 FDA DDI guideline.

Conclusion(s): Results of UGT1A9-DDI simulations were consistent with those of the clinical study. The prospective UGT1A1-DDI simulation results suggest a low potential for vericiguat to be subject to DDI when co-administered with UGT1A1 inhibitors.