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Pharmacodynamic interaction study of a long-acting nitrate co-administered with vericiguat in patients with stable coronary artery disease

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Background/Introduction: Vericiguat is a novel stimulator of soluble guanylate cyclase in development for treatment of chronic heart failure (HF) for once-daily oral administration. Guidelines recommend short- and long-acting nitrates for acute treatment and prophylaxis of angina in patients (pts) with coronary artery disease (CAD; a common comorbidity in HF). Co-administration of the short-acting nitrate nitroglycerin (NTG) with vericiguat in animal studies as well as in healthy volunteers (EudraCT 2014-001235-36) and in pts with CAD (NCT02617550) demonstrates that this combination is well tolerated.

Purpose: This study aimed to investigate the pharmacodynamic (PD) drug–drug interaction (DDI) between co-administered isosorbide mononitrate (ISMN) extended-release (ER) and vericiguat in pts with stable CAD (± HF).

Methods: The Vericiguat ISOsoRbide Mononitrate Interaction (VISOR) study (NCT03255512), a multicentre, double-blind, placebo (PBO)-controlled comparison study, investigated the co-administration of ER ISMN 60 mg with vericiguat in 41 pts. Pts were randomised to vericiguat + ISMN (n=28) or PBO + ISMN (n=13). Pts were administered ISMN once-daily for 2 weeks followed by co-administration with PBO/vericiguat. Up-titration of PBO/vericiguat from 2.5 to 5 to 10 mg once-daily was performed in 2-week increments; pts on PBO/vericiguat 10 mg + ISMN were monitored for 2 weeks. The primary objective was to evaluate PD DDIs between vericiguat and ISMN (assessed by blood pressure [BP] and heart rate [HR]); the secondary objectives were to evaluate safety and tolerability.

Results: In total, 35 pts completed treatment (n=12 and 23 for the PBO and vericiguat groups, respectively). Co-administration of vericiguat + ISMN led to mean baseline- and PBO-adjusted reductions in systolic BP (SBP) of 1.4–5.1 mmHg and diastolic BP (DBP) of 0.4–2.9 mmHg and changes in HR of 0.0 to 1.8 bpm (Table 1). These changes were not deemed clinically relevant. No consistent vericiguat dose-dependent PD effects were observed. Two discontinuations due to adverse events (AEs) occurred in the study; one patient

terminated the study due to ISMN-related AEs; the other patient due to unstable angina; discontinuations were not related to PBO or vericiguat. The incidence of AEs was comparable between treatment groups (92.3% and 66.7% in the vericiguat + ISMN and PBO + ISMN groups, respectively).

Conclusion(s): Based on the lack of symptoms associated with the changes in BP and HR in pts taking vericiguat + ISMN, these changes were not considered to be clinically relevant. This combination was well tolerated and is supported by the consistency of results from previous preclinical and human studies. Concomitant use of short- and long-acting nitrates with vericiguat is unlikely to cause clinically significant AEs beyond those known for NTG and ISMN.

Parameter (unit)	Day (profile)	Vericiguat dose (mg)	Difference "Vericiguat−Placebo"	90% CI Lower	90% CI Upper
SBP (mmHg)	0 (first dose)	2.5	−2.0	−6.7	2.7
	13 (SS)	2.5	−4.1	−7.8	−0.5
	14 (first dose)	5	−1.4	−6.6	3.8
	27 (SS)	5	−4.9	−9.7	−0.1
	28 (first dose)	10	−5.1	−9.6	−0.6
	41 (SS)	10	−2.6	−6.6	1.3
DBP (mmHg)	0 (first dose)	2.5	−0.6	−3.0	1.7
	13 (SS)	2.5	−1.0	−3.7	1.8
	14 (first dose)	5	−0.4	−2.8	2.0
	27 (SS)	5	−1.5	−4.2	1.2
	28 (first dose)	10	−2.9	−5.8	0.1
	41 (SS)	10	−1.8	−4.3	0.8
HR (bpm)	0 (first dose	2.5	0.0	−2.3	2.3
	13 (SS)	2.5	1.4	−1.3	4.1
	14 (first dose)	5	1.6	−0.8	4.0
	27 (SS)	5	1.8	−1.3	4.9
	28 (first dose)	10	1.3	−1.1	3.7
	41 (SS)	10	1.6	−2.1	5.3

bpm, beats per minute; CI, confidence interval; DBP, diastolic blood pressure; HR, heart rate; SBP, systolic blood pressure; SS, steady state