PROTOCOL SUMMARY

Rivaroxaban real world effectiveness in patients with atrial fibrillation (GUARDIAN)

Prospective, observational, international, multicenter non-interventional clinical study

Operating name: GUARDIAN

Protocol number: KPASES09/2021-GUARDIAN

Study protocol version: 1.0

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ABBREVIATIONS

AF	Atrial fibrillation
CAD	Coronary artery disease
CKD	Chronic kidney disease
DOAC	Direct oral anticoagulants
GDPR	General Data Protection Regulation
GVP	Good Pharmacovigilance Practice
HF	Heart failure
NOAC	New oral anticoagulants
NVAF	Non-valvular atrial fibrillation
OAC	Oral anticoagulants
OSA	Obstructive sleep apnoea
SmPC	Summary of Product Characteristics
UFH	Unfractionated heparin
VKA	Vitamin K antagonist

PROTOCOL SUMMARY

SPONSOR	Representative offices or companies of Krka d.d., Novo mesto who participated in the study.
PROTOCOL NUMBER	KPASES09/2021-GUARDIAN
TITLE	Rivaroxaban real world effectiveness in patients with atrial fibrillation
RATIONALE FOR THE STUDY	Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in adults.[1,2] AF is associated with substantial morbidity and mortality, thus portending significant burden to patients, societal health and health economy.[1] The currently estimated prevalence of AF in adults is between 2 % and 4 %, and a 2,3-fold rise is expected, owing to extended longevity in the general population and intensifying search for undiagnosed AF.[1,3] Increasing age is a prominent AF risk factor, but increasing burden of other comorbidities including hypertension, diabetes mellitus, heart failure (HF), coronary artery disease (CAD), chronic kidney disease (CKD), obesity, and obstructive sleep apnoea (OSA) is also important.[1,4,5] AF can be divided into different types, based on causes and on duration of the AF episode. When AF is undetected or untreated, it can lead to serious complications, the most important is creation of blood clots that can lead to stroke. Overall AF increases the risk of stroke five-fold.[1,7] Oral anticoagulants (OAC) represent the cornerstone therapy in stroke prevention. Latest guidelines for diagnosis and management of AF recommend new oral anticoagulants (NOAC) as preferred alternative to vitamin K antagonists (VKA, i.e. warfarin) for

	reducing the stroke risk associated with AF, as VKA are associated with certain limitations including numerous food and drug interactions and the need for regular coagulation monitoring. [1] Rivaroxaban is one of four NOAC that have been approved for the reduction of stroke risk and systemic embolism in patients with AF and first in the class that directly inhibits both free and clot-bound Factor Xa and prevents the formation of new clots and the extension of existing clots. Other main advantages include once daily dosing, no need for frequent monitoring, no food interactions and faster and more predictable dose response vs warfarin. Based on the currently available published data, there are not many real world clinical studies done with rivaroxaban. Many different risk factors can influence the effectiveness and safety of rivaroxaban treatment, therefore real clinical data on wider patient population and different patient subgroups are very beneficial for improving treatment management.[1,9] This non-interventional study will evaluate the real-world effectiveness of Xerdoxo® in heterogeneous population with variety of risk factors. The study will provide important therapeutic data, reflecting actual clinical aspects in the field of treatment with rivaroxaban, understanding the role and value of Xerdoxo® in improving patients' outcomes and consequently help investigators to take informed decisions on the treatment of patients with AF. 1. ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. EHJ 2020; 00: 1–125. 2. Wyndham C. Atrial Fibrillation: the most common arrhythmia. Tex Heart Inst J 2000; 27 (3): 257–67. 3. Turakhia M, Shafrin J, Bognar K et al. Estimated prevalence of undiagnosed atrial fibrillation in the United States. Plos One 2018; 13 (4): e0195088. 4. Staerk L, Sherer J, Ko D. Benjamin E. Atrial fibrillation: epidemiology, pathophysiology and clinical outcomes. Circulation research 2017; 120 (9): 1501–17. 5. Jean-Louis G, Zizi F, McFarlane S. Obstructive sleep apnea and cardiovascular disease: role of the metabolic syndrome and its components. J Clin Sleep Med 2008; 4 (3): 261–72. 6. Staerk L, Wang B, Preis S et al. Lifetime risk of atrial fibrillation according to optimal, borderline, or elevated levels of risk factors: cohort study based on longitudinal data from the Framingham Heart Study. BMJ 2018; 361: k1453. 7. Gutierrez C, Blanchard D. Diagnosis and treatment of atrial fibrillation. American Family Physician 2016; 94 (6): 442–52. 8. Fauchier L, Philippart R, Clementy N, et al. How to define valvular atrial fibrillation? Arch Cardiovasc Dis. 2015; 108 (10): 530–9. *9.* SmPC Xerdoxo®
STUDY OBJECTIVES	The main objective of the study is to provide therapeutic data about effectiveness of Xerdoxo® across the broad range of patient risk profiles encountered in the setting of routine clinical practice. The data collected during the course of the study will provide a comprehensive overview of the outcomes associated with Xerdoxo® therapy and factors influencing its use in the clinical management of stroke prophylaxis in AF patients.
STUDY DESIGN AND DURATION	This is an international, non-interventional, observational, prospective, multicentre study evaluating the effectiveness and safety of Xerdoxo® in patients with AF according to the investigator's consideration and in compliance with indications stated in SmPC of Xerdoxo®. Only patients, who would be otherwise also treated with Xerdoxo® in local regular clinical

	practice, will be enrolled in this non-interventional study. The decision to prescribe Xerdoxo® is at the sole discretion of the treating investigator, including dose and duration of Xerdoxo® therapy. Each investigator will enrol agreed number of his/hers consecutive patients in line with inclusion/exclusion criteria. The diagnostic, choice of the medicine and treatment procedures will be in line with local regular clinical practice. The period of observation is defined based on data, obtained from regular clinical practice, guidelines, SmPC of Xerdoxo® and other studies with rivaroxaban. Considering guidelines, monitoring of DOAC (direct anticoagulants) treated patients is preferably in 1-3 months after the initiation of the therapy and then every 6 months. [10] In the study, patient's controls will be performed as in local regular clinical practice and expected follow-up visits are in the interval of 1 month, 6 months and 1 year after the baseline. The process of data collection will be in line with local regular clinical practice. Data can be collected at on-site visits or remotely via phone or electronic media (not applicable for baseline visit). 10. Conway S, Hwang A, Ponte C, Gums J. Laboratory and Clinical Monitoring of Direct Acting Oral Anticoagulants: What Clinicians Need to Know. Pharmacotherapy 2017; 37 (2): 236–48.
SELECTION OF INVESTIGATORS	Only cardiologists who routinely treat patients with AF and its complications will be included in this study as study investigators. The selected investigator will be eligible for enrolment of patients in the study, if the investigator has the right specialization for the therapeutic area, is appropriately educated and trained for performing the study, has experiences and capacity for study conductance and if the contract for study performance at investigator's site is signed.

SELECTION OF PATIENTS	**Inclusion criteria**
	• Female or male patients, aged 18 years or more.
	• Patients with diagnosed non-valvular atrial fibrillation (NVAF)* who are indicated for treatment with Xerdoxo® according to valid SmPC;
	  ○ naïve patients (patients who never took anticoagulants in the past) or
	  ○ patients already treated with anticoagulants (except rivaroxaban) but unsatisfied (uncontrolled or experiencing adverse events) on existing therapy.
	• Patients who agreed with informed consent form.
	• Patients who consent for collection, analyses and processing of personal data as well as publication of study results.
	
	**AF is considered valvular when it's seen in patients with moderate-to-severe mitral stenosis or a prostethic heart valve. NVAF generally refers to AF caused by other things, such as high blood pressure, stress, heart attack, lung disease, smoking, etc.[11,13]*
	
	• **Exclusion criteria**
	• Participation in other clinical study.
	• Patients, who are unable to follow clinical practice for any reasons.
	• In line with contraindications in Summary of product characteristics of Xerdoxo®.

	• Hypersensitivity to the active substance or to any of the excipients of Xerdoxo®. • Active clinically significant bleeding. • Lesion or condition, if considered to be a significant risk for major bleeding. This may include current or recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities. • Concomitant treatment with any other anticoagulants, e.g. unfractionated heparin (UFH), low molecular weight heparins (enoxaparin, dalteparin, etc.), heparin derivatives (fondaparinux, etc.), oral anticoagulants (warfarin, dabigatran etexilate, apixaban, etc.) except under specific circumstances of switching anticoagulant therapy or when UFH is given at doses necessary to maintain an open central venous or arterial catheter. • Female participants who are breastfeeding or pregnant or who are intending to become pregnant. • Hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C. **Withdrawal criteria** • The occurrence of serious adverse reaction during the observational period in this study. • Death. • Other safety reasons (e.g. investigator's decision to exclude the patient from the study to his/her best interest, adverse events required medicinal intervention or withdrawal of therapy). • Patient's decision to stop the treatment and withdrawal of his/her informed consent. • An acute disease requiring the use of a medicine, not permitted to be concomitantly used with Xerdoxo® according to the SmPC. • The deterioration of a disease requiring treatment not permitted to be concomitantly used with Xerdoxo® according to the SmPC.
STUDY ENDPOINTS	**Primary endpoints** All primary and secondary endpoints will be assessed for all enrolled* patients together and also within medical subgroups based on baseline characteristics. • Assessing the incidence of major bleeding events in the observed study period. • Assessing the incidence of stroke and/or embolism mortality in the observed study period. • Assessing the incidence of treatment-emergent adverse reactions in the observed study period.

	*Enrolled patient is a patient who meets all inclusion and exclusion criteria and receive Xerdoxo®. **Secondary endpoints** Secondary outcomes: Includes 18 items. At the baseline this includes the assessment of the patient profiles, risk factors (sex, age, BMI, smoking habits, alcohol consumption), proportions of newly diagnosed patients, proportion of patients with comorbidities, evaluation of CHA2DS2-VASc score, evaluation of HAS-BLED score, proportion of patients previously treated with anticoagulants (except rivaroxaban) and proportion of treatment naïve patients. Secondary outcomes at each data capture include the assessment of incidence of symptomatic thromboembolic events (stroke, TIA and systemic embolism or myocardial infarction), the incidence of major bleeding events (fatal bleeding, symptomatic bleeding in a critical area or organ, or a bleeding caused by a fall of haemoglobin level of 1.24 mmol/l (20g/L) or more, or need for transfusion of 2 or more units of packed red blood cells or whole blood), the incidence of non-major bleeding events (any bleeding event that does not meet the criteria for major bleeding event), proportion of patients who need additional treatment of AF besides rivaroxaban, incidence of stroke and/or embolism mortality, incidence of treatment-emergent adverse reactions, evaluation of patient's satisfaction to Xerdoxo® therapy in comparison to previous anticoagulant therapy, patient's satisfaction with dosing regimen of Xerdoxo®, patient's and investigator's general satisfaction to Xerdoxo® therapy, evaluation of reasons for discontinuation of treatment and the incidence of all-cause mortality marked as either vascular or non-vascular.
MONITORING AND DATA QUALITY CONTROL	During the study the authorised person of sponsor can implement different activities to assure compliance with the study protocol; provide information and support to investigators, monitor the study and record and report adverse events either by on-site or remote monitoring.
ASSESSMENT OF SAFETY	Adverse events will be monitored from the moment, when patient agrees with Informed Consent Form and signs GDPR Form until the maximum 4th data capture point. The investigator is going to collect data and report adverse events in appropriate timing to sponsor. Sponsor is responsible for forwarding appropriate information about adverse events to competent health authorities. Recording and reporting of adverse events should follow GVP (Good pharmacovigilance practices) and local legislation related to pharmacovigilance.
ETHICAL ASPECTS	This study will be implemented in accordance with the ethical principles set out at the 18th World Medical Association General Assembly (Helsinki, 1964) and in all amendments thereto, and in accordance with the applicable local legislation on epidemiological studies.

STATISTICAL METHODOLOGY	Summary statistics consists of the number of patients/observations, frequencies and corresponding percentages for categorical variables, and of the number of patients/observations, mean, median, standard deviation, minimum and maximum, first and third quartile for numeric variables. Some variables (numeric discrete variables with few possible values) are summarized both as categorical variables and as numeric variables. For inferential assessment of proportions, the two-sided “equal-tails” Clopper-Pearson exact 95% - confidence interval will be employed. For the assessment of means and mean differences, the standard 95%-confidence interval for the mean (with unknown variance) based on the limiting distribution of the standardized sample mean will be employed.