PROTOCOL SUMMARY

Etoricoxib in real-world clinical setting: its treatment outcome in patients with rheumatic diseases

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

Operating name: RED

Protocol number: KPASES09/2020–RED

Study protocol version: 1.0

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ABBREVIATIONS

COX	Cyclooxygenase
GI	Gastrointestinal
KOOS	Knee Injury and Osteoarthritis Outcome Score
NSAID	Nonsteroidal anti-inflammatory drugs
OA	Osteoarthritis
RA	Rheumatoid arthritis
SmPC	Summary of product characteristics

PROTOCOL SUMMARY

SPONSOR	Representative offices or companies of Krka d.d., Novo mesto who participated in the study.
PROTOCOL NUMBER	KPASES09/2020-RED
TITLE	Etoricoxib in real-world clinical setting: it's treatment outcome in patients with rheumatic diseases
RATIONALE FOR THE STUDY	Rheumatic diseases (osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, acute gouty arthritis) constitute of one of the most widespread, crippling and painful group of conditions (1). Osteoarthritis (OA) and rheumatoid arthritis (RA) are two of the most common rheumatic conditions, which account for a large percentage of disability and chronic pain in adults worldwide (2). It is known that knee osteoarthritis is the most common joint localization of OA, where OA is the most prevalent form of arthritis (3, 4). One of the main and most disabling symptoms accompanying these conditions is pain (1). Nonsteroidal anti-inflammatory drugs (NSAIDs) represent the cornerstone of pain and inflammation therapy (5, 6). Those medications often arise upper gastrointestinal problems, which might be the cause of discontinuation of therapy. Cyclooxygenase-2 selective inhibitors (COX-2), medicines used in pain and inflammation treatment, offer major advantage of reduced gastrointestinal (GI) toxicity, compared to non-selective NSAIDs (5). Etoricoxib, COX-2 selective inhibitor, has been well studied in patients with different rheumatic diseases, however mostly in randomized clinical trials (7-10), which may not accurately represent daily regular clinical practice characterized by heterogeneous population of patients. This non-interventional clinical study with Krka's etoricoxib in real-world setting on heterogeneous population of patients will provide information about medicine performance in the real-world clinical practice and furthermore help us understand the role and value of Krka's etoricoxib in improving patients'

	outcomes. The study will provide important therapeutic data, reflecting actual clinical aspects in the field of rheumatic diseases and pain management; additionally the study will evaluate the real-world effectiveness of Krka's etoricoxib and consequently help investigators to take informed decisions on the treatment of patients with rheumatic diseases, especially osteoarthritis. *1. Börsch-Supan A, Kneip T, Litwin H, et al. Ageing in Europe - Supporting Policies for an Inclusive Society. Walter de Gruyter GmbH & Co KG, 2015.* *2. Abdolrazaghnejad A, Banaie M, Tavakoli N, Safdari M, Rajabpour-Sanati A. Pain Management in the Emergency Department: a Review Article on Options and Methods. Adv J Emerg Med. 2018;2(4):e45* *3. Metsios GS, Kitas G. Should patients with rheumatic diseases take pain medication in order to engage in exercise? Expert Rev Clin Immunol. 2020 Mar;16(3):235-237.* *4. EULAR. 10 things you should know about rheumatic diseases [internet]. [cited 2020 December 17]. Available from: https://www.eular.org/myUploadData/files/10%20things%20on%20RD.pdf* *5. Sangha O. Epidemiology of rheumatic diseases. Rheumatology (Oxford). 2000;39 Suppl 2:3-12.* *6. WHO. Chronic diseases and health promotion: Chronic rheumatic conditions. [internet]. [cited 2020 December 17]. Available from: https://www.who.int/chp/topics/rheumatic/en/* *7. Wittenauer R, Smith L, Aden K. Background Paper 6.12: Osteoarthritis (update on 2004 Background Paper). [internet]. 2013 [cited 2020 December 17]. Available from: http://www.who.int/medicines/areas/priority_medicines/BP6_12Osteo.pdf* *8. MayoClinic. Osteoarthritis. [internet]. 2020 [cited 2020 December 17]. Available from: https://www.mayoclinic.org/diseases-conditions/osteoarthritis/symptoms-causes/syc-20351925* *9. MayoClinic. Rheumatoid arthritis. [internet]. 2019 [cited 2020 December 17]. Available at http://www.mayoclinic.org/diseases-conditions/rheumatoid-arthritis/home/ovc-20197388* *10. Collantes E, Curtis SP, Lee KW et al. A multinational randomized, controlled, clinical trial of etoricoxib in the treatment of rheumatoid arthritis. BMC Family Practice 2002, 3:10.*
STUDY OBJECTIVES	The main study aim is to evaluate the real-world effectiveness of Krka's etoricoxib, assessing pain intensity of patients, diagnosed with different rheumatic diseases. Throughout the study period, the study will assess possible advantages of single-dose regimen and determine gastrointestinal (GI) tolerability as well as cardiovascular safety of treatment with Krka's etoricoxib. Moreover, in patients with knee osteoarthritis, the study will evaluate presence of common symptoms, pain intensity, patient's function in daily living, sports and recreation as well as knee related quality of life.
STUDY DESIGN AND DURATION	This is an international, non-interventional, observational, prospective, multicenter study evaluating the effectiveness of Krka's etoricoxib in patients with rheumatic diseases (osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, acute gouty arthritis) according to the investigator's consideration and in compliance with indications stated in SmPC of Krka's etoricoxib. Only patient, who would be otherwise also treated with Krka's etoricoxib in local regular clinical practice, will be enrolled in this international non-interventional study. Each investigator will enroll 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. Patients will be observed over the course of 8±4 weeks, where the investigator will record the required data at two data captures. At the first data capture, the investigator will collect baseline variables at patient's enrolment in the study. At 2nd data capture, in the time point 8±4 weeks after the baseline, the investigator will collect follow-up variables from the first routine-controlled visit. Patient's controls will be perfomed as in local regular clinical practice. The process of data collection depends on local regular clinical practice. Data can be collected at on-site visits or remotely via phone or electronic media (applicable only for 2nd data capture, premature exclusion and conclusion of the study).
SELECTION OF INVESTIGATORS	The study will include general practioners, internists, rheumatologists, orthopaedists and other specialists who routinely treat patients with rheumatic diseases in their local everyday clinical practice. A representative sample of investigators will be provided by including investigators of different specialisation relevant for the treatment of rheumatic diseases and considering the geographical distribution of the specialty. Participating investigators will include patients according to the indications they are specialised (qualified) in.
SELECTION OF PATIENTS	**Inclusion criteria** • Female and male patients, aged between 18-79 (age limits included). • Patients with symptomatic rheumatic diseases (osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, acute gouty arthritis) who are indicated for treatment with etoricoxib and obtain Krka's etoricoxib according SmPC. • Patients who agreed with informed consent form and consent for collection, analyses and processing of personal data as well as publication of study results. **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 Krka's etoricoxib. **Withdrawal criteria** • The occurrence of serious adverse event during the observational period in this study. • Patient's decision to stop the treatment and withdrawal of his/her informed consent. • Patient's safety (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). • An acute disease requiring the use of a medicine, not permitted to be

	concomitantly used with Krka's etoricoxib according to the SmPC. • The deterioration of a disease requiring treatment not permitted to be concomitantly used with Krka's etoricoxib according to the SmPC.
STUDY ENDPOINTS	**Primary endpoints** All primary endpoints will be assessed for all enrolled* patients together and separately for each participating country. • Assessing the mean absolute and relative reduction of pain intensity** on VAS scale in patients with rheumatic diseases from 1st till 2nd data capture. • Assessing proportion of patients with rheumatic diseases with clinically meaningful** improvement of pain management at 2nd data capture. • Assessing the mean absolute improvement of five outcomes (pain, symptoms, function in daily living, sport and recreation function, knee-related quality of life) with KOOS questionnaire in patients with knee osteoarthritis from 1st till 2nd data capture. **An enrolled patient is a patient who meets all inclusion and exclusion criteria.* *** Reduction of pain intensity is considered as clinically meaningful, if pain intensity does not exceed 30 mm on VAS or if the baseline intensity is reduced by at least 50 %.* **Secondary endpoints** The secondary endpoints encompass 12 items realted with: previous teatments with rheumatic agents and/or analgesics, evaluation of reasons for discontinuing previous treatment with NSAIDs, evaluation of patient's and investigator's satisfaction with the Krka's etoricoxib treatment, assessing cardiovascular safety of treatment with Krka's etoricoxib, satisfaction with Krka's etoricoxib dosign regimen, assessing proportion of patients with gastrointestinal problems, assessing proportion of patients who need in addition to Krka's etoricoxib treatment with other rheumatic agent/analgesic, assessing average time till the first follow-up, evaluating Krka's etoricoxib average dose and daily dose, assessing proportion of patients with comorbidities, evaluation of reasons for Krka's etoricoxib change at 2nd data capture, assessing the proportion of patient who experienced improvement in KOOS values, safety evaluation.
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 2nd 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	The statistical report will include standard descriptive statistics. For numerical variables and each group (population) in question, we will record the largest and the smallest value in the associated sample, the sample mean and the sample standard deviation. For categorical variables and each group in question, the numeri and percentages of the categories present in the associated sample will be listed in tabular form. The sample size calculation is is based on the requirement of the width of the confidence interval for the primary endpoint proportion of patients with rheumatic diseases with clinically meaningful improvement of pain intensity at the 2nd data capture. In this study, only the full analysis set (FAS) will be considered. The full analysis set (FAS) is defined as the set of all screened patients with baseline record of pain intensity on VAS 0-100mm.