PROTOCOL SUMMARY

Impact of naproxen sodium (Nalgesin® forte) treatment on the performance of daily activities in patients with low back pain or osteoarthritis in regular clinical practice (QLIFE)

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

Operating name: QLIFE

Protocol number: KPASES21/2022-QLIFE

Study protocol version: 1.0

Version date: 8.11.2022

ABBREVIATIONS

GDPR	General Data Protection Regulation
GVP	Good Pharmacovigilance Practice
LBP	Low Back Pain
NRS	Numeric Rating Scale
NSAID	Nonsteroidal Anti-Inflammatory Drug
OA	Osteoarthritis
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	KPASES21/2022-QLIFE
TITLE	Impact of naproxen sodium (Nalgesin® forte) treatment on the performance of daily activities in patients with low back pain or osteoarthritis in regular clinical practice
RATIONALE FOR THE STUDY	Low back pain (LBP) is one of the most prevalent health problems worldwide, which affects personal lives, causing activity limitations and work absence. For treatment of patients with acute LBP, most guidelines endorse recommendations for patient education, reassurance about a favorable prognosis and advice on returning to normal activities, and avoiding bed rest, and NSAIDs as first line of pharmacological treatments. The aim of the treatment is often improving the functional ability and quality of life of the patient (1). Osteoarthritis (OA) is the most common form of arthritis and is a leading cause of disability among older adults. OA is characterized by pathology involving the whole joint, including cartilage degradation, bone remodeling, osteophyte formation, and synovial inflammation, leading to pain, stiffness, swelling, and loss of normal joint function. Oral NSAIDs are strongly recommended for patients with knee, hip, and/or hand OA and remain the mainstay of the pharmacologic management of OA. Patients with moderate to severe pain due to OA have a high impact on the quality of life. Due to the impact of osteoarthritis on quality of life, many therapies are used to improve symptoms in these patients, although no treatment delays or prevents osteoarthritis or provides long term relief of symptoms (2,3,4). The purpose of study is to assess and explore effect of treatment with Krka's naproxen sodium on pain, mobility and function of patients with low back pain or osteoarthritis in regular clinical practice.

	Results will provide information on correlation between pain control and patient's ability to perform different activities of daily living, which will be further communicated to health care professionals.1. van der Gaag, Wendelien H et al. "Non-steroidal anti-inflammatory drugs for acute low back pain." The Cochrane database of systematic reviews vol. 4,4 CD013581. 16 Apr. 2020, doi:10.1002/14651858.CD013581 2. Kolasinski, Sharon L et al. "2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee." Arthritis care & research vol. 72,2 (2020): 149-162. doi:10.1002/acr.24131 3. Magni, Alberto et al. "Management of Osteoarthritis: Expert Opinion on NSAIDs." Pain and therapy vol. 10,2 (2021): 783-808. doi:10.1007/s40122-021-00260-1 4. Shalhoub, M., Anaya, M., Deek, S. et al. The impact of pain on quality of life in patients with osteoarthritis: a cross-sectional study from Palestine. BMC Musculoskelet Disord 23, 248 (2022). https://doi.org/10.1186/s12891-022-05207-x
STUDY OBJECTIVES	The main study objective is to provide therapeutic data about the effectiveness of Krka's naproxen sodium in reducing pain in correlation with improving ability to perform activities of daily living in patients with LBP or OA encountered in regular clinical practice. Collected data will also provide the frequency of adverse events of treatment with Krka's naproxen sodium throughout the study period.
STUDY DESIGN AND DURATION	This is an international, non-interventional, observational, prospective, multicenter, study evaluating the influence of treatment effect of Krka's naproxen sodium 550 mg on the performance of activities of daily living in patients with LBP or OA encountered in regular clinical practice. The duration of the patient's observation is up to 4 weeks and it is based on observation period from similar studies, guidelines, reports on achieving maximal analgesic and anti-inflammatory effect from NSAID treatment etc. This period is also in line with regular clinical practices in participating countries and we assume that with this duration the evaluation the study hypothesis and study objectives will be possible. Patient's visits at doctor will be performed as in local regular clinical practice. There will be 2 data capture points: • **1st data capture** (on-site visit): start of observation (collection of baseline variables); • **2nd data capture** (on-site or remotely): collection of follow up variables from the first routine control visit after start of observation within 4 weeks, but not sooner than 10 days after start of observation if performed.
SELECTION OF INVESTIGATORS	**General practitioners** or/and **specialists** (i.e. neurologists, orthopedists, rheumatologists…) who are having patients with low back pain or osteoarthritis in their daily clinical practice will be included in this study as study investigators. The selected investigator will be eligible for observation of patients, if the investigator has the right specialization for the therapeutic area, is appropriately educated and trained for performing the study and if the contract for study performance at investigator's site is signed.

SELECTION OF PATIENTS	**Inclusion criteria** • Female or male patients, aged 18 year or more. • Patients with LBP or OA. • Patients with average pain intensity in last 24 hours of ≥ 3 on Numeric Rating Scale (NRS). • Patients eligible for treatment with Krka's naproxen sodium 550 mg according to SmPC and investigator's decision based on his regular clinical practice. • Patients who agreed with informed consent form and consent for collection, analyses and processing of personal data as well as publication of study results. • Patients, to whom Krka's naproxen sodium 550 mg would be prescribed in regular clinical practice (independent of this non-interventional study). **Exclusion criteria** • Patients with contraindications listed in SmPC of Krka's naproxen sodium 550 mg. • Participation in other clinical study. • Female patients who are breastfeeding or pregnant or who are intending to become pregnant, • Patients, who are unable to follow clinical practice for any reasons. **Withdrawal criteria** • The occurrence of serious adverse reaction during the therapy with Krka's naproxen sodium 550 mg. • Patient's decision to stop the treatment and withdrawal of his/her informed consent. • Adverse events requiring medical intervention or withdrawal of therapy.
STUDY ENDPOINTS	**Primary endpoint** Proportion of patients with improved ability to perform overall activities of daily living after an up to 4-week treatment with Krka's naproxen sodium 550 mg as described in this protocol for all patients. **Secondary endpoints** The secondary endpoints encompass 15 items related to proportions of patients with improved ability to perform activities of daily living, separately for mobility, daily routine, socializing, general well-being/mood swings; absolute and relative changes of current pain intensity, average pain intensity and worst pain intensity in the last 24h, comparison of absolute and relative mean changes of all three pain intensities among patients, treated with a 2-times-daily dosing regimen vs. other dosing regimen and patients adhering to prescribed therapy with Krka's naproxen sodium 550 mg vs. patients not adhering to prescribed therapy with Krka's naproxen sodium 550 mg; evaluation of prescription practices of general practitioners vs. specialist; evaluation of additional prescription for managing of pain; assessment of patient's satisfaction with the treatment in general and separately with twice daily dosing regimen; assessment of patient's condition improvement; comparison of incidence of gastrointestinal adverse events between patients with and without prescription of gastro-protective

	agents and evaluation of tolerability of treatment with Krka's naproxen sodium 550 mg. Additionally primary endpoint and selected secondary endpoints will be evaluated also separately for group of patients only with LBP and group of patients only with OA.
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	Summary statistics will consist of number of patients/observations, frequencies, and corresponding percentages for categorical variables. For numeric variables, descriptive statistics (number of patients/observations, mean, median, standard deviation, minimum and maximum, first and third quartile) will be tabulated. Proportions will be assessed with the standard Clopper-Pearson 95%-confidence interval. Means (and paired mean differences) of numeric variables will be assessed with the standard 95%-confidence interval for the mean (with unknown variance) based on the limiting normal distribution of the normalized sample mean. In case of small samples in subpopulations of interest, suitable small-sample methods will be employed. The nominal level of significance will be 0.05; by inversion, the nominal confidence level for confidence intervals will be 0.95.