PROTOCOL SUMMARY

Real world management of pain: Do patient-specific factors influence treatment decisions and its outcomes?

Observational, prospective, non-interventional, international, multicenter epidemiological study

Operating name: RELIEF

Protocol number: KEPSU13/2020–RELIEF

Study protocol summary version: 1.0

Version date: 29.11.2023

ABBREVIATIONS

AE	Adverse event
AR	Adverse reaction
BA	Bosnia and Herzegovina
CGI-I	Clinical Global Impressions – Improvement
CV	Cardiovascular
eCRF	Electronic case report form
GP	General practitioner
INN	International non-proprietary name
NSAID	Nonsteroidal anti-inflammatory drug
SmPCS	Summary of product characteristics
VAS	Visual Analogue Scale
WHO	World Health Organisation

PROTOCOL SUMMARY

SPONSOR	Representative offices or companies of Krka d.d., Novo mesto in Bosnia and Herzegovina, Croatia, Czech Republic, North Macedonia and Serbia
PROTOCOL NUMBER	KEPSU13/2020–RELIEF
TITLE	Real world management of pain: Do patient-specific factors influence treatment decisions and its outcomes?
PARTICIPATING COUNTRIES	Bosnia and Herzegovina, Croatia, Czech Republic, North Macedonia and Serbia
RATIONALE FOR THE STUDY	Pain of any type is the most common reason to consult the doctor and is one of the leading domains of disability worldwide.[1] It is estimated that 40–60 % of patients with chronic pain have inadequate management of their pain, while also management of acute pain remains inadequate across various treatment settings.[2,3] When it is not effectively treated and relieved, pain has a detrimental effect on all aspects of quality of life.[4] Rarely pain is the only patient's medical condition. Because of that management of pain must consider different patient-specific factors, including type, intensity and duration of pain, comorbidities and concomitant medications, in order to provide a safe and effective treatment tailored to patient's requirements.[1,5] The WHO's 3-step ladder of pain control is still considered a gold standard of pain management. Pharmacologic agents recommended as a first-step for the symptomatic treatment of mild to moderate pain are non-opioid analgesics, such as paracetamol or a nonsteroidal anti-inflammatory drug (NSAID). NSAIDs are a heterogeneous group of non-opioid analgesics and

	anti-inflammatory agents with unique pharmacokinetic and safety profile, especially with regard to gastrointestinal, cardiovascular, hepatic and renal side effects. Together with side effect profile and pharmacokinetic, the choice between medications recommended as first-step thus should depend on the type of pain and patients risk factors. If these first-step recommended agents are not sufficient, weak opioids and medications that target separate pathways simultaneously, such as paracetamol/opioid combination, are reasonable choices. Severe acute pain is typically treated with potent opioids. At each step, multimodal approach is recommended and adjuvant medications directed at the underlying condition can be used.[6-7] With this epidemiological study we want to explore if and how patient-specific factors play a role in the selection of medications for pain management, especially NSAIDs and paracetamol/tramadol combination. As quality of life is increasingly being recognized as one of the most important parameters to be measured in the evaluation of pain management therapies[9,10], we would additionally observe influence of pain and corresponding treatment choices on patient's quality of life in usual care settings. Obtained findings will be transferred to professional public in order to improve pain management in daily practice and consequently to improve patients' quality of life. *References:* 1. *Davis JA, Robinson RL, Le TK, Xie J. Incidence and impact of pain conditions and comorbid illnesses. J Pain Res. 2011;4:331-345.* 2. *Mills S, Torrance N, Smith BH. Identification and Management of Chronic Pain in Primary Care: a Review. Curr Psychiatry Rep. 2016;18(2):22.* 3. *Sinatra R. Causes and consequences of inadequate management of acute pain. Pain Medicine 2010; 11:2859-1871.* 4. *Katz N. The impact of pain management on quality of life. J Pain Symptom Manage 2020; 24 (Suppl 1):S38-47.* 5. *Weiner RS. Pain Management: A Practical Guide for Clinicians, Sixth Edition. Washington, D.C.:CRC Press, 2001.* 6. *World Health Organization (WHO) [internet]. WHO's pain ladder [cited 17.6.2020]. Available from: http://www.who.int/cancer/palliative/painladder/en/.* 7. *Cameron C. Non-steroidal anti-inflammatory drugs (NSAIDs): Making safer treatment choices. Best Practice Journal 2013; 55.* 8. *Pergolizzi JV Jr, van de Laar M, Langford R, et al. Tramadol/paracetamol fixed-dose combination in the treatment of moderate to severe pain. J Pain Res. 2012;5:327-346.* 9. *Katz N. The impact of pain management on quality of life. J Pain Symptom Manage 2020; 24(1):S38-S47.* 10. *Carr AJ, Higginson IJ. Are quality of life measures patient centred?. BMJ. 2001;322(7298):1357-1360.*
STUDY OBJECTIVES	The main study objective is to find out if and how patient-specific risk factors (gastrointestinal, cardiovascular, renal and hepatic), intensity, type and duration of pain determine the choice of analgesic treatment, such as NSAIDs and/or tramadol/paracetamol combination. Additionally, we will also focus on the influence of pain and corresponding treatment choices on quality of life (mobility, usual life, social life, sleep and mood). We would also find out the differences in prescribing NSAIDs and/or tramadol/paracetamol combination among doctors in participating countries.

STUDY DESIGN AND DURATION	This is an observational, prospective, non-interventional, international, multicentre, epidemiological study in which patients with pain, who need treatment with NSAIDs and/or tramadol/paracetamol combination, will be included according to the physician's consideration and in compliance with inclusion and exclusion criteria. Patients will be observed over the course of 12 ± 2 weeks. The physician will record data at two time points. The first data capture point will be collection of baseline variables at patient's inclusion in the study and the second data capture point at week 12 ± 2 from inclusion (collection of follow-up variables). We will capture the data generated over a period in accordance with everyday clinical practice. If according to his clinical practice doctor schedules additional controls earlier or in case of patient's need, patient will attend additional optional controls between 1st and 2nd data capture point and data will be collected as optional data captures. Data can be collected from on-site visits or remotely via phone or electronic media. Only baseline data capture will be held exclusively on-site. The way of data collection is chosen by investigator according to current situation in clinical practice. The investigator will remotely collect only data that can be collected by phone call or electronic media. This protocol will not influence the decision of attending physician regarding patient management. Any diagnostic method or therapeutic decision made by a physician should be independent from the inclusion of a patient in the study. There is no restriction regarding the selection of other treatments and no influence upon the recommended dose regimens.
SELECTION OF INVESTIGATORS	General practitioners, rheumatologists, othopedists and other specialists, by whom patients with pain are routinely treated in every day clinical practice.
SELECTION OF PATIENTS	**Inclusion criteria** ○ Female and male subjects, aged 18 and more ○ Patient with pain (regardless of the type, level of intensity and duration) ○ Patients who need treatment with NSAIDs and/or tramadol/paracetamol combination, alone or in combination with other analgesics ○ Patients who agreed with informed consent form and consent for statistical evaluation of personal data **Exclusion criteria** ○ Female participants who are breastfeeding or pregnant or who are intending to become pregnant ○ Hypersensitivity to the active substance or any of the excepients of used medications for pain management

	○ Patients with conditions or treatments, listed as contraindications in SmPCs of used medications for pain management ○ Severe medical condition, which might interfere with the participation in the study ○ Participation in other clinical study ○ The patient refuses the informed consent form and/or consent for statistical evaluation of personal data **Withdrawal criteria** ○ The occurrence of serious adverse reactions during the therapy with analgesic medicinal products ○ Patient's decision to stop the treatment and withdrawal of his/her informed consent ○ The patient's safety (investigator's decision to exclude the patient from the study to his/her best interest) ○ An acute disease or a deterioration of an existing disease during the study, which requires the use of medicines not permitted in association with SmPCs of used medicines for pain management ○ Adverse events requiring medical intervention or withdrawal of therapy
STUDY ENDPOINTS	**Primary endpoints:** • To evaluate how average intensity of pain in last 24 hours on VAS scale influences the prescription of analgesics* and to compare these influences among physicians in participating countries • To evaluate how patient's risk factors (cardiovascular, gastrointestinal, renal and hepatic) influence the prescription of analgesics* and to compare these variations among participating countries *NSAIDs and/or tramadol/paracetamol combination **Secondary endpoints:** • The secondary endpoints encompass 11 items realted with: demographic, risk factors, concomitant diseases, duration of pain**, type of pain, quality of life, pain intensity, adherence, patient's and investigator's satisfaction with the treatment, investigator's specialties, safety evaluation. ** Duration of pain: Acute pain: Patient's pain has persisted for less than 3 months. Chronic pain: Patient's pain has persisted for 3 months or more or has recurred several times in the last 3 months.

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 based on performance of the employed confidence intervals in terms of their width and on power of the employed tests, with focus on the first listed primary endpoint.