SUMMARY OF FINAL REPORT OF NON-INTERVENTIONAL STUDY RED (Analysis of data obtained from Hungary and Latvia, participating countries)

Study Title:

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

Study acronym: RED study

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1 LIST OF ABBREVIATIONS

AE	Adverse event
ADL	Activities of daily living
AR	Adverse reaction
CGI-I	Clinical Global Impressions – Improvement
CV	Cardiovascular
GI	Gastrointestinal
GP	General practitioner
INN	International non-proprietary name
KOOS	Knee Injury and Osteoarthritis Outcome Score
NSAID	Nonsteroidal anti-inflammatory drug
Sport/Rec	Sports/Recreation
VAS	Visual Analogue Scale

2 RESULTS

The non-interventional RED study was conducted internationally across two European countries (Hungary and Latvia) and focused on assessing the real-world treatment outcomes of Krka's etoricoxib in patients with rheumatic diseases. The study engaged **91 investigators**, of them 67.0% general practitioners and 30.8% rheumatologists. Almost all participating investigators in Hungary were rheumatologist and in Latvia GPs, which influenced the type of patients they were treating, their corresponding diagnosis, pain intensity, and consequently the prescribed dose of Krka's etoricoxib. The study gathered data from 1,201 patients, with a full analysis performed on **1,188** eligible patients. The 2nd data capture was performed in **1,169 patients** in average 52.1 ±17.4 days after the baseline visit. The average age of included patients was 59.8 ±11.6 years, while 63.8% of patients were female and 36.2% male. Both investigated hypotheses of the study were confirmed. These were:

- The primary hypothesis of the study was that **Krka's etoricoxib** treatment **significantly reduces intensity of pain** *(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%.)* in majority of patients with rheumatic diseases.
    - The reduction of pain intensity was clinically meaningful in 70.9% (n=829) of patients at the 2nd data capture as the pain intensity for these patients at the 2nd data capture did not exceed 30 mm on VAS or the baseline intensity was reduced by at least 50%.
- Another hypothesis assumed that **treatment with Krka's etoricoxib improves majority of parameters** (sub-scores) assessed by Knee Injury and Osteoarthritis Outcome Score (**KOOS) questionnaire in patients with knee osteoarthritis.**
    - Increases of all KOOS questionnaire subscales at the 2nd data capture are statistically significant ($p<0.001$).

The study revealed a diverse spectrum of rheumatic disease, as almost half of patients (48.4%) were diagnosed with **osteoarthritis (excluding knee osteoarthritis)**, 20.2% with **knee osteoarthritis,** and others were diagnosed with rheumatoid arthritis, gouty arthritis, ankylosing spondylitis or other conditions (e.g. low back pain). Around 5% of patients were diagnosed at the baseline visit, whereas others were diagnosed in average 3.7 years prior to the baseline visit.

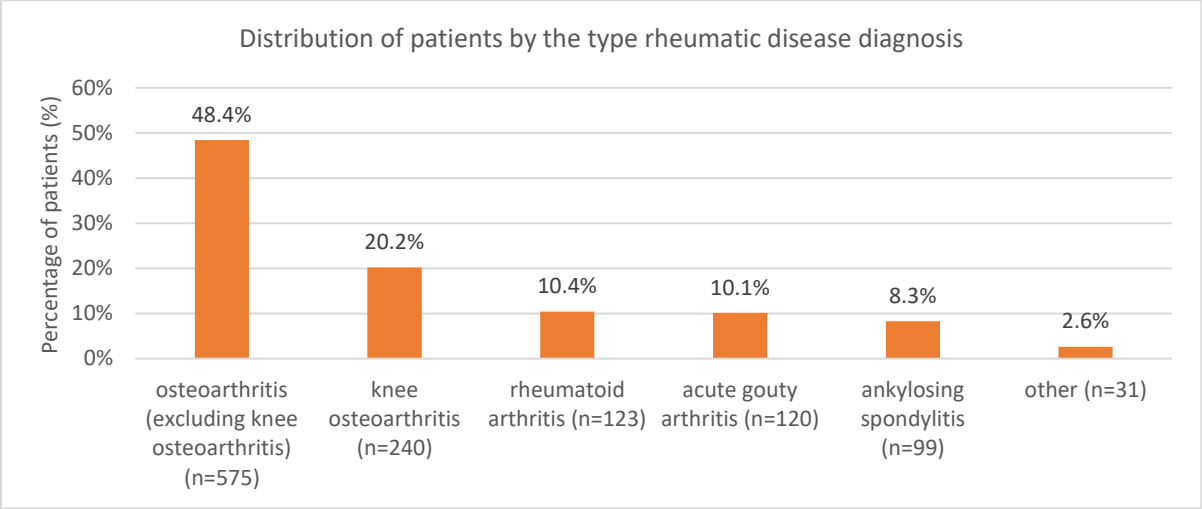


Figure 1: Distribution of patients by the type of rheumatic disease diagnosis.

2.1 KOOS scales (patients with knee osteoarthritis)

The study found a statistically **significant increase in all KOOS subscales** from the 1st to the 2nd data capture, showcasing a reduction in rheumatic disease impact on the functionality of patients with knee osteoarthritis. At the 2nd data capture, the lowest average KOOS score, meaning the highest influence of pain on patient's functionality, was in the subscale Sports/Recreation (Sport/Rec), the same as at the 1st data capture, QoL followed. The importance of improving Sport/Rec subscale is particularly reflected in the improvement of patients' mobility and consequently their independence (empowerment of patients) or even enabling an active life style in all age groups. The remaining three KOOS subscales (Pain, Symptoms, Activities of daily living (ADL)) scored higher at both data captures, presenting less influence on patient's functionality. In average **87.8%** of patients were considered **responders** (patients with the value on the given scale at the 2nd data capture greater than the corresponding value at the 1st data capture) on all subscales. Interestingly, average KOOS questionnaire subscales at the 1st data capture were lower for previously treated patients than for naïve patients. Not appropriately managed acute pain can often lead to chronic pain which is more difficult to treat, and consequently it is more difficult to improve situation in previously treated patients than in naïve ones. However, differences in KOOS subscales between patient subgroups were almost non-existent at the 2nd data capture.

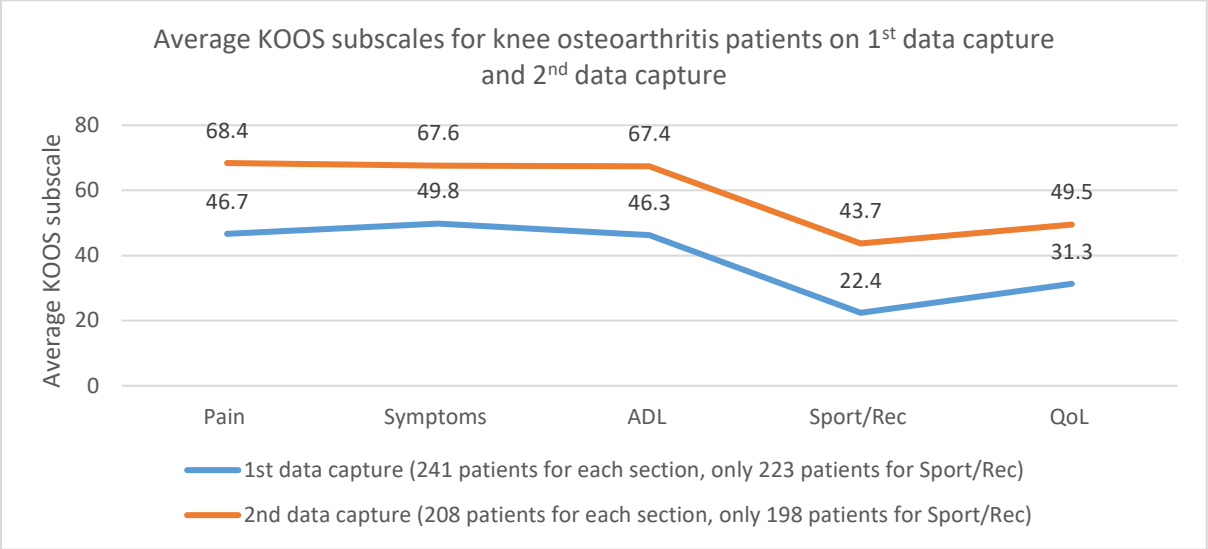


Figure 2: KOOS subscales for patients at 1st and 2nd data capture. Higher KOOS subscale score shows lesser influence of the diagnosis on any of the activities.

2.2 Pain intensity

Pain **intensity reduction was deemed clinically meaningful for 70.9%** of patients at the 2nd data capture. Total average value of pain intensity on VAS decreased significantly, with the relative difference **of -59%** (from 69.1 at the baseline visit to 28.1 mm; absolute difference -41.0) at the 2nd data capture. Major improvement in pain scores was expected as etoricoxib is deemed one of the most effective NSAIDs. This is supported also by data from other studies.[2, 3, 4]

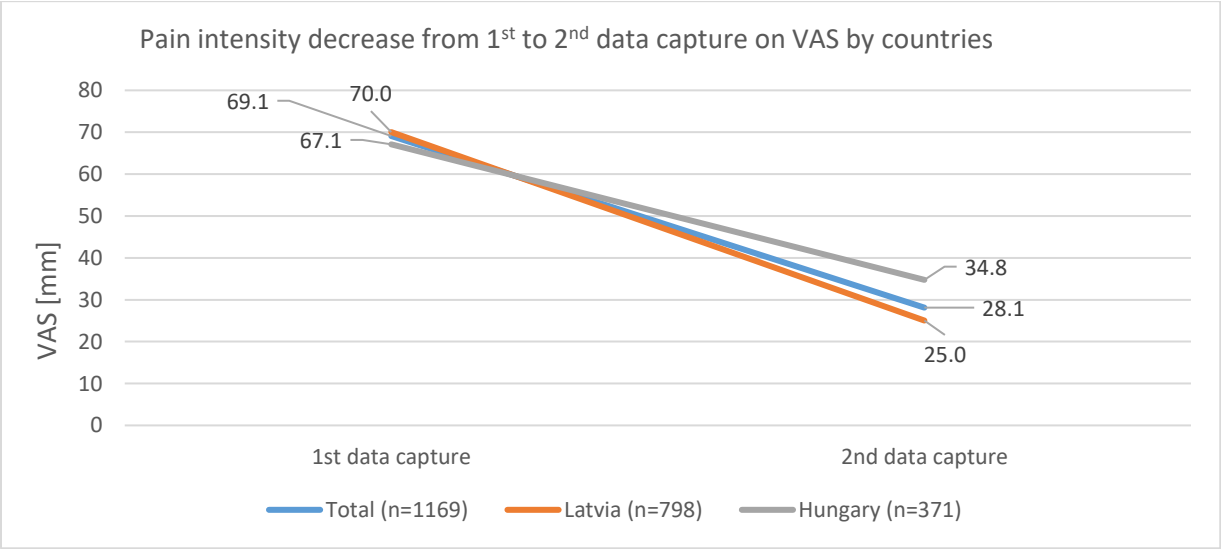


Figure 3: Decrease of pain intensity on VAS scale from 1st to 2nd data capture by country.

At the 2nd data capture, 44.7% of patients reported pain intensity between 0 mm and 20 mm. At both data captures, previously treated patients' pain intensity on VAS was higher compared to naïve

patients. The reason may lay in that previously treated patient could have longer disease duration compared to naïve one and therefore the severity of pain perception could be greater in previously treated patients. The underlying reason is the continuance and intensity of initial stimulus, which as a consequence aggravates pain perception due to both, peripheral and central sensitisation.[5]

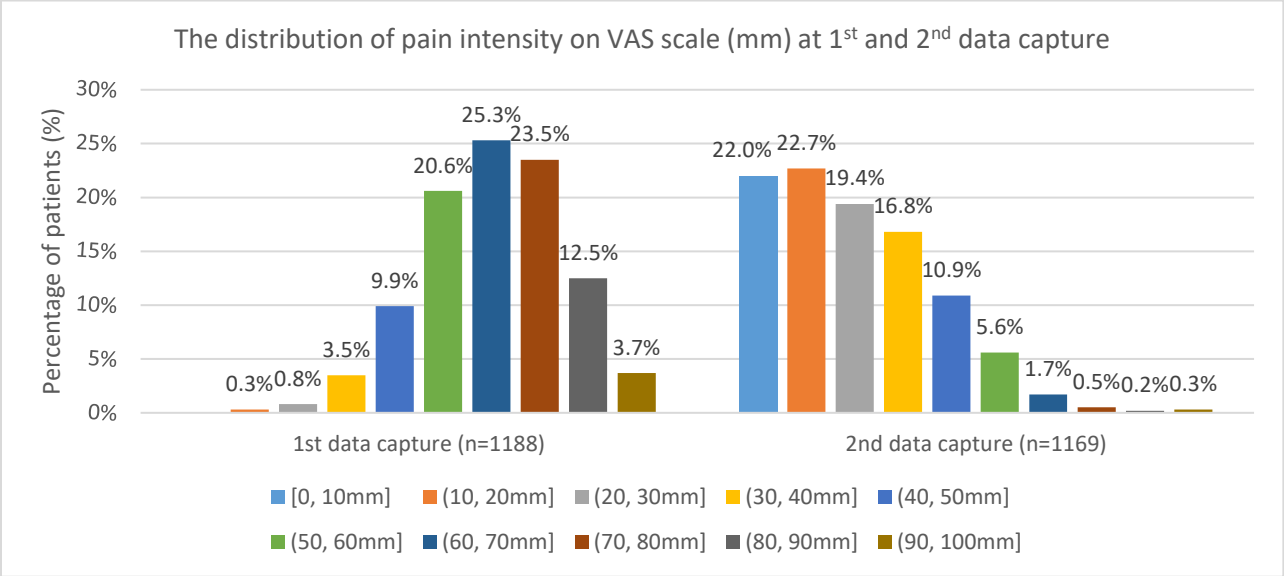


Figure 4: Distribution of pain intensity on VAS scale at 1st and 2nd data capture.

Notably, the type of rheumatic disease influenced pain intensity on VAS, with acute gouty arthritis patients experiencing the highest recorded pain at the 1st data capture (75.6 mm). The lowest average pain was recorded in patients diagnosed with other rheumatic diseases and patients diagnosed with osteoarthritis (excluding knee osteoarthritis). The biggest decrease of pain intensity at the 2nd data capture was observed in patients diagnosed with acute gouty arthritis, by more than 50 mm. This is consistent with the data that most patients with acute gouty arthritis experience severe or extreme pain and that etoricoxib provides effective and clinically meaningful pain relief in no more than 4 hours after dosing.[6] The lowest decrease on the pain intensity scale was recorded in patients diagnosed with knee osteoarthritis, around 35 mm.

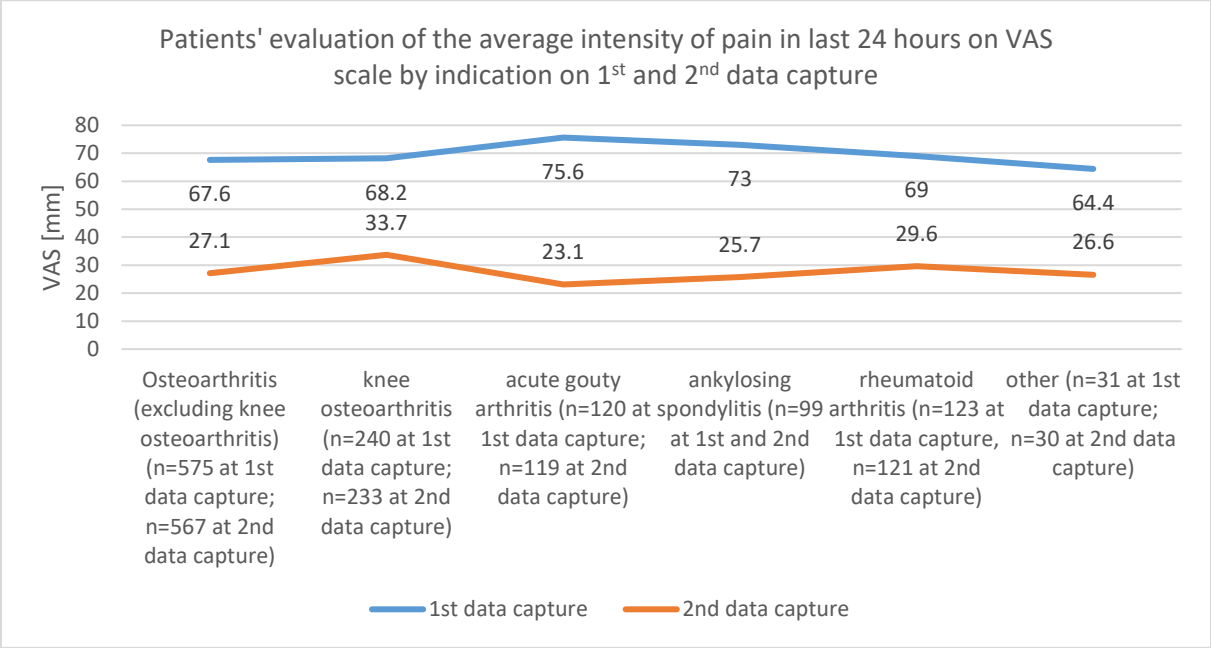


Figure 5: Patients' evaluation of average intensity of pain in the last 24 hours on VAS scale by indication at 1st and 2nd data capture.

2.3 Gastrointestinal symptoms

The proposed advantage of COX-2 inhibitors is a reduction in risk of gastrointestinal (GI) symptoms compared to conventional NSAIDs.[7, 8] GI safety of etoricoxib was confirmed also in this study as the proportion of patients with GI symptoms **decreased from 12.4% to less than 2%** (n=20; 1.7%) at the 2nd data capture. Approximately 60% of patients at the 2nd data capture reported only one GI symptoms, whereas at the 1st data capture these symptoms were reported by 45% of patients. The most common GI symptoms at both visits were heartburn/acid reflux and dyspepsia/epigastric discomfort.

2.4 Krka's etoricoxib daily dose

The average daily dose of Krka's etoricoxib at the baseline visit was **87.0 mg ±21.0 mg**. There was only a small difference in the average daily dose between the subgroups of previously treated and naïve patients. The reason is that the dose of the medicine depends on the underlying disease and not the treatment history. Nearly all patients at baseline visit received **one dose of Krka's etoricoxib per day** (n=1,181; 99.4%). It should be noted that treatment decisions regarding Krka's etoricoxib dosage regime in certain patients are subject to the patient's indication, differences in clinical practice and acting in the best interest of each patient. The final decision about the treatment is based also on doctor's past experiences and deeper knowledge of the individual patient.

In **88.4%** of patients at the 2nd data capture, **the therapy with Krka's etoricoxib was not changed** from the baseline visit. For the remaining 11.6% of patients with treatment change, the most common reason in half of patients was that therapy was not needed anymore, followed by the simplification of treatment. Out of those patients whose therapy was changed, 75% did not continue with the treatment with Krka's etoricoxib, while in the remaining patients either the dose of the medicines or the number of doses per day was changed. The average daily dose of Krka's etoricoxib at the 2nd data capture was similar (86.9 ±20.7) to the baseline visit.

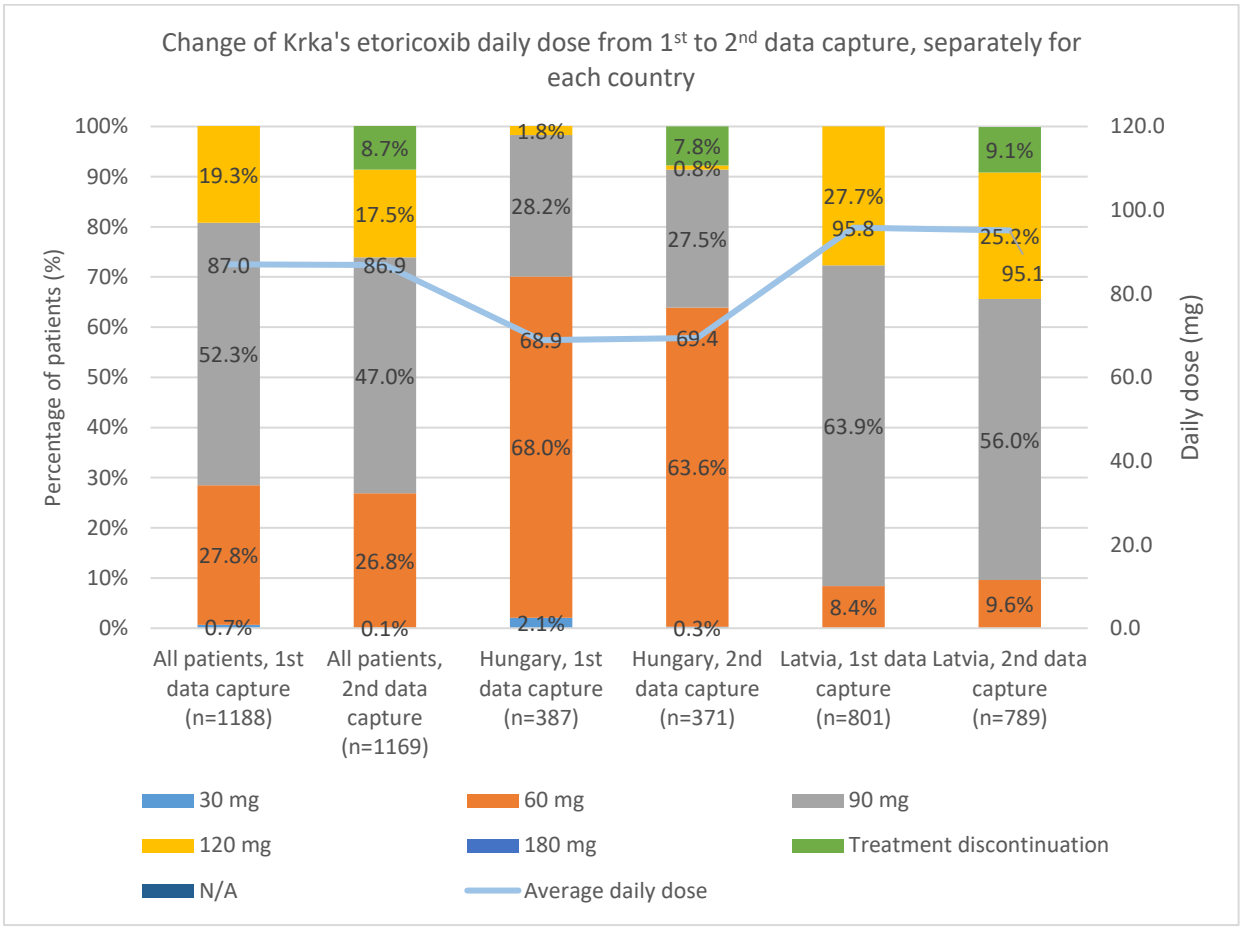
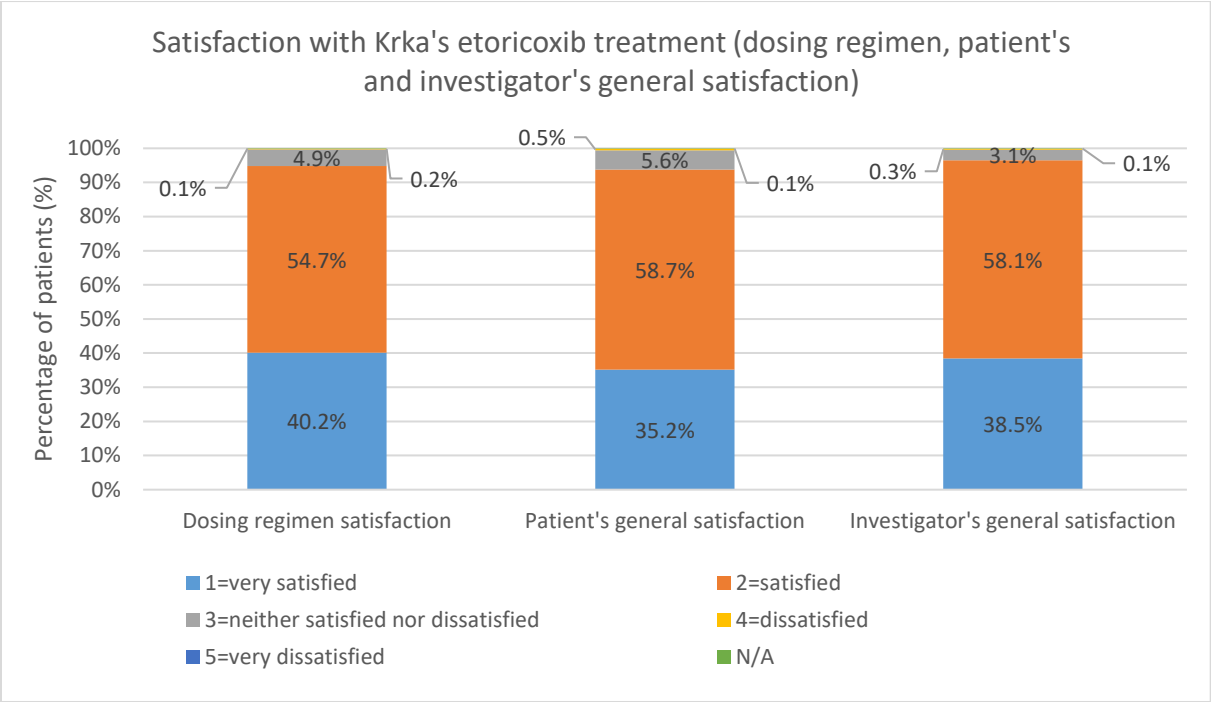


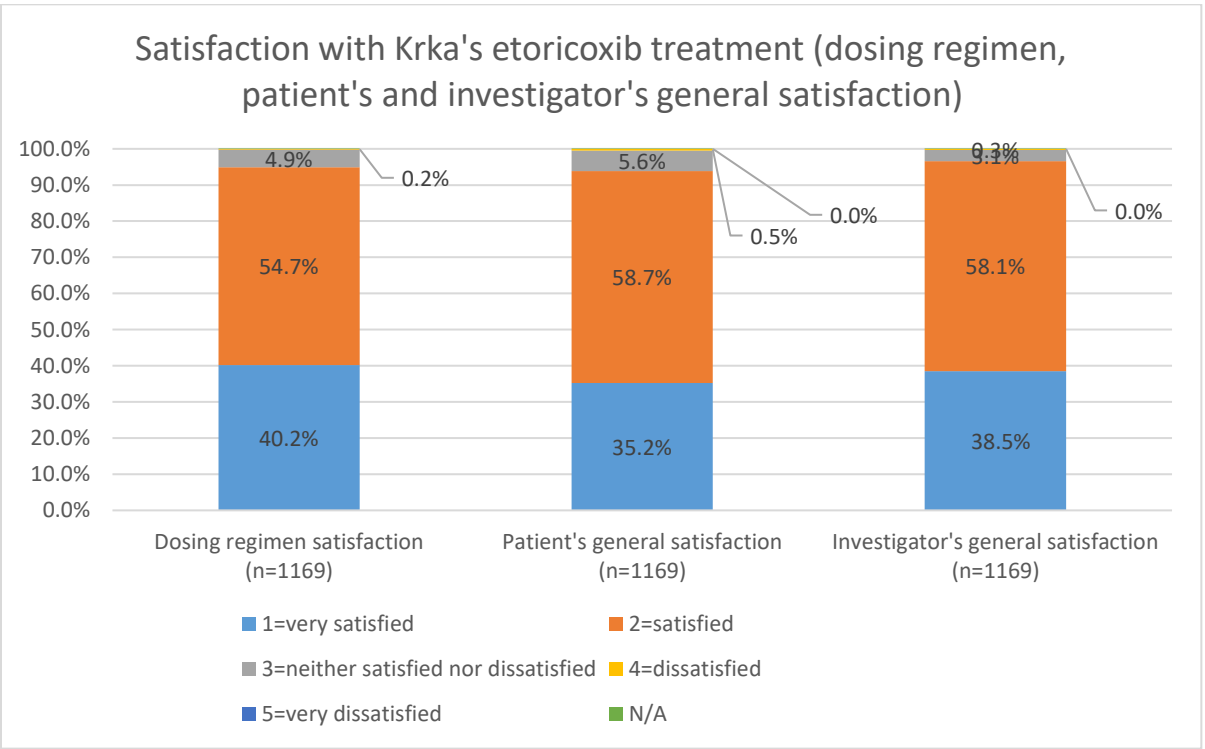
Figure 6: Change in Krka's etoricoxib daily dose from 1st to 2nd data capture, separately for each country. Proportions are calculated with respect to all patients at a data capture.

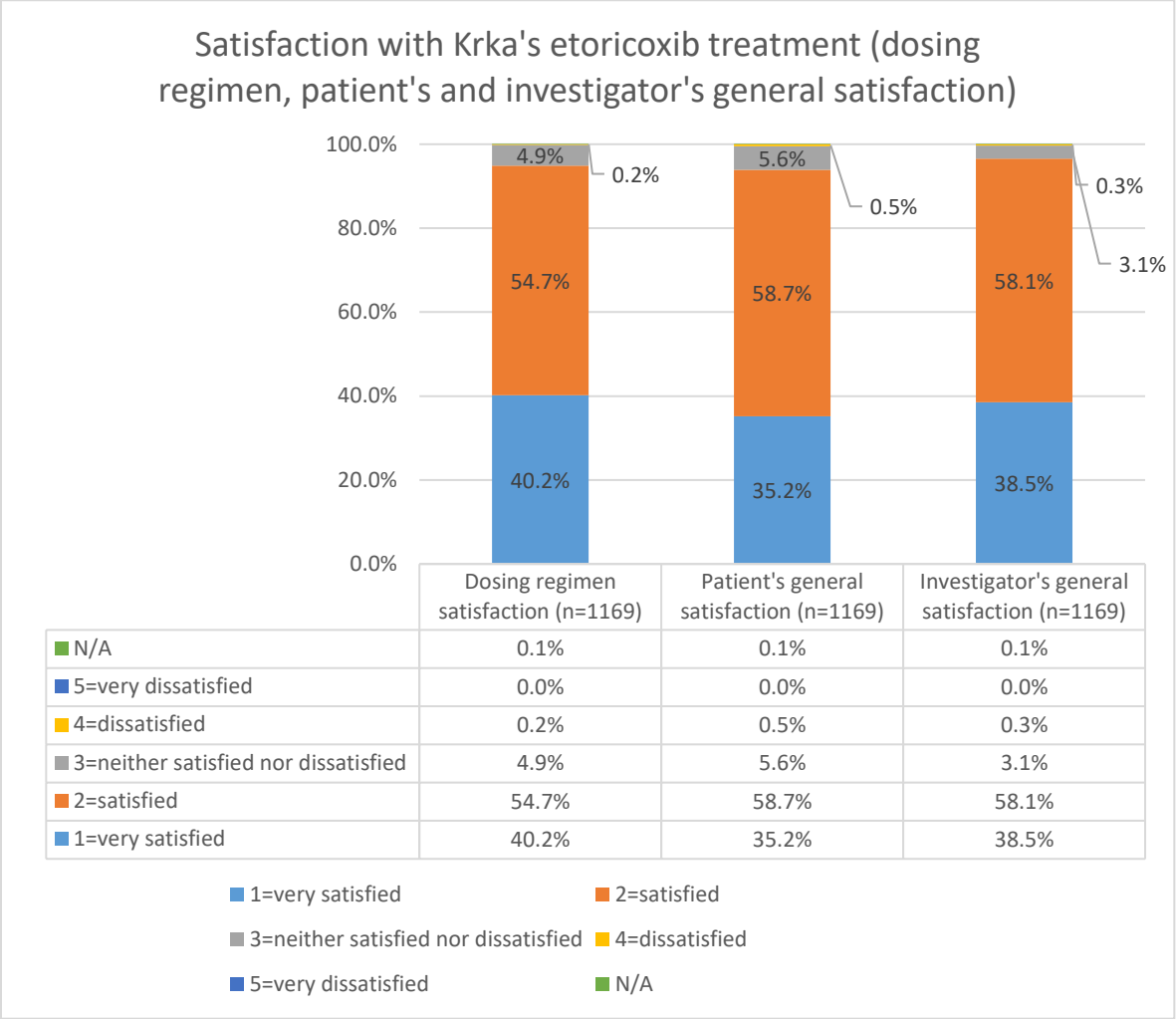
2.5 Satisfaction

At the 2nd data capture, over 40% of patients were **very satisfied and** more than half of the patients **satisfied with the dosing regimen** of Krka's etoricoxib. More than 80% of patients who were previously treated with NSAIDs assessed that their **condition has much to very much improved since the initiation of Krka's etoricoxib** in comparison to previous NSAID therapy. Similarly, more than 80% of patients were **satisfied to very satisfied with Krka's etoricoxib treatment in general**. More than 95%

of participating investigators were **satisfied to very satisfied with Krka's etoricoxib treatment of their patients** in general.







	Dosing regimen satisfaction (n=1169)	Patient's general satisfaction (n=1169)	Investigator's general satisfaction (n=1169)
N/A	0.1%	0.1%	0.1%
5=very dissatisfied	0.0%	0.0%	0.0%
4=dissatisfied	0.2%	0.5%	0.3%
3=neither satisfied nor dissatisfied	4.9%	5.6%	3.1%
2=satisfied	54.7%	58.7%	58.1%
1=very satisfied	40.2%	35.2%	38.5%

Figure 7: Distribution of patient's satisfaction with Krka's etoricoxib dosing regimen, patient's assessment of response to Krka's etoricoxib therapy in comparison with response to previous NSAID therapy, patient's general satisfaction with Krka's etoricoxib and investigator's satisfaction with Krka's etoricoxib in general.

2.6 Other rheumatic disease treatment (previous treatment and rheumatic disease treatment in addition to Krka's etoricoxib)

Approximately **half** of patients at the baseline visit were previously treated with different rheumatic agents, most commonly with NSAIDs (88.0%), predominantly with diclofenac, ibuprofen, aceclofenac, meloxicam, and nimesulide. The most frequently recorded reason for NSAID discontinuation at the baseline visit was ineffective treatment. At the end of the 1st data capture, **only 9.0% of patients continued with other ongoing rheumatic disease treatment,** and at the 2nd data capture this was observed in 10.2% of patients. At the end of the 1st data capture and at the 2nd data capture, the most common classes of these rheumatic agents, in addition to Krka's etoricoxib, were other analgesics and synthetic DMARDs (Disease-modifying antirheumatic drugs). Interestingly, not only the class of other rheumatic disease treatment at the end of the 1st data capture and at the 2nd data capture differed

from the previous treatment, but also the exact INNs were different, with **methotrexate being the most often prescribed.**

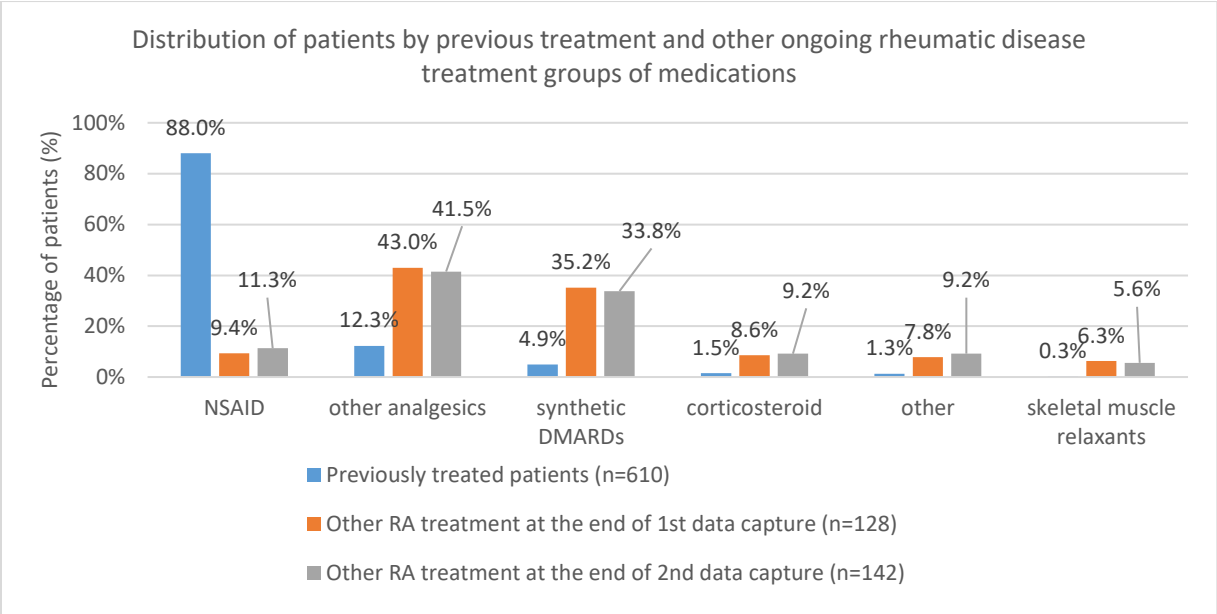


Figure 8: Distribution of patients by previous treatment and other ongoing rheumatic disease treatment at the 1st and 2nd data captures by groups classes of medications. Percentages Proportions (%) are taken calculated with respect to patients with other ongoing rheumatic disease treatment. One patient can have more than one treatment.

2.7 Comorbidities and concomitant treatment

Half of patients had concomitant diseases in addition to rheumatic disease, of those **slightly over two thirds of patients had hypertension**, followed by diabetes mellitus, gastrointestinal diseases, diseases of the musculoskeletal system or connective tissue, endocrine diseases, hyperlipoproteinemia, cardiovascular diseases and others. There was only a slight **difference in average daily dose in patients with hypertension or other cardiovascular diseases compared to patients without** these diseases at both 1st and 2nd data captures.

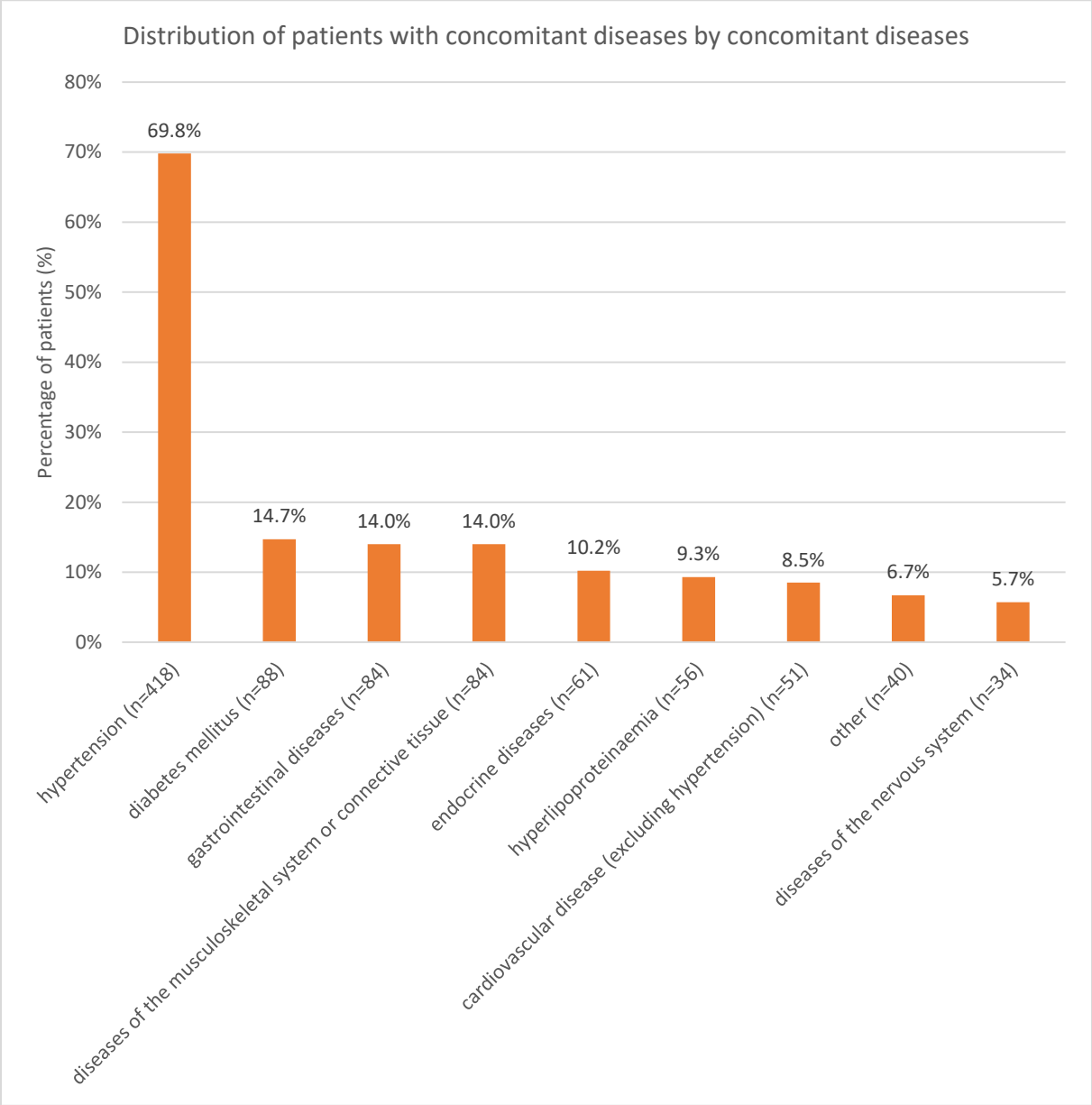


Figure 9: Distribution of patients with concomitant diseases. Percentages Proportions (%) are taken calculated with respect to all patients at the 1st data capture with data on comorbidities. One patient can have more than one disease.

2.8 Safety assessment

Out of all 1,201 patients included in the safety analysis, 10 patients experienced adverse events (0.8%), of them **eight patients experienced non-serious adverse** events related to Krka's etoricoxib treatment (hypertension, abdominal pain, dyspepsia, epigastric discomfort, constipation and others), while adverse events of two patients were not related **to the treatment**. Moreover, particular attention was paid to the incidence and nature of adverse events due to a suggested connection between selective COX-2 inhibitors and increased incidence of cardiovascular events.[9, 10] No serious cardiovascular or other adverse events related to Krka's etoricoxib treatment were recorded in patients taking Krka's

etoricoxib, even in patients who had hypertension. This indicates a good safety profile of Krka's etoricoxib in patients with or without CV diseases.

3 CONCLUSION

In conclusion, the RED study provides valuable insights into the real-world treatment outcomes of Krka's etoricoxib in patients with rheumatic diseases. The international study engaged a diverse group of 91 investigators, including general practitioners and rheumatologists. Based on data about 1,188 eligible patients, the study explored the impact of Krka's etoricoxib on pain intensity, functionality, and various parameters assessed by the Knee Injury and Osteoarthritis Outcome Score (KOOS) questionnaire.

The RED study demonstrated clinically meaningful reduction of pain intensity in majority of patients treated with Krka's etoricoxib once daily. Notably, the diverse spectrum of rheumatic diseases, including osteoarthritis and knee osteoarthritis, showcased the broad applicability of Krka's etoricoxib in addressing different conditions. Krka's etoricoxib treatment resulted in statistically significant increase in all KOOS subscales, with patients having most restrictions due to affected knee in Sports/Rec, followed by the QoL area. The average daily dose of Krka's etoricoxib remained stable throughout observational period, emphasising the medication's consistent effectiveness. Treatment changes were not frequent, and high satisfaction rates were reported among patients as well as participating investigators. The study revealed a decrease in gastrointestinal problems and a low incidence of adverse events related to Krka's etoricoxib. Therefore, the treatment with Krka's etoricoxib is considered as an effective and generally well-tolerated option for the treatment of different rheumatic diseases. However, to reach conclusive data and draw meaningful conclusions, longer duration of follow-up and measurement of other cardiovascular parameters should be studied.

Both study hypotheses (Krka's etoricoxib treatment significantly reduces intensity of pain, and treatment with Krka's etoricoxib improves majority of parameters in KOOS questionnaires) are supported by evidence. Obtained findings serve as a starting point for optimising the clinical management of rheumatic diseases and consequently further improving different areas of patient's life. We suggest that in future studies more emphasis is placed on showing the importance of appropriate pain management, especially in improving patient's function in sport and recreation, as this is the subscale that affected the patients the most. In this manner, incorporating QoL measurement suitable for all selected indications would add even more value to the study.

The findings from this study indicate that Krka's etoricoxib is a well-tolerated and effective option for managing rheumatic diseases, offering substantial pain relief and improving functionality, as shown by KOOS outcomes.

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