Original article
UDC: 616.72-007.248

# COMPLEX USE OF BI-LURON SUPPLEMENT IN KNEE OSTEORATHROIS: A PROSPECTIVE RANDOMIZED STUDY

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**ABSTRACT**

**INTRODUCTION**. Knee osteoarthritis (KO) among the adult population often leads to permanent disability, a sharp decrease in the quality of life, and chronic use of analgesics. At the same time, according to the clinical guidelines for osteoarthritis treatment of the Russian Rheumatology Association, hyaluronic acid medications are included in the list recommended for KO, and they are particularly effective in stages I-II of the disease.

**AIM**. Evaluation of the efficiency of the dietary supplement «Bi-Luron» registered in Russia for KO patients within 12 weeks therapy.

**MATERIAL AND METHODS**. A total of 70 patients with stage I-II deforming osteoarthrosis (DOA) were followed up, consecutively included in the study from December 14, 2021 to January 31, 2022, for an average of 90 days (3 months).

**RESULTS AND DISCUSSION**. The efficiency «Bi-Luron» for I-II DOA stages was shown: a statistically significant decrease in the level of pain in knee joints, an improvement in the function of the joint were revealed compared to the initial state. The analysis of objective data showed a positive trend in ultrasound parameters and MRI features of joint inflammation, and a decrease in the need for analgesics within 12 weeks.

**CONCLUSION**. In a prospective randomized clinical trial with 70 knee DOA patients as a part of the combination therapy (12 weeks use) with non-steroidal anti-inflammatory drugs the dietary supplement «Bi-Luron» showed its effectiveness for stages I-II of the disease; there was a positive trend in ultrasound parameters and MRI signs of inflammation in the joints as well as a decrease in the need for non-steroidal anti-inflammatory drug use.

**KEYWORDS**: arthrosis of the knee joint, osteoarthritis, Bi-Luron, hyaluronic acid preparations, analgesics, quality of life.

For citation:

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Article received: 06.12.2022

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## INTRODUCTION

Data of epidemiological studies indicate that the incidence of osteoarthritis of the knee (knee OA) among the adult population of the world varies from 6,9 to 38,5% which makes about a third of all persons with permanent disability due to joint diseases. The goal of conservative treatment is to reduce pain and stabilize the degenerative-dystrophic process. The use of hyaluronic acid for treatment of patients with knee osteoarthritis has been the subject of continuous discussions for many decades, because based on data from published studies it is difficult to draw an unambiguous conclusion about their effectiveness, although safety, from the point of view of professional communities, is beyond doubt. According to the clinical guidelines "Osteoarthritis" (ICD 10: M15, M15.1, M15.2, M16, M17, M18, M19), approved by the All-Russian public organization "Association of Rheumatologists of Russia" in 2016, agreed by the scientific council of the Ministry of Health of Russia, hyaluronic acid medications are included in the list of recommended medications for treatment of osteoarthritis. At the same time, the status of medications containing hyaluronic acid (food supplement or medication) is not specified. In the Russian Federation, sodium hyaluronate is represented by one registered substance in the Register of Medicinal Products, but there are no medicinal products containing hyaluronic acid registered for oral use. It allows to use only food supplements for treatment of OA with medications containing hialuronic acid. Since dietary supplements with hialuronic acid registered in Russian Federation have different levels of hialuronic acid in the recommended daily intake (powders, capsules, syrups, etc.), they are likely to have different effectiveness. It seems appropriate to study the effectiveness of the use of Bi-Luron food supplement registered in Russia (Certificate of State Registration on the territory of the EAEU No. 0245593 dated November 14, 2013, with no time limit) for treatment of OA in patients with OA of knee joints.

## PURPOSE OF THE STUDY

The main goal of the study was to evaluate the effectiveness of Bi-Luron food supplement in patients with OA of knee joint in comparison with standard therapy with non-steroidal anti-inflammatory drugs (NSAIDs) "on demand". The objectives of the study included the evaluation of such parameters of the course of OA as pain syndrome according to 10-point NRS scale (indicator of knee pain at 0, 2, 4, 8, 12 weeks of therapy/placebo), dynamics according to ultrasound and MRI of knee joints, changes in the index of pain and function of knee joints according to 2000 IKDC scale and quality of life according to EQ5D questionnaire. Adherence to therapy was measured using the Morisky 8-Item Medication Adherence Scale. The consumption of NSAIDs (“Naproxen” tablets 250 mg) was calculated for correction of pain syndrome and level of inflammatory biomarkers in blood was determined by a quantitative method (measuring the level of C-reactive protein).

## MATERIAL AND METHODS

This single-center, randomized, placebo-controlled, double-blind study was conducted according to a protocol approved by an independent ethical committee at the clinical base of the Saratov State Medical University named after V.I. Razumovsky of the Ministry of Health of Russia. The food supplement was provided by the sponsor of the study Adelon LLC (manufacturer - Gramme-Revit, Germany, valid registration certificate in Russia RU.77.99.11.003.E.009773.12.13).

**The main criteria of inclusion:** age from 18 to 65, diagnosis of knee joint DOA II degree, informed consent to participate in the study.

**The main criteria for non-inclusion:** contraindications to taking Bi-Luron.

**Exclusion criteria:** development of undesirable symptoms after taking Bi-Luron.

A total of 70 patients with stage I-II deforming osteoarthrosis (DOA) were followed up, consecutively included in the study from December 14, 2021 to January 31, 2022, for an average of 90 days (3 months). DOA and its stage for all patients at the time of inclusion were confirmed radiographically.

When analyzing the representativeness of the selection and comparing Bi-Luron and Placebo groups, no significant differences were found between them in terms of such parameters as height, weight, body mass index (BMI), age. The number of overweight patients (BMI≥25) was 45 (64.3%). The main characteristics of the groups of patients who took "Bi-Luron" and "Placebo" are presented in Table 1. Therefore the groups were initially comparable in terms of the main clinical characteristics.

***Table 1. Key Clinical Characteristics of Bi-Luron and Placebo Patient Groups at Visit 0***
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| **Parameters Parameters** | **Bi-Luron Group Bi-Luron Group n=35** | **Placebo Group Placebo Group n=35** | **Reliability of differences Reliability of differences** |
|---|---|---|---|
| Height, cm Height, cm | 167,29±1,307 | 165,3±1,387 | Differences are not statistically significant Differences are not statistically significant (p=0,319) |
| Weight, kg Weight, kg | 75,77±2,724 | 74,43±2,463 | Differences are not statistically significant Differences are not statistically significant (p=0,716) |
| BMI BMI | 27,03±0,831 | 27,23±0,864 | Differences are not statistically significant Differences are not statistically significant (p=0,870) |
| Age, years Age, years | 52,11±1,590 | 50,89±1,619 | Differences are not statistically significant Differences are not statistically significant (p=0,590) |
| Number of individuals with stage I DOA Number of individuals with stage I DOA | 28 | 26 | Differences are not statistically significant Differences are not statistically significant (p=0,553) |
| DOA of both knee joints DOA of both knee joints | 15 | 19 | Differences are not statistically significant Differences are not statistically significant (p=0,093) |

Among included people, the following distribution by DOA stages was observed: among the persons in the group taking Bi-Luron, the number of persons with DOA stage I was 28 people, and with DOA stage II - 8 people. Among the patients taking "Placebo", 26 people had stage I DOA, and 9 people had stage II DOA. DOA lesions of both knee joints were observed in 15 people out of 35 included in the Bi-Luron group and in 19 people in the Placebo group. Additionally, on the day of inclusion and on the day of exclusion from the study, ultrasound of knee joint was performed on both sides (both in the group of patients who took Bi-Luron dietary supplement and

in the group of patients who took Placebo). MRI of the knee joints was randomly performed on the side of the larger lesion in 20% of patients. Both studies were repeated on the day of the last visit.

**RESULTS AND DISCUSSION**

A study was made of the dependence of patients' self-assessment of pain and joint function on BMI. Analysis of the correlation between BMI, pain level and self-assessment of joint function at the stage of inclusion of patients in the study showed a statistically significant direct correlation of average strength (0,431) between BMI and pain level at the p=0,01 level, as well as an inverse relationship of average strength between the pain level and assessment of joint function (-0,347). The obtained data confirm the regularities described in literature for the selected patient model (DOA stage I-II).

Effectiveness of Bi-Luron was evaluated by its effect on pain level assessment on VAS scale, joint function on IKDC2020 scale, as well as on the results of objective examination (ultrasound of knee joints - in 100% of patients, MRI - in 20% of patients in each selection) .

During the study, a comparison was made between the groups of patients who took Bi-Luron and those who took Placebo at different Visits on the main scales of subjective assessment: VAS pain assessment, EQ5D3L quality of life assessment scale, self-assessment of joint functions IKDS2020, the Morisky 8-Item Medication Adherence Scale.

Results of analysis of studied parameters according to scales for assessing pain and self-assessment of joint function in dynamics from Visit 0 to Visit 4 (Fig. 1) are graphically presented below.

The results obtained by patients assessing the severity of pain syndrome (on VAS scale) indicate that by the 8th week of observation, this indicator had statistically reliably improved in patients taking Bi-Luron compared to Placebo. The difference in pain score between Visit 0 and Visit 4 in Bi-Luron group was 15,71 units. The difference in pain score between Visit 0 and Visit 4 in Placebo group was 9,28 units. It should be noted that the most intense statistically significant decrease in the severity of pain syndrome (by 30% on average) was observed in the range "Visit 0 - Visit 3" (Fig. 1).

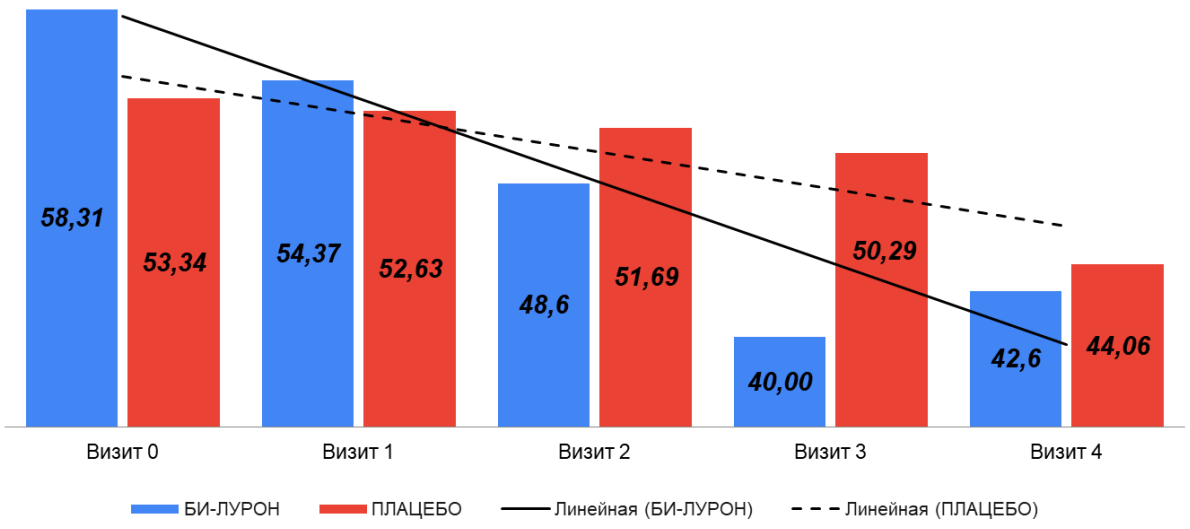


***Fig. 1. Dynamics by the pain rating scale from Visit 0 to Visit 4***

***Fig. 1. Dynamics by the pain rating scale from Visit 0 to Visit 4***

Initially, (at Visit 0), in the group of patients randomized to take Placebo the index of self-assessment of joint function was statistically reliably higher than in the group of patients

randomized to take Bi-Luron. Also at Visit 1, Placebo group of patients had statistically reliably better results than Bi-Luron group of patients.

However, the analysis of dynamics of self-assessment of joint function shows that in the group taking Placebo, it remains at almost the same level in the range "Visit 0 - Visit 4" (71,08 and 71,34, respectively). On the contrary, there is a statistically significant positive trend in improving the joints function in the group of patients who took Bi-Luron, in the range "Visit 0-Visit 4" (67,74 and 72,26, respectively) (Fig. 2).

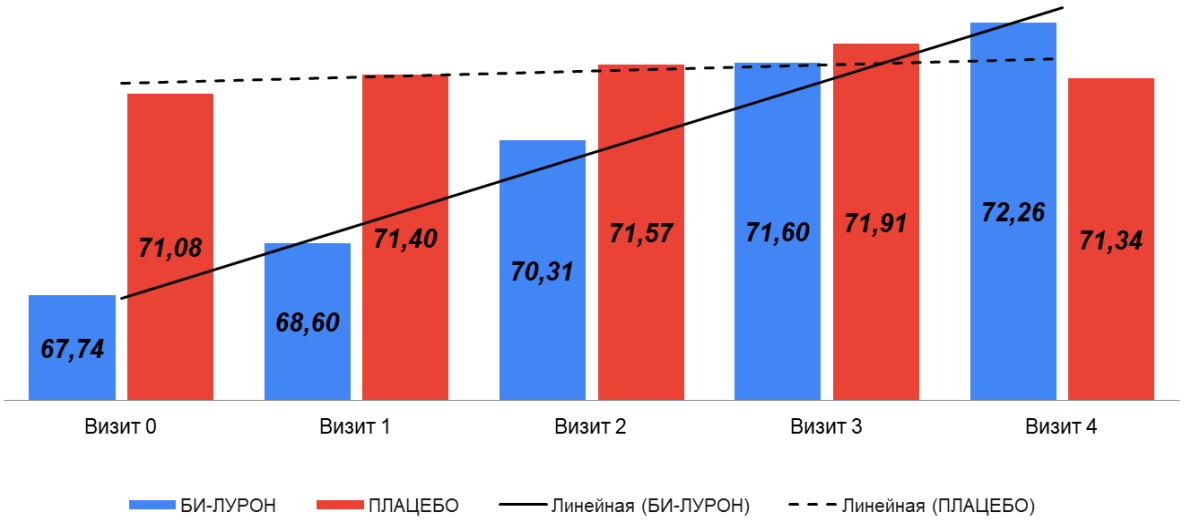


***Fig. 2. Dynamics of the joint function self-assessment from Visit 0 to Visit 4***
***Fig. 2. Dynamics of the joint function self-assessment from Visit 0 to Visit 4***

Therefore, in the group of patients who took Bi-Luron were indicated statistically reliable (and therefore not random) significant improvements in pain scores (42,60±2,382 vs. 58,31±1,351), self-assessment of joint function (72,26±0,696 versus 67,74±0,894) and assessment of quality of life (1 (1;1)) versus 2 (2;2)) in the interval between the inclusion of patients in the study (Visit 0) and Visit 4. It should be noted that pain and limited joint function are the main subjective symptoms of knee osteoarthritis and, therefore, the target criteria for the effectiveness of treatment and medical and social well-being of patients.

The observed statistically significant positive dynamics of indicators on the scale of pain and assessment of quality of life in the group of patients who took Placebo may be connected with taking the Naproxen medication in the recommended dosage on demand.

During 12 weeks of therapy we evaluated the dynamics the Naproxen medication dose the groups Bi-Luron and Placebo during the study period. Patients were instructed to take Naproxen only “on demand” in case of pain, and to daily note the medication intake (number of tablets taken) in the patient's diary. There was a more active trend towards a decrease in the number of weekly Naproxen tablets taken in the indicated period in Bi-Luron group (Fig. 3).

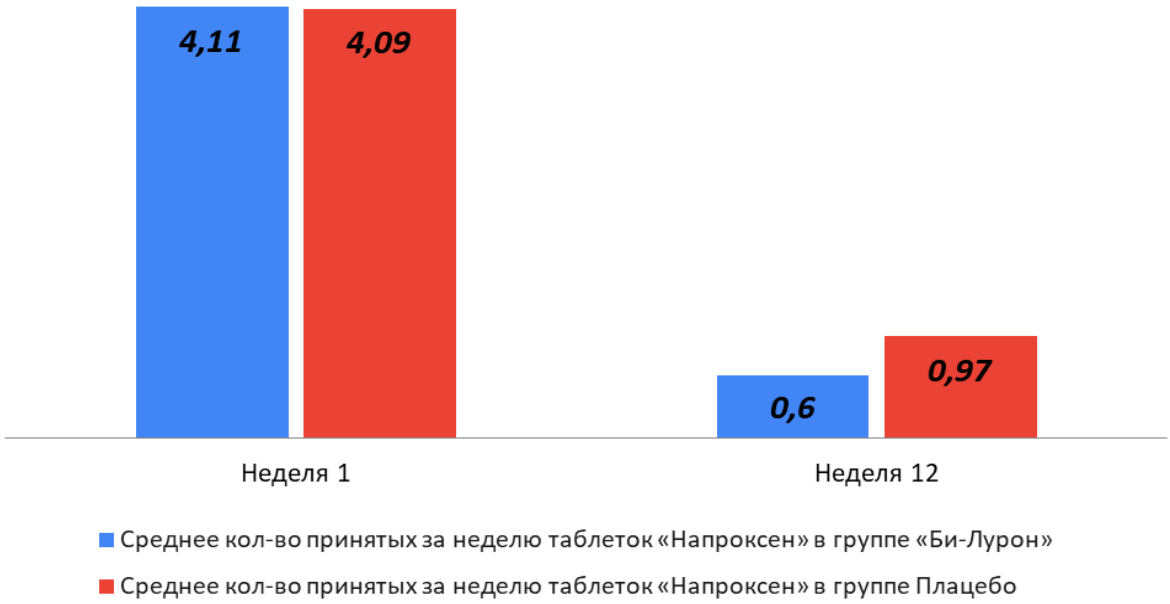


***Fig. 3. Dynamics of taking «Naproxen» in the range «Week 1-Week 12»***
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The effectiveness of Bi-Luron was also evaluated by its effect on synovitis dynamics based on the results of objective examination (knee joints ultrasound was performed in 100% of patients at Visit 0 and at Visit 4, and MRI was performed in 20% of patients of each selection at Visit 0 and at Visit 4). Dynamics based on the results of an objective examination is presented in the form of medical cases.

In some patients taking Bi-Luron, signs of synovitis disappeared by the end of the third month of treatment, however, in some patients they persisted, which confirms the literature data on necessity of longer therapy with medications containing chondroitin sulfate and hyaluronic acid in order to achieve remission of DOA. Taking these medications, according to recommendations of the European Society of orthopedists and traumatologists, should continue for life, and morphological positive changes can be observed with long-term therapy - from 6 months to 1 year, in patients with early stages of DOA (stages I-II according to Kellgren-Lawrence ).

**Medical cases**

***Medical case №1. Bi-Luron group***

Patient S., aged 50, was included in the clinical study with a diagnosis: Primary bilateral knee osteoarthritis, stage II (M17.0). The patient took Bi-Luron (data obtained at unblinding at the end and after receiving and consideration of all the results of the study). Complaints at the time of inclusion on periodic pain in left knee joint, aggravated after a long stay in a standing position, crunching when moving. These symptoms have been noted for the last 5 years, with episodic deterioration caused by increased physical activity. She had not previously consulted a doctor about DOA, was not examined, and did not take hyaluronic acid and chondroitin sulfate medications. Has a history of surgery (ovarian resection due to a cyst in 2003, endometriosis).

Objective examination did not reveal significant deviations from the norm in organs and systems, with the exception of knee joints pathology and excess fat mass (BMI - 32.05, obesity of the first degree). When examining knee joints, a slight swelling of the periarticular tissues was found on the right, moderate on the left, crunch during movements on both sides and pain on palpation in the projection of the joint space on the left.

X-ray: osteophytes and slight narrowing of the joint space on both sides, which corresponds to stage II of DOA according to the Kellgren-Lawrence classification (there are signs of patellofemoral arthrosis, uneven narrowing of the joint space of the right knee joint, intercondylar eminences are pointed, articular surfaces are smooth).

Ultrasound examination showed signs of a small synovitis on the left, degenerative changes in the medial meniscus of both knee joints. The patient's quality of life was evaluated using the validated EQ5D-3L questionnaire, knee joint function using the IKDS-2000 scale, pain level using the visual analogue scale (from 0 to 100), and compliance using the Morisky 8-Item Medication Adherence Scale. During the study, the patient showed a noticeable improvement in joint function and a decrease in pain level. The patient took the Naproxen medication on demand in the first 3 weeks from the moment of inclusion, 4, 5 and 3 tablets respectively, subsequently painkillers were not required, which indicates a decrease in the activity of the local inflammatory process in the knee joints while taking Bi-Luron. There was a positive trend in the knee joint sonography: disappearance of synovitis, disappearance of signs of inflammation of the synovial membrane (Fig. 4).

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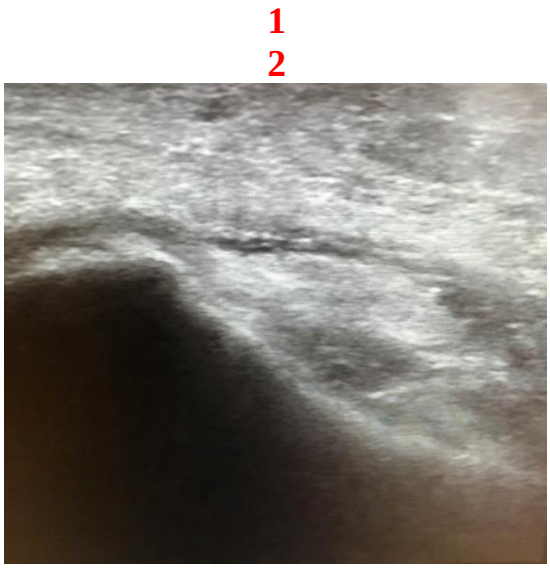
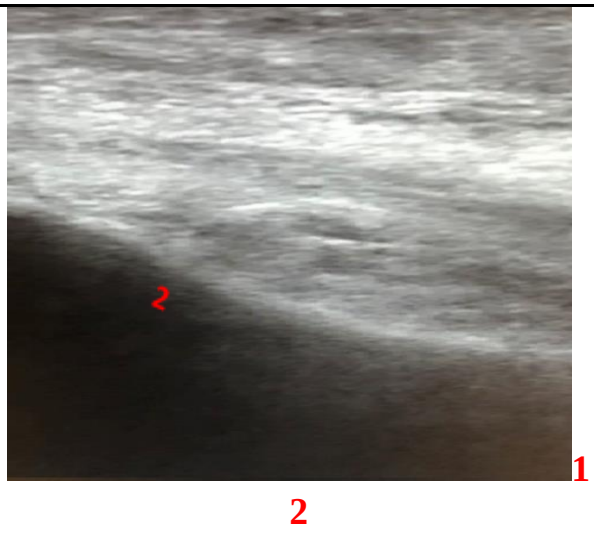
|  |  |
| *a* | *b* |
| Ultrasound image of the left knee joint at inclusion (20.12.2021): the joint cavity is enlarged with small amount of homogeneous fluid (1), moderate thickening of the synovial membrane (2).<br>Ultrasound image of the left knee joint at inclusion (December 20, 2021): the joint cavity is enlarged with small amount of homogeneous fluid (1), moderate thickening of the synovial membrane (2). | Ultrasound image of the left knee joint at visit 4 (14.03.2022): the joint cavity is not enlarged (1), the synovial membrane is not thickened (2).<br><br>Ultrasound image of the left knee joint at visit 4 (March 14, 2022): the joint cavity is not enlarged (1), the synovial membrane is not thickened (2). |

***Fig. 4. Ultrasound image of the knee joints of patient S., 50 years old, before and after taking dietary supplement Bi-Luron***

***Fig. 4. Ultrasound image of the knee joints of patient S., 50 years old, before and after taking dietary supplement Bi-Luron***

Small degenerative phenomena in the meniscus persisted. The patient is recommended to continue therapy with medications containing chondroitin sulfate and hyaluronic acid.

***Medical case №2. Placebo group***

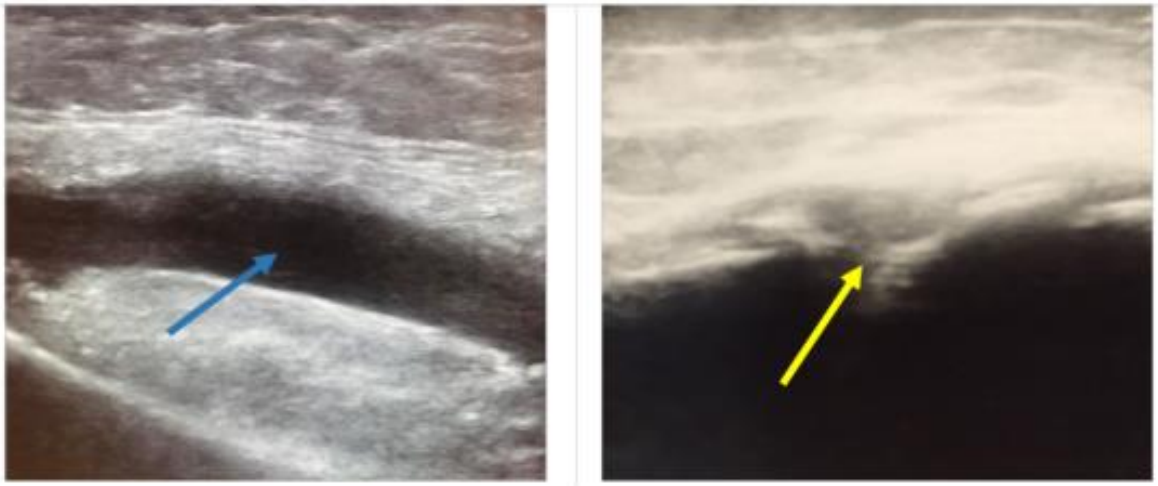
Patient G., 43 years old, was included in the clinical study with a diagnosis of Primary bilateral knee osteoarthritis, stage 0-I (M17.0). The patient took Placebo (data obtained at

unblinding at the end and after receiving and consideration of all the results of the study). Complaints at the time of inclusion on periodic minor pain in both knee joints, aggravated after a long activity, crunching during active movements. These symptoms have been noted for the last 3 years. She had not previously consulted a doctor about DOA, was not examined, and did not take hyaluronic acid and chondroitin sulfate medications. Has a history of 2 operations (caesarean section in 2004 and 2020).

An objective examination did not reveal significant deviations from the norm in organs and systems, with the exception of the pathology of knee joints (BMI - 20.0 - normal). Examination of the knee joints revealed crepitation during active and passive movements on both sides in knee joints.

X-ray: on both sides - a slight narrowing of the joint space, which corresponds to stage I of DOA according to the Kellgren-Lawrence classification (signs of uneven narrowing of the joint space of both knee joints, the articular surfaces are smooth).

Ultrasound examination at the time of inclusion showed signs of knee joints pathology (***Fig. 5***): in the cavity of the left knee joint there was an insignificant amount of free fluid, the outer and inner menisci homogeneous, with a smooth and clear contour. At the end of participation in the study, there were signs of degenerative changes in the hyaline cartilage and knee joint meniscus.



| a | b |
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| | |
| Ultrasound image of the left knee joint at inclusion (29.12.2021): there is a small amount of free fluid in the cavity of the left knee joint, the outer and inner menisci are homogeneous, with a smooth and clear contour.<br>Ultrasound image of the left knee joint at inclusion (December 29, 2021): there is a small amount of free fluid in the cavity of the left knee joint, the outer and inner menisci are homogeneous, with a smooth and clear contour. | Ultrasound image of the left knee joint at the end of the study (2022-03-24): signs of degenerative changes in the hyaline cartilage and menisci of the knee joint.<br>Ultrasound image of the left knee joint at the end of the study (March 24, 2022): signs of degenerative changes in the hyaline cartilage and menisci of the knee joint. |

***Fig. 5. Ultrasound image of the knee joints of patient G., 43 years old, while taking Placebo***

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The patient was regularly taking Naproxen on demand for 8 weeks out of 12 weeks of therapy, including the last, twelfth week, which indicates the preservation of the activity of the local inflammatory process in the knee joints while taking Placebo.

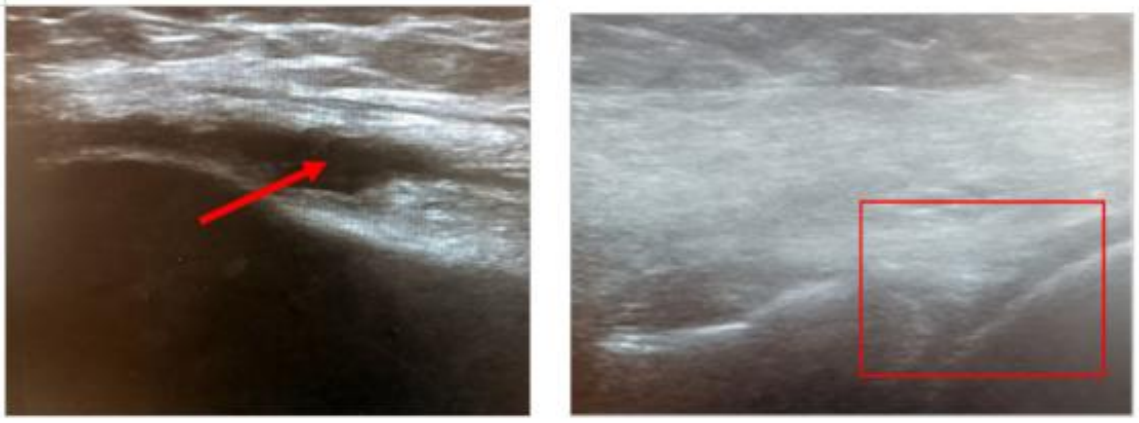
The patient's quality of life was evaluated using the validated EQ5D-3L questionnaire, knee joint function using the IKDS-2000 scale, pain level using the visual analogue scale (from 0 to 100), and compliance using the Morisky 8-Item Medication Adherence Scale. Therefore, for this patient, while taking Placebo, there was no improvement in the functions of the joints and pain level decrease, nor a change in the objective picture during instrumental examination. For 3 months, she had signs of synovitis, degenerative changes in the bone and cartilage structures of the knee joint, and there was also a deterioration in the course of DOA - the appearance of MR-morphological signs of damage to the posterior horn of the meniscus medialis of stage I-II according to Stoller.

***Medical case №3. Bi-Luron group***

Patient G., 62 years old, included in the clinical study with a diagnosis of Primary bilateral knee osteoarthritis, stage II (M17.0). The patient took Bi-Luron (data obtained at unblinding at the end and after receiving and consideration of all the results of the study). Complaints at the time of inclusion in the study: pain in knee joints, more on the left, aggravated in the evening and at night, crunching and clicking in knee joints during movement. These symptoms have been observed since the age of 25. He had not previously consulted a doctor about DOA, was not examined, and did not take hyaluronic acid and chondroitin sulfate medications. Medical background: surgery (polypectomy of nasal polyps in 2017); bronchial intermittent asthma since 2021, taking bronchial spasmolytic "on demand".

An objective examination did not reveal significant deviations from the norm in organs and systems, with the exception of knee joints pathology and periodically occurring allergic reactions to certain foods. Examination of knee joints revealed a moderate swelling of the periarticular tissues on the left, crunch during movements on both sides.

X-ray: on both sides - osteophytes and a slight narrowing of the joint space, which corresponds to stage II DOA according to the Kellgren-Lawrence classification. Ultrasound examination showed signs of a small synovitis on the left, degenerative changes in the medial meniscus of both knee joints (*Fig.6*).



| a | b |
|---|---|
| Ultrasound image of the left knee joint at inclusion (14.12.2021): the joint cavity is enlarged with a small amount of homogeneous fluid in the joint cavity, the internal meniscus is of a heterogeneous structure with an uneven contour in the anterior horn.<br>Ultrasound image of the left knee joint at inclusion (December 14, 2021): the joint cavity is enlarged with a small amount of homogeneous fluid in the joint cavity, the | Ultrasound image of the left knee joint at the final visit (09.03.2022): the joint cavity is not dilated, free fluid in the joint cavity is not detected, the internal meniscus is of a heterogeneous structure, with an uneven contour in the anterior horn.<br>Ultrasound image of the left knee joint at the final visit (March 09, 2022): the joint cavity is not dilated, free fluid in the joint cavity is not detected, the internal meniscus is of a heterogeneous structure, with an uneven contour in the anterior horn. |

| | |
|---|---|
| internal meniscus is of a heterogeneous structure with an uneven contour in the anterior horn. | |

***Fig. 6. Ultrasound image of the knee joints of patient G., 62 years old, before and after taking Bi-Luron***

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The patient's quality of life was evaluated using the validated EQ5D-3L questionnaire, knee joint function using the IKDS-2000 scale, pain level using the visual analogue scale (from 0 to 100), and compliance using the Morisky 8-Item Medication Adherence Scale. Thus, there was a noticeable improvement in joint function and pain level decrease. The patient took Naproxen on demand for 9 weeks from the moment of inclusion, subsequently painkillers were not required, which indicates a decrease in the activity of the local inflammatory process in knee joints while taking Bi-Luron.

## CONCLUSION

1. The biological supplement "Bi-Luron" in a clinical study on 70 patients with knee osteoarthritis (duration of therapy 12 weeks) in combination therapy with non-steroidal anti-inflammatory drugs showed its effectiveness in stages I-II of the disease: noted a statistically significant decrease (compared to the initial state) of knee joint pain level, improving joint function.

2. Analysis of objective data showed a positive trend in ultrasound parameters and MRI signs of joint inflammation, which is clearly illustrated by the three presented clinical cases.

3. While taking food supplement Bi-Luron in a clinical study in 35 patients with knee joints osteoarthritis, there was a decrease in the need of non-steroidal anti-inflammatory medication use for 12 weeks.

**Transparency of the study.** The study was conducted with support of Adelon LLC.

## ADDITIONAL INFORMATION

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**Authors' contribution:**
All authors confirm their authorship according to the ICMJE criteria (all authors contributed significantly to the conception, study design and preparation of the article, read and approved the final version before publication).
The largest contributions are distributed as follows: Kalyuta T.Yu., Fedonnikov A.S. – development of the study concept and design, writing the text of the article; Ulyanov V.Yu. – selection and examination of patients, editing the article, writing the text of the article; Fedonnikov A.S., Ulyanov V.Yu. – data analysis and interpretation; Fedonnikov A.S. – statistical processing of the findings; **Yurkovets A.A.** – patients handling and processing of the findings; **Romakina N.A.** – selection and examination of patients, processing of the findings.

**Source of funding:**
Funding Source: The authors declare funding as part of the contract work in planning and conducting the study.
**Conflict of interest:**
The authors declare no apparent or potential conflicts of interest related to the publication of this article.
**Ethical affirmation:**
The authors claim that all procedures used in this work comply with the ethical standards of the institutions that conducted the study and the Basic Laws on the Health Protection of the citizens of the Russian Federation, as well as the Declaration of Helsinki of 2013 edition. The study was approved by the local ethics committee of the Saratov State Medical University named after V.I. Razumovsky of the Ministry of Health of the Russian Federation (protocol No. 13 dated August 16, 2022).
**Informed consent to publication:**
The consent of patients (their representatives) for processing and publication of non-personalized data was obtained.

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All authors confirm their authorship according to the ICMJE criteria (all authors contributed significantly to the conception, study design and preparation of the article, read and approved the final version before publication).
The largest contributions are distributed as follows: Kalyuta T.Yu., Fedonnikov A.S. – development of the study concept and design, writing the text of the article; Ulyanov V.Yu. – selection and examination of patients, editing the article, writing the text of the article; Fedonnikov A.S., Ulyanov V.Yu. – data analysis and interpretation; Fedonnikov A.S. – statistical processing of the findings; Yurkovets A.A. – patients handling and processing of the findings; Romakina N.A. – selection and examination of patients, processing of the findings.

**Funding Source:** The authors declare funding as part of the contract work in planning and conducting the study.
**Disclosure:** The authors declare no apparent or potential conflicts of interest related to the publication of this article.

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