# CLINICAL STUDY PROTOCOL

IA/PAAG-SI/OA/2023

**Survey Data Analysis to Assess the Long-term Efficacy and Safety of Intra-articular HBISA Endoprosthesis of Synovial Fluid (NOLTREX™) in Knee Osteoarthritis**

ClinicalTrials.gov Identifier: NCT06523491

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Study sponsor

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# List of abbreviations

| Abbreviation | Meaning |
|---|---|
| BP | Blood pressure |
| ALT | Alanine aminotransferase |
| anti-HCV | Total antibodies to Hepatitis C Virus |
| AST | Aspartate aminotransferase |
| ATC | Anatomical-therapeutic-chemical classification |
| APTT | Activated partial thromboplastin time |
| VAS | Visual-analog scale |
| HIV | Human immunodeficiency virus |
| GGTP | Gamma-glutamyl transpeptidase |
| DEE | Confidence interval |
| CS | Clinical study |
| CRO | Contract research organization |
| MD | Medical device |
| GCP | Good clinical practice |
| NSAIDs | Non-steroidal anti-inflammatory drugs |
| IEC | Independent ethics committee |
| AE | Adverse event |
| OA | Osteoarthrosis |
| PT | Prothrombin time |
| SAE | Serious adverse event |
| SOP | Standard operating procedure |
| ESR | Erythrocyte sedimentation rate |
| CRD | Chronic renal disease |
| RR | Respiration rate |
| HR | Heart rate |
| ALP | Alkaline phosphatase |
| eCRF | electronic Case Report Form |
| ACR | American College of Rheumatology |
| HBs-Ag | hepatitis B surface antigen |

| | |
|---|---|
| ICH | International council for harmonization of technical requirements for pharmaceuticals for human use |
| JSN | Joint space narrowing |
| JSW | Joint space width |
| MedDRA | Medical Dictionary for Regulatory Activities |
| OEI | Evaluation of the treatment effectiveness by the investigator |
| OEP | Evaluation of the treatment effectiveness by the patient |
| WOMAC | Western Ontario and McMaster Universities Osteoarthritis |
| WOMAC-A | Subscale of pain according to the osteoarthritis index developed by researchers at the Western Ontario and McMaster Universities Osteoarthritis |
| WOMAC-B | Subscale of stiffness according to the osteoarthritis index developed by researchers at the Western Ontario and McMaster Universities Osteoarthritis |
| WOMAC-C | Subscale of function according to the osteoarthritis index developed by researchers at the Western Ontario and McMaster Universities Osteoarthritis |
| WOMAC-T | Change in the total score on the scale of the osteoarthritis index, developed by the researchers at the Western Ontario and McMaster Universities Osteoarthritis |

# Synopsis

**Name of the study**

1-year follow-up of a randomized controlled trial IA/PAAG-SI/OA/2019 with open-label extension IA/PAAG-SI/OA/2020 to assess the long-term efficacy and safety of Intra-articular HBISA Endoprosthesis of Synovial Fluid NOLTREX™ in patients with symptomatic Kellgren and Lawrence (KL) grade 2 and 3 knee OA.

**Protocol number**

IA/PAAG-SI/OA/2023

**Studied MD**

HBISA endoprosthesis of synovial fluid NOLTREX™ (hereinafter referred to as NOLTREX™)

HBISA (polyacrylamide hydrogel, hereinafter - PAAG) is intended for the symptomatic treatment of adult patients with osteoarthritis (OA) reducing joint pain and improving mobility. The aim of the 1-year follow-up is to evaluate the long-term safety and efficacy of one and two intra-articular PAAG courses in patients with symptomatic Kellgren and Lawrence (KL) grade 2 and 3 knee OA.

**Duration of treatment:**

A course of two weekly intra-articular (IA) injections of 4.0 ml NOLTREX™ (2.5 + 1.5 ml, or 2.0 + 2.0 ml from two syringes through one needle [one injection]). The number of injections was determined by the doctor depending on the stage of knee OA and the clinical response. In order to avoid overfilling the joint with a dense, slowly resorbable material, with a good clinical result (a decrease in the severity of joint pain according to 100-mm VAS by more than 40% compared to the basal level), the course of injections was discontinued.

A repeated course of NOLTREX™ IA injections was carried out after a re-evaluation of the feasibility and possibility of a repeated course of NOLTREX™ injections after 6 months, after 9 months and after 12 months after the start of the IA/PAAG-SI/OA/2019 study.

**Comparison MD**

Not applicable

**The duration of the study, the number of research centers and patients**

This study was 1-year follow-up involving patients with knee OA who received IA injections of NOLTREX™ in the RCT IA/PAAG-SI/OA/2019 (CS1) and OLE IA/PAAG-SI/OA/2020 (CS2). The follow-up data were collected through telephone interview (using questionnaire) conducted in April-July 2022, 12 months after the completion of OLE IA/PAAG-SI/OA/2020. Analysis included data collected at Visit 1 (week 1) of the parent study IA/PAAG-SI/OA/2019, visit 0 (screening) and Visit 5 (week 23) of OLE.

**Number of patients:**

The survey was conducted in a population that included 57 patients, divided into 3 subgroups depending on the treatment they received: 30 patients (52.63%) received 2 courses of therapy; 17 patients (29.82%) received 1 course of therapy; 10 patients (17.54%) patients received placebo The placebo group was very small for statistical assessment for most parameters and was not mainly analyzed in main part of them. That is why it is single arm study in comparation of 1 or 2 course of Noltrex (47 patients).

**Purpose of research**

The aim of 1-year follow-up is to evaluate the long-term safety and efficacy of a single or repeated course of IA NOLTREX™ in patients with symptomatic Kellgren and Lawrence (KL) grade 2 and 3 knee OA.

**Study design and methodology:**

The 1-year follow-up study involved patients with knee OA who had received a course of IA injections of NOLTREX™ or placebo in the RCT IA/PAAG-SI/OA/2019 and OLE IA/PAAG-SI/OA/2020. The follow-up data were collected during a telephone interview/questionnaire conducted in April–July 2022 – 12 months after the completion of OLE. Analysis included data collected at Visit 1 (week 1) of the parent study IA/PAAG-SI/OA/2019, visit 0 (screening) and Visit 5 (week 23) of OLE.

The multicenter, double-blind, randomized, comparative, placebo-controlled trial of the efficacy and safety of IA NOLTREX™ in the treatment of knee OA IA/PAAG-SI/OA/2019 (CS1) involved 72 patients over 50 years of age with a verified diagnosis of gonarthrosis in accordance with the criteria of the American College of Rheumatology (ACR) II-III radiographic stage according to the Kellgren-Lawrence classification. These patients received 1 to 2 injections (at an interval of 1 week) of MI NOLTREX™ into the most affected (target) knee joint.

The OLE IA/PAAG-SI/OA/2020 (CS2) included patients who had received at least one intra-articular injection of NOLTREX™ in the RCT, completed Visit 5 and signed an informed consent form for participation in OLE.

This study aimed to assess the long-term efficacy and safety of IA NOLTREX™ based on data from CS1, CS2 and the results of a telephone interview/questionnaire for patients conducted in April-July 2022. The survey/questionnaire was conducted according to the following scheme:

1. Patient survey - current pain status on a visual analogue scale (VAS) and 3 questions about treatment after completion of the study, which is filled in from the patient's words.

2. Questionnaire for the physician about treatment after completion of the study, which is filled in by collecting the history of the disease and the methods of treatment used after exiting the study(s), from medical records, a medical information storage system (if applicable).

3. The Osteoarthritis Index questionnaire, developed by employees of the University of Western Ontario and McMaster Universities Osteoarthritis (WOMAC) for completion from the patient's words - identical to that previously used in the clinical studies of the MI "BVISA endoprosthesis of synovial fluid NOLTREX" under two study protocols: CS1and CS2.

Since the WOMAC osteoarthritis index and VAS pain scores are similar to those used in CS1 and CS2, the aim of this study was to jointly analyze the data obtained in CS1, CS2, and the survey/questionnaire.

**Diagnosis and main inclusion criteria:**

Current study (IA/PAAG-SI/OA/2023- CS3) included patients who had previously participated in the IA/PAAG-SI/OA/2020 and/or IA/PAAG-SI/OA/2019 studies. Patients were included in these studies in accordance with the following criteria:

**Inclusion criteria for the IA/PAAG-SI/OA/2019 (CS1) study**

1. Men and women over 50 years old;

2. Verified gonarthrosis according to the ACR criteria (knee pain in combination with one of the following signs: age over 50 years, crepitus in the joint or morning stiffness in the joint lasting less than 30 minutes in combination with radiographic signs of gonarthrosis);

3. II–III radiographic stage of gonarthrosis according to the Kellgren-Lawrence classification with predominant damage to the medial tibiofemoral region of the knee joint;

4. Radiographic joint space width (JSW) of the target knee joint of at least 2.5 mm.

**Inclusion criteria for the IA/PAAG-SI/OA/2020 (CS2) study**

**1**. Men and women over 50 years of age;

2. Signed informed consent form by the study participant;

3. Verified gonarthrosis according to the ACR criteria (knee pain in combination with one of the following: age over 50 years, crepitus in the joint or morning stiffness in the joint lasting less than 30 minutes in combination with radiographic signs of gonarthrosis);

4. II–III radiographic stage of gonarthrosis according to the Kellgren-Lawrence classification with predominant damage to the medial tibiofemoral region of the knee joint

Completion of participation in the clinical study IA/PAAG-SI/OA/2019 in the NOLTREX™ medical device group with the completion of visit 5 procedures (25 weeks).

**Evaluation criteria:**

**Efficacy:**

The integral assessment of efficacy was based on the statistical analysis of the main efficacy parameters.

**The efficacy of the study MD was assessed by the following endpoints.**

**Primary Outcome Measure(s):**

1. Change in the total WOMAC score (WOMAC-T) 12 months after completion of CS2 compared with the baseline value at Visit 0 (screening) of the IA/PAAG-SI/OA/2020 study, compared with the baseline value at Visit 1 (week 1) of the IA/PAAG-SI/OA/2019 study and the last value at Visit 5 (week 23) of the IA/PAAG-SI/OA/2020 study;

**Secondary Outcome Measure(s):**

2. Change in the WOMAC Pain (WOMAC-A) Score 12 months after completion of CS2 compared to the baseline value at Visit 0 (screening) of the CS2 study, compared to the baseline value at Visit 1 (week 1) of the IA/PAAG-SI/OA/2019 study and the last value at Visit 5 (week 23) of the CS2 study;

3. Change in the WOMAC Stiffness (WOMAC-B) score 12 months after completion of CS2 compared to the baseline value at Visit 0 (screening) of the CS2 study, compared to the baseline value at Visit 1 (week 1) of the IA/PAAG-SI/OA/2019 study and the last value at Visit 5 (week 23) of the CS2 study;

4. Change in the WOMAC Physical Function (WOMAC-C) Score 12 months after completion of CS2 compared with the baseline value at Visit 0 (screening) of the CS 2 study, compared with the baseline value at Visit 1 (week 1) of the CS1 study and the last value at Visit 5 (week 23) of the CS2 study;

5. Change in the 100-mm VAS Pain Score 12 months after completion of CI2 compared with the baseline value at Visit 0 (screening) of the IA/PAAG-SI/OA/2020 study, compared with the baseline value at Visit 1 (week 1) of the CS1 study and the latest value at Visit 5 (week 23) of the CS2 study;

**Safety:**

This study did not specifically collect or analyze adverse event data.

The current CS 3 assessed safety using medical absolute and relative contraindications for repeated intra-articular treatment, as well as physician-reported data, including information on pain medication use.

**Statistical methods:**

Statistical analysis was performed using the R statistical software package (R: A language and environment for statistical computing. R Core Team. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/ ) version 4.x.x, using package version control adapted and validated by Microsoft (Microsoft R Open. Microsoft and R Core Team. Microsoft, Redmond, Washington. URL https://mran.microsoft.com/ ) using "A Guidance Document for the Use of R in Regulated Clinical Trial Environments" (https://www.r-project.org/doc/R-FDA.pdf ).

Statistical analysis was performed for data on all patients who participated in the study in accordance with the definitions of the populations for the analysis.

All available patient data were used for the analysis; due to the lack of a statistical hypothesis and the planned statistical analysis of any parameters, only the results of the descriptive analysis are presented.

Demographic, efficacy, and safety data were presented using descriptive statistics:

Continuous (quantitative) data were presented using the following parameters:

• Number of observations (n);

• Arithmetic mean (M);

• Standard deviation (SD);

• 95% confidence interval for the mean (95% CI);

• Minimum value (min);

• Maximum value (max);

• Median (Me);

• Interquartile range (ICR).

For variables presented as qualitative and ordinal indicators, absolute (n) and relative (%) frequencies for each category, as well as 95% CI, were calculated.

**Analysis of demographic, baseline, and follow-up data**

For patients included in this study, baseline assessment of parameters collected within the framework of CS1 (IA/PAAG-SI/OA/2019) and CS2 (IA/PAAG-SI/OA/2020) were presented.

Comparison of baseline and follow-up characteristics of patients included in this study was performed in subgroups.

For quantitative variables, groups were compared using one-way ANOVA or the Kruskal-Wallis test, depending on the results of the normality test in the groups using the Shapiro-Wilk test.

For categorical variables, groups were compared using the Pearson chi-square test ($\chi 2$). If the expected frequencies in any of the cells of the contingency table were less than 5, Fisher's exact test was used for comparison.