Clinical Study Protocol IA/PAAG-SI/OA/2020

HBISA Endoprosthesis of synovial fluid NOLTREX™

Open-label Multicenter Postmarketing Extension Study of Efficacy and Safety of Intra-articular HBISA Endoprosthesis of Synovial Fluid NOLTREX™ per TU 9398-00152820385-2015 in Knee Osteoarthritis

ClinicalTrials.gov Identifier: NCT06429319

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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

Multicenter open post-registration study of the safety and effectiveness of the medical device HBIS endoprosthesis of synovial fluid NOLTREX™ for intraarticular administration in the treatment of gonarthrosis.

Protocol number

IA/PAAG-SI/OA/2020

Studied MD

HBIS endoprosthesis of synovial fluid NOLTREX™ according to TU 9398-00152820385-2015 (hereinafter referred to as NOLTREX™)

Comparison MD

Not applicable

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

From 29.05.2020 to 31.05.2021, the number of research centers is 4.

Number of patients: a maximum of 72

Purpose of research

Evaluation of the safety and effectiveness of the medical device (MD) NOLTREX™ for intraarticular administration in the treatment of gonarthrosis of the II–III x–ray stage according to Kellgren-Lawrence.

Tasks of research

1. Evaluation of the safety of MD NOLTREX™ at intraarticular administration in the treatment of gonarthrosis of the II-III radiological stage by Kellgren-Lawrence;
2. Evaluation of the effect of MD NOLTREX™ at intraarticular administration in the treatment of Kellgren-Lawrence stage II–III gonarthrosis on knee function and the need for paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs).

Research method

Study design:

Open-label interventional study in one group with gonarthrosis patients who received a single or double course of injections of MD NOLTREX™ as part of the IA/PAAG-SI/OA/2019 study.

MD NOLTREX™ (synovial fluid endoprosthesis) has been registered for the treatment of osteoarthritis since 2003, and according to annual post-marketing observations it is an effective and safe medical device. A multicenter, double-blind, randomized, comparative, placebo-controlled study of the efficacy and safety of NOLTREX™ for intraarticular administration in the treatment of

gonarthrosis (IA/PAAG-SI/OA/2019) was conducted, in which 72 patients aged over 50 years with a verified diagnosis of gonarthrosis in accordance with the criteria of the American College of Rheumatology (ACR) II-III radiological stage classification Kellgren-Lawrence received 1 to 2 injections (at 1-week intervals) of 4 mL of MD NOLTREX™ into the most affected (target) knee joint. The second injection was not performed if the severity of pain in the target knee joint decreased by 40─ or more a week after the first injection. The study was performed to evaluate the effectiveness and safety of MD NOLTREX™ with this method of use in comparison with placebo.

The current study is planned to include patients who received at least one intra-articular injection of MY NOLTREX™ in IA/PAAG-SI/OA/2019 study and underwent procedures during the 5-week Visit (25 weeks – 6 months after the injection). After completing all the procedures of Visit 5 and completing the corresponding electronic individual registration card (eCRF) forms in the IA/PAAG-SI/OA/2019 study, the investigator receives information about which group in the IA/PAAG-SI/OA/2019 study the patient was assigned to, i.e. whether he received injections of the study MD or placebo. After that, patients who received the studied MD will be asked to sign an informed consent form to participate in the open clinical trial IA/PAAG-SI/OA/2020.

Procedures of Visit 5 (25 weeks - 6 months after injection) of the placebo-controlled trial IA/PAAG-SI/OA/2019, if they coincide with the screening procedures of Visit 0 of the open trial IA/PAAG-SI/OA/2020 for patients who have agreed to participate in this study and are eligible to participate, will be considered as procedures Visit 0 of the open trial IA/PAAG-SI/OA/2020. Thus, Visit 5 of the IA/PAAG-SI/OA/2019 study coincides with the screening Visit (Visit 0) of the IA/PAAG-SI/OA/2020 study.

Patients who signed the informed consent form to participate in an open study IA/PAAG-SI/OA/2020 to evaluate the safety and effectiveness of MD NOLTREX™, in the case when pain in the target knee joint in the study IA/PAAG-SI/OA/2019 remained the same or increased (on a 100-mm visual analogue scale [VAS]) compared to the rating at Visit 1 of the study IA/PAAG-SI/OA/2019 (or if a decrease in pain severity is less than 40─ compared to the rating at Visit 1 of the study IA/PAAG-SI/OA/2019), will receive the injection of MD NOLTREX™ in the target knee (Group A). MD will be administered in accordance with the instructions for use of MD NOLTREX™: 4.0 ml per injection (2.5 + 1.5 ml, or 2.0 + 2.0 ml from two syringes through one needle [one puncture]) at intervals of one week. The course in an open study is a maximum of 2 injections (the first - at Visit 1, the second - at Visit 2). The number of injections is determined by the doctor depending on the stage of gonarthrosis and the clinical response. In order to avoid overfilling the joint with dense slowly resorbable material, at the good clinical result (reducing the pain severity on a 100 mm VAS by Visit

2 by more than 40─ compared to the basal level in the open study[1]), the course of injections will be discontinued.

Patients included in the open part of the study, who have the severity of pain in the target knee joint at the time of inclusion in the open part of the study decreased by 40─ or more compared to the assessment on Visit 1 of the IA/PAAG-SI/OA/2019 study, or those who cannot be re-injected with MD NOLTREX™, a re-injection of MD NOLTREX™ will not be performed on Visits 1 and 2 of the open study (Group B).

A repeated course of MD NOLTREX™ injections in an open study is not possible if any of the following criteria are met:

1. Documented intolerance of the studied MD NOLTREX™;
2. Active inflammation in the target knee joint (edema, hyperemia, effusion) at the time of inclusion in the study;
3. Inflammatory diseases of the skin and soft tissues in the area of the intended introduction of the studied MD into the target joint;
4. History of venous thrombosis and thromboembolism;
5. Deviations from the norm in the coagulogram (activated partial thromboplastin time [APTT], prothrombin time [PT], prothrombin index, fibrinogen);
6. Hemophilia and other hemorrhagic diatheses, as well as taking anticoagulants and disaggregants;
7. Inflammatory changes in clinical blood analysis (leukocytosis, increased erythrocyte sedimentation rate [ESR]);
8. Deviation from the norm (in accordance with the standards of the local laboratory) of the number of platelets;
9. Type 1 or type 2 diabetes;
10. Acute infectious diseases or infectious exacerbations of chronic diseases (including respiratory tract infections) during the month prior to inclusion in the study.

At Visit 3 additional evaluation will be conducted to assess the feasibility and possibility of re-injections with MD NOLTREX™ among patients of group B. If at Visit 3 of the open study pain remains the same in the target joint of the study IA/PAAG-SI/OA/2019 or increases in intensity (as per 100-mm VAS) in comparison with the assessment at Visit 1 of the study IA/PAAG-SI/OA/2019 (or if a decrease in pain severity is less than 40% when compared to the rating at Visit 1 of the study IA/PAAG-SI/OA/2019), in the absence of the above criteria for non-treatment with the studied MD, at Visit 3 of open study the injection of MD NOLTREX™ into the target knee joint will be performed. MD will be administered in accordance with the instructions for medical use of MD NOLTREX™:

4.0 ml per injection (2.5 + 1.5 ml, or 2.0 + 2.0 ml from two syringes through one needle [one puncture]) once or twice at intervals of one week. The treatment course in the framework of an open study among patients of Group B is a maximum of 2 injections (the first - at Visit 3, the second - at Visit 4). The number of injections is determined by the doctor depending on the stage of gonarthrosis and the clinical response. In order to avoid overfilling the joint with dense slowly resorbable material, at the good clinical result (reducing the pain severity on a 100 mm VAS by Visit 2 by more than 40─ compared to the basal level in the open study[1]), the course of injections will be discontinued.

The open nature of the study in one group is determined by the main purpose of the study - to assess the safety of MD NOLTREX™ with a single or repeated course of use. Placebo safety data at the 6-month point (visit 5) in the IA/PAAG-SI/OA/2019 study will be used as a control. It is assumed that continued monitoring of patients in the placebo group will not lead to the detection of new adverse events (AE), the frequency of which should be compared with the frequency in the active therapy group, and is connected to unethical restriction of patients in the placebo group in the possibility of using potentially effective synovial fluid endoprostheses.

The open study provides follow-up of patients for 6 months (up to 25 weeks from Visit 1).

Thus, the maximum duration of participation in the study for one patient will be a maximum of 172 days.

Patient visits

Visit 0 (Day 0, -24 h -0 h, screening)

Procedures at Visit 5 of study IA/PAAG-SI/OA/2019 (hereinafter referred to in the Protocol as Clinical study 1 - CS1) that coincide with the screening Visit procedures (Visit 0) in study IA/PAAG-SI/OA/2020 will be counted as the procedures of Visit 0 of study IA/PAAG-SI/OA/2020, there is no need to repeat the identical procedures of these visits.

The following procedures must be performed during the visit:

- The signing of the informed consent;
- The collection of demographic data;
- Measurement of the body weight;
- Collection of complaints and anamnesis;
- Registration of concomitant therapy;
- Assessment of the main vital signs (blood pressure [BP], heart rate [HR], number of respiratory movements [RR], body temperature);
- Physical examination of joints;

- Completing an algofunctional questionnaire for evaluating the osteoarthritis index developed by researchers at the Western Ontario and McMaster Universities Osteoarthritis, WOMAC with an assessment of subscale pain (WOMAC-A), stiffness (WOMAC-B), and functional performance (WOMAC-C) (from *Visit 5 of CS1*);
- Assessment of the severity of pain in the target knee joint by 100-mm VAS (from *Visit 5 of CS1*);
- Evaluation of the effectiveness of treatment by the patient, parameter OEP (from *Visit 5 of CS1*);
- Evaluation of the effectiveness of treatment by the investigator, parameter OEI (from *Visit 5 of CS1*);
- Documenting the target knee joint (the same joint that was identified as the target in the IA/PAAG-SI/OA/2019 study);
- Clinical blood test (hemoglobin level, hematocrit, red blood cell count, white blood cell count, white blood cell formula, platelet count, ESR) (from *Visit 5 of CS1*);
- Biochemical analysis of blood (glucose, alanine aminotransferase [SPGT], aspartate aminotransferase [AST], alkaline phosphatase [ALP], gamma-glutamyltranspeptidase [GGTP], total bilirubin, creatinine, uric acid, rheumatoid factor) (from *Visit 5 of CS1*);
- Coagulogram (APTT, PT, prothrombin index, fibrinogen) (from *Visit 5 of CS1*);
- Blood tests for antibodies to human immunodeficiency virus (HIV), hepatitis b surface antigen (HBsAg) and antibodies to Hepatitis C Virus (anti-HCV]), syphilis (RW);
- General urinalysis (color, transparency, relative density, pH, glucose, protein, ketone bodies, urobilinogen) (from *Visit 5 of CS1*);
- Rapid urine test for pregnancy in women with preserved reproductive potential (from *Visit 5 of CS1*);
- Evaluation of inclusion/non-inclusion criteria;
- Issuing a patient's diary;
- Check AE and serious AE (SAE).

Visit 1 (Week 0, Day 1, start of treatment)

The following procedures must be performed during the visit:

- Measurement of the body weight;
- Collection of complaints and anamnesis;
- Registration of concomitant therapy;

- Assessment of the main vital signs (BP, HR, RR, body temperature);
- Physical examination of joints;
- Evaluation of inclusion/non-inclusion criteria;
- Injection of the studies MD into the cavity of the target joint (only for group A patients who are shown to receive the injection in accordance with the criteria specified in the Protocol);
- Registration of AE and SAE;
- Evaluation of exclusion criteria.

Every 2 weeks between Visit 1 and Visit 3 (weeks 3, 5, 7, 9 and 11), telephone contacts are made with the patient to clarify complaints, AE and the need for taking paracetamol or NSAIDs for the past 2 weeks. If AE is detected, or the need to take paracetamol or NSAIDs more than 4 days a week in each of the consecutive 2 weeks, the patient is invited to the clinic for an unscheduled Visit or a Visit to prematurely complete participation in the study (depending on the reason for the visit).

Visit 2 (Week 1, Day 8, treatment and follow-up) - as indicated

Only patients who received an injection of MD NOLTREX™ into the target knee joint on Visit 1 are eligible for Visit 2.

The following procedures must be performed during the visit:

- Measurement of the body weight;
- Collection of complaints and anamnesis;
- Registration of concomitant therapy;
- Assessment of the main vital signs (BP, HR, RR, body temperature);
- Physical examination of joints;
- Assessment of the severity of pain in the target knee joint using 100-mm VAS;
- Injection of the studied MD into the target joint cavity (only for patients of group A, in which the severity of pain in the target knee joint using 100 mm VAS did not decrease by 40% or more compared to the assessment on the Visit 0);
- Evaluation of the patient's diary;
- Return of the diary to the patient;
- Registration of AE and SAE;
- Evaluation of exclusion criteria.

Visit 3 (Week 13, Day 84 ± 2, treatment and follow-up)

The following procedures must be performed during the visit:

- Measurement of the body weight;
- Collection of complaints and anamnesis;
- Registration of concomitant therapy;
- Assessment of the main vital signs (BP, HR, RR, body temperature);
- Physical examination of joints;
- Filling out algofunctional questionnaire WOMAC with an assessment of the subscales of pain (WOMAC-A), stiffness (WOMAC-B) and functional performance (WOMAC-C);
- Assessment of the severity of pain in the target knee joint using 100-mm VAS;
- Evaluation of the effectiveness of treatment by the patient, OEP parameter;
- Evaluation of the effectiveness of treatment by the investigator, OEI parameter;
- Clinical blood test (hemoglobin level, hematocrit, red blood cell count, white blood cell count, white blood cell formula, platelet count, ESR);
- Biochemical blood test (glucose, ALT, AST, ALP, GGTP, total bilirubin, creatinine, uric acid, rheumatoid factor);
- Coagulogram (APTT, PT, prothrombin index, fibrinogen)
- General urinalysis (color, transparency, relative density, pH, glucose, protein, ketone bodies, urobilinogen);
- Injection of the studied MD into the cavity of the target joint (only for patients of Group B who are shown to receive the injection according to the criteria specified in the Protocol, and didn't receive the injection at Visit 1);
- Evaluation of the patient's diary;
- Evaluation of the total number of paracetamol tablets taken (one tablet = 500 mg) using patient's diary, PARACETAMOL parameter;
- Evaluation of the patient's diary of the total number of NSAIDs allowed by the Protocol in case of paracetamol inefficiency (NSAIDs allowed by the Protocol in case of paracetamol inefficiency: diclofenac potassium tablets 50 mg, diclofenac sodium tablets 75 mg, naproxen tablets 500 mg, naproxen sodium tablets 550 mg, meloxicam tablets 7.5 mg, celecoxib tablets 200 mg), NSAID parameter;
- Issuing a new patient diary to the patient;
- Registration of AE and SAE;
- Evaluation of exclusion criteria.

Every 2 weeks, between Visit 3 and Visit 4 (weeks 15, 17, 19, 21 and 23), telephone contacts are made with the patient to clarify complaints, AE and the need for taking paracetamol or NSAIDs for the past 2 weeks. If AE is detected, or the need to take paracetamol or NSAIDs more than 4 days a

week in each of the consecutive 2 weeks, the patient is invited to the clinic for an unscheduled Visit or a Visit to prematurely complete participation in the study (depending on the reason for the visit).

Visit 4 (Week 14, Day 91 ± 2, treatment and follow-up) - as indicated

Only patients who received an injection of MD NOLTREX™ into the target knee joint on Visit 3 are eligible for Visit 4.

The following procedures must be performed during the visit:

- Measurement of the body weight;
- Collection of complaints and anamnesis;
- Registration of concomitant therapy;
- Assessment of the main vital signs (BP, HR, RR, body temperature);
- Physical examination of joints;
- Assessment of the severity of pain in the target knee joint using 100-mm VAS;
- Injection of the studied MD into the target joint cavity (only for patients of Group B, in which the severity of pain in the target knee joint using 100 mm VAS did not decrease by 40% or more compared to the assessment at Visit 3)
- Evaluation of the patient's diary;
- Return of the diary to the patient;
- Registration of AE and SAE;
- Evaluation of exclusion criteria.

Visit 5 (Week 25, Day 169 ± 2, follow-up)

The following procedures must be performed during the visit:

- Measurement of the body weight;
- Collection of complaints and anamnesis;
- Registration of concomitant therapy;
- Assessment of the main vital signs (BP, HR, RR, body temperature);
- Physical examination of joints;
- Radiography of the knee joints and documentation of parameters of joint space width (JSW) and joint space narrowing (JSN);
- Filling out algofunctional questionnaire WOMAC with an assessment of the subscales of pain (WOMAC-A), stiffness (WOMAC-B) and functional performance (WOMAC-C);

- Assessment of the severity of pain in the target knee joint using 100-mm VAS;
- Evaluation of the effectiveness of treatment by the patient, OEP parameter;
- Evaluation of the effectiveness of treatment by the investigator, OEI parameter;
- Clinical blood test (hemoglobin level, hematocrit, red blood cell count, white blood cell count, white blood cell formula, platelet count, ESR);
- Biochemical blood test (glucose, ALT, AST, ALP, GGTP, total bilirubin, creatinine, uric acid, rheumatoid factor);
- Coagulogram (APTT, PT, prothrombin index, fibrinogen);
- General urinalysis (color, transparency, relative density, pH, glucose, protein, ketone bodies, urobilinogen);
- Evaluation of the patient's diary;
- Evaluation of the total number of paracetamol tablets taken (one tablet = 500 mg) using patient's diary, PARACETAMOL parameter;
- As per patient’s diary, evaluation of the total number of NSAIDs allowed by the Protocol in case of paracetamol inefficiency (NSAIDs allowed by the Protocol in case of paracetamol inefficiency: diclofenac potassium tablets 50 mg, diclofenac sodium tablets 75 mg, naproxen tablets 500 mg, naproxen sodium tablets 550 mg, meloxicam tablets 7.5 mg, celecoxib tablets 200 mg), NSAID parameter;
- Registration of AE and SAE;
- Evaluation of exclusion criteria.

An unscheduled visit

The following procedures must be performed during the visit:

- Measurement of the body weight
- Collection of complaints and anamnesis;
- Registration of concomitant therapy;
- Assessment of the main vital signs (BP, HR, RR, body temperature);
- Physical examination of joints;
- Evaluation of the patient's diary;
- Registration of AE and SAE;
- Evaluation of exclusion criteria.

At the time of unscheduled Visit, any of the research procedures can be additionally performed by the decision of the Chief investigator.

Visit to the prematurely end the participation in the study

The following procedures must be performed during the visit:

- Measurement of the body weight
- Collection of complaints and anamnesis;
- Registration of concomitant therapy;
- Assessment of the main vital signs (BP, HR, RR, body temperature);
- Physical examination of joints;
- Filling out algofunctional questionnaire WOMAC with an assessment of the subscales of pain (WOMAC-A), stiffness (WOMAC-B) and functional performance (WOMAC-C);
- Assessment of the severity of pain in the target knee joint on a 100-mm visual-analog scale (100-mm VAS);
- Evaluation of the effectiveness of treatment by the patient, OEP parameter;
- Evaluation of the effectiveness of treatment by the investigator, OEI parameter;
- Clinical blood test (hemoglobin level, hematocrit, red blood cell count, white blood cell count, white blood cell formula, platelet count, ESR);
- Biochemical blood test (glucose, ALT, AST, ALP, GGTP, total bilirubin, creatinine, uric acid, rheumatoid factor);
- Coagulogram (APTT, PT, prothrombin index, fibrinogen);
- General urinalysis (color, transparency, relative density, pH, glucose, protein, ketone bodies, urobilinogen);
- Rapid urine test for pregnancy in women with preserved reproductive potential;
- Evaluation of the patient's diary;
- Evaluation of the total number of paracetamol tablets taken (one tablet = 500 mg) using patient's diary, PARACETAMOL parameter;
- As per patient’s diary, evaluation of the total number of NSAIDs allowed by the Protocol in case of paracetamol inefficiency (NSAIDs allowed by the Protocol in case of paracetamol inefficiency: diclofenac potassium tablets 50 mg, diclofenac sodium tablets 75 mg, naproxen tablets 500 mg, naproxen sodium tablets 550 mg, meloxicam tablets 7.5 mg, celecoxib tablets 200 mg), NSAID parameter;
- Registration of AE and SAE;
- Evaluation of exclusion criteria.

The main parameters of evaluation of efficacy and safety

Basic safety parameters:

1. The frequency of AE and/or SAE;
2. Overall assessment of the tolerability of therapy by the investigator and the patient;
3. The main parameters of vital signs (HR, BP, RR, body temperature)
4. Results of physical examination;
5. Results of laboratory and instrumental examination.

Separately, it is planned to evaluate the cumulative (in the framework of a double-blind and open study) frequency of the most likely complications associated with periprocedural or temporary postprocedural (no more than 72 hours) pain or burning. These AE can be stopped with paracetamol or non-steroidal anti-inflammatory drugs.

Other possible side effects and complications of special interest related to the method of administration by intra-articular injection:

- pain or swelling at the injection site, feeling of bursting, burning, arthralgia, effusion in the joint, synovitis, aseptic acute arthritis;
- infections (pyogenic arthritis, direct infection of the joint at infectious diseases, osteomyelitis, sepsis, etc.);
- subcutaneous neuropathies, drug-induced vascular embolism.

It is assumed that the AEs are divided into groups: somatic AEs and AEs associated with the pathology of the target joint, as well as the frequency of both these groups and each AE, according to the following classification:

- Very common ≥10%;
- Common (frequent) < 10%, but ≥ 1%;
- Uncommon < 1%, but ≥ 0.1%;
- Rare < 0.1%, but ≥ 0.01%;
- Very rare < 0.01%.

The main parameters of the effectiveness of the studied MD:

1. Change in the overall score on the WOMAC scale (WOMAC-T) at Visit 3 (week 13), Visit 5 (week 25) compared to the basal value at Visit 0 (screening) of the open study and compared to the basal value at Visit 1 (week 1) of the IA/PAAG-SI/OA/2019 study;
2. Change in the pain subscale score (WOMAC-A) at Visit 3 (week 13), at Visit 5 (week 25) compared to the basal value at Visit 0 (screening) of the open study and compared to the basal value at Visit 1 (week 1) of the IA/PAAG-SI/OA/2019 study;

3. Change in the score for stiffness subscale (WOMAC-B) and functional performance (WOMAC-C) at Visit 3 (week 13), Visit 5 (week 25) compared to the basal value at Visit 0 (screening) of open study and compared to the basal value at Visit 1 (week 1) of the study IA/PAAG-SI/OA/2019;
4. The change in the severity of pain in the target knee on a 100-mm visual analogue scale (100 mm VAS) at Visit 2 (week 1), Visit 3 (week 13), Visit 5 (week 25) compared to the basal value at Visit 0 (screening) open security research and compared to the basal value at Visit 1 (week 1) study IA/PAAG-SI/OA/2019;
5. Evaluation of the effectiveness of treatment by the patient, parameter (on a scale from 1-clear deterioration to 6-significant improvement) on Visits 3 and 5 (parameters OEP-w_{13} and OEP-w_{25}, respectively);
6. Evaluation of the effectiveness of treatment by the investigator, parameter (on a scale from 1-clear deterioration to 6-significant improvement) on Visits 3 and 5 (parameters OEI-w_{13}, OEI-w_{25}, respectively);
7. Assessment of the total number of paracetamol tablets taken (one tablet = 500 mg) starting from day 1 at Visit 3 and 5 (parameters PARACETAMOL-w_{13} and PARACETAMOL-w_{25}, respectively);
8. Assessment of the total number of NSAID tablets taken starting from day 1 at Visits 3 and 5 (parameters NSAID-w_{13} and NSAID-w_{25}, respectively);
9. The parameter JSN of the target knee joint at Visit 5 of the open study compared to the basal value on Visit 0 of the IA/PAAG-SI/OA/2019 study retrospectively.

All performance parameters will be analyzed among all patients included in open study no. IA/PAAG-SI/OA/2020, as well as in subgroups of patients:

- who received only one course of injections in the placebo-controlled study IA/PAAG-SI/OA/2019;
- those who received two courses of therapy – both in the placebo-controlled and at Visit 1 (and as per the indications at Visit 2) of the open study;
- those who received two courses of therapy – both in the placebo-controlled and at Visit 3 (and as per the indications at Visit 4) of the open study.

Inclusion criteria

The study will include patients who meet all these criteria:

1. Men and women over 50 years of age;
2. Signed informed consent form for the study participants;
3. Verified gonarthrosis according to ACR criteria (knee pain in combination with one of the following signs: age over 50 years, crepitation in the joint or morning stiffness in the joint lasting less than 30 minutes in combination with radiological signs of gonarthrosis);
4. II-III radiological stage of gonarthrosis according to the Kellgren-Lawrence classification with a predominant lesion of the medial tibiofemoral section of the knee joint;
5. Completion of participation in the IA/PAAG-SI/OA/2019 clinical trial in the group with NOLTREX™ medical device through Visit 5 (25 weeks).

Non-inclusion criteria

Patients cannot be included in the study if they have at least one of the following criteria for non-inclusion:

1. Pregnancy or breast-feeding;
2. History of injury or surgery on the target knee joint;
3. Instability of the target knee joint;
4. Microcrystalline arthropathies (according to anamnesis and taking into account clinical manifestations);
5. Systemic inflammatory diseases (rheumatoid arthritis, systemic lupus erythematosus, etc.);
6. Seronegative spondyloarthritis and reactive arthritis;
7. Increasing the level of rheumatoid factor;
8. Increased uric acid level > 360 mmol/l;
9. Intra-articular injection into the target knee joint:
    - hyaluronates – within past 12 months before the patient is included in the study;
    - other synovial fluid endoprostheses (other than NOLTREX™ in the IA/PAAG-SI/OA/2019 study) within past 24 months;
    - glucocorticosteroids – within 1 month before inclusion in the study;
    - NSAIDs - intra-articular administration at any time in the anamnesis.
10. Systemic painkillers (NSAIDs, opioid analgesics) within 1 week before the Visit 0;
11. Effusion in the target joint;
12. The presence of inflammation or infection in the target joint, synovitis;
13. The need for stable use of glucocorticosteroids in any dosage form;

14. Use of paracetamol within 48 hours before the Visit 0;
15. A positive blood test result for one or more of the following infections: HIV, viral hepatitis B and C, syphilis;
16. Severe liver pathology, defined as an increase in the level of one of the indicators: ALT, AST, ALP, total bilirubin, GGTP more than 3 times compared to the upper limit of the norm;
17. Kidney diseases with glomerular filtration rate when evaluated using the Cocraft-Gault formula less than 60 ml/min/1.73 m2 (chronic kidney disease stages III–V);
18. Clinically manifested coxarthrosis;
19. Severe decompensated chronic or acute diseases and other conditions or other causes that, in the opinion of the research doctor, may hinder the patient's participation in the study or affect the results of the study;
20. Participation in any other clinical trial other than the IA/PAAG-SI/OA/2019 trial within past 90 days prior to inclusion in the study.

Exclusion criteria

In the following cases, patients will be excluded from the study:

a. The Ethics Committee, regulatory authorities, or the Sponsor will terminate the study or participation in the study of this clinical center for any reason;
b. The investigator decided that the patient should be excluded in the interests of the patient;
c. Withdrawal of informed consent (unwillingness of the patient to continue participating in the study);
d. Serious deviation from the research Protocol;
e. Erroneous inclusion (for example, the patient was included in violation of the Protocol's inclusion/non-inclusion criteria);
f. The patient receives/needs additional treatment that may affect the outcome of the study or the patient's safety (for more information, see the section "Prohibited concomitant therapy");
g. Injury to the target knee joint;
h. Other conditions or events that, in the opinion of the research doctor, require the patient to be excluded from the study.

If patients included in the study are found to have reasons for completing the study prematurely, they are excluded from the study at the stage of identifying these reasons. Each case of premature completion of the study by the patient or withdrawal of the patient from the study must be documented with the mandatory indication of the reason for premature completion/withdrawal from the study, as well as reporting to the Sponsor within 7 business days.

Prohibited concomitant therapy

1. Glucocorticosteroids in any dosage form;

2. Any intra-articular and periarticular injections;

3. Use of NSAIDs and painkillers that are not approved by the Protocol, including local ones (with the exception of paracetamol and NSAIDs allowed by the Protocol in case of ineffectiveness of paracetamol);

4. Use of paracetamol at a dose of more than 4000 mg per day;

5. Use of one of the Protocol-approved NSAIDs in doses exceeding the permitted doses (permitted drugs and doses: diclofenac potassium 50 mg 2 times a day, diclofenac sodium tablets 75 mg 2 times a day, naproxen tablets 500 mg 2 times a day, naproxen sodium tablets 550 mg 2 times a day, meloxicam tablets 7.5 mg once a day, celecoxib tablets 200 mg 2 times a day);

6. Use of a combination of paracetamol with NSAIDs or a combination of two or more NSAIDs;

7. Surgical interventions and arthroscopies on the target knee joint.

Justification of the sample size

This open-label MD NOLTREX™ safety assessment study includes eligible and non-eligible patients who received MD NOLTREX™ as part of the IA/PAAG-SI/OA/2019 study. Therefore, no formal calculation of the sample size was performed. The maximum expected number of study participants is the number of patients who were randomized to the MD NOLTREX™ group in the IA/PAAG-SI/OA/2019 study, i.e. 72 patients.

Blinding, randomization

This study is planned as an open-label study in a single group with subsequent division into subgroups depending on the actual need for treatment. In this regard, the Protocol does not provide for blinding and randomization.