A Two-Phase, Multicenter, Randomized Study Comparing Autologous Protein Solution (APS) with Hyaluronic Acid (HA) Intra Articular Injections in Patients with Knee Osteoarthritis (OA)

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Primary ObjectiveThe primary objective of this study is to determine whether nSTRIDE APS is superior to HA in mean Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) LK 3.1 pain score (change from baseline to 12 months post-...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Joint disorders
Study type	Interventional

Summary

ID

NL-OMON55437

Source
ToetsingOnline

Brief title
PROGRESS V

Condition

- Joint disorders

Synonym
arthritis in the knee, cartilage wear in the knee

Research involving
Human

Sponsors and support

Primary sponsor: Zimmer Biomet
Source(s) of monetary or material Support: Zimmer Biomet

Intervention

Keyword: Knee, nSTRIDE Autologous Protein Solution, Osteoarthritis, Pain relief

Outcome measures

Primary outcome

The Western Ontario and McMaster Universities Osteoarthritis Index using the Likert scale, Version 3.1:

The WOMAC LK 3.1 questionnaire is a validated tool used for assessing knee pain, stiffness, and function. The WOMAC LK 3.1 has 24 items; 5 items assessing knee pain, 2 items assessing knee stiffness, and 17 items assessing physical function. Each item is answered on a 5-point Likert scale, with grading from 0 (none or never) to 4 (extreme or always). A higher score indicates worse pain, stiffness, or functional limitation.

Secondary outcome

The EuroQol-5 Dimensions

The EuroQol-5 Dimensions (EQ-5D) is a validated instrument which assesses an individual*s current health status and heath related quality of life. The EQ-5D-3L descriptive component assesses five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression over three levels of severity. The EQ visual analogue scale (EQ VAS) assesses the respondent*s self-rated overall health state on a scale from 0 (worst imaginable health state) to 100 (best imaginable health state).

Numeric Rating Scale

The NRS is a validated measure of knee pain. The NRS is an 11 point Likert type scale anchored by 0 *no pain* and 10 *worst possible pain*. Subjects rate their average pain over the last 48 hours.

Patient Preference Questionnaire

Patient preferences are concerned with determining patient-related factors such as patients* adherence to treatment, patients* satisfaction with treatment, and health outcomes. Patient preferences will be measured utilizing questions to elicit patients* preferences following their knee OA treatment.

Resource Utilization and Costing

Health economics will be evaluated throughout the study. Healthcare resource utilization for each subject will be recorded to capture information about healthcare costs following index treatment with nSTRIDE APS or HA and follow-up.

Study description

Background summary

Osteoarthritis (OA) is a degenerative and disabling articulating joint disease that affects both younger, more active patients (e.g., patients with trauma or who have prolonged participation in highly demanding sports) and the elderly. The disease is progressive and debilitating, eventually resulting in pain that may be so severe that restive sleep is impossible, along with life-altering loss of function.
Inflammatory and catabolic cytokines are strongly implicated in the OA degenerative process. Inhibiting their action may be beneficial clinically. Anti-inflammatory and anabolic cytokines found in and concentrated from whole blood may reduce or reverse the degenerative process. Autologous Protein Solution (APS), produced using the nSTRIDE APS Kit, contains concentrated levels of anti-inflammatory cytokines and anabolic cytokines, associated with

cartilage genesis. APS is designed to halt and potentially reverse the OA disease process by rebalancing cytokine activity.
The study proposed here builds upon decades of research into the causes of OA. This study is designed to determine whether rebalancing of cytokines with APS prepared using the nSTRIDE APS Kit as suggested by OA literature, finally yield an effective treatment for early to moderate OA of the knee that targets the causes of this painful and debilitating disease.

Cell assay studies demonstrated that APS inhibits deleterious enzyme production, consistent with the proposed mechanism of action. In addition, animal studies provided safety and efficacy data showing that APS reduces pain and improves function in horses with OA.

Following these studies, an open-label feasibility study of a single intra-articular injection of APS in subjects with OA of the knee was conducted in The Netherlands. The primary study objective was to assess safety. Nine of 11 subjects (seven male) reported 22 AEs (total). There were no deaths or Serious Adverse Events (SAEs). The investigator deemed every AE to be unrelated to the device. All were rated *mild* in severity. The most frequent AEs were joint effusion (n=9) and arthralgia (n=5). These were most likely related to the injection procedure and not to the device per se. One subject withdrew from the study subsequent to continued knee pain.

Western Ontario and McMaster Universities Osteoarthritis index using the Likert scale, Version 3.1 (WOMAC LK 3.1) scores improved significantly by the second week post-injection and continued to improve as the study progressed. By 12 weeks, 80% of both physicians and subjects rated the condition under investigation as *very much* or *much* improved as determined by the Clinical Global Impression - Change scale (CGI-C). At 26 weeks follow-up, the Outcome Measures in Rheumatology - Osteoarthritis Research Society International (OMERACT-OARSI) high pain responder criteria were met by 8 of 11 subjects (73%). At final follow-up, mean WOMAC pain reduced by 72% (89% in the 8 responders). WOMAC stiffness and function scores improved by 53% and by 68%, respectively. After study completion, a long-term analysis was performed at an average of 78 weeks (18 months) after subjects were enrolled. Six of the 11 subjects returned WOMAC and Patient Global Impression-Change (PGI-C) questionnaires and reported pain reduction from baseline measures. The data presented here suggest that the treatment is safe and show a complication profile that is mild and consistent with similar treatments. A single injection of APS for treatment of early to moderate knee OA led to symptom improvement over the study course.

After completion of the open-label feasibility study, a multicenter, prospective, randomized, double-blind, saline-controlled trial was conducted at three enrolling centers in Europe. A total of 46 patients with unilateral OA (K-L 2 or 3) knee pain were randomized into two groups. Group 1 (31 patients) received a single ultrasound-guided injection of APS, and Group 2 (15 patients)

received a single saline injection. Patient reported outcomes and AEs were collected at 2 weeks, 1, 3, 6, and 12 months post-injection. The patients and evaluators were blinded to the treatment allocation, and the outcome was evaluated through Visual Analog Scale (VAS), WOMAC, and Knee Injury and Osteoarthritis Outcome Score (KOOS) scores. Imaging evaluation was also performed with X-Ray and Magnetic Resonance Imaging (MRI) before and after the treatment (12 months and 3 and 12 months, respectively).

The demographics were similar between the groups. The change from baseline to 12 months in WOMAC pain score was 65% in Group 1 and 41% in Group 2 ($p = 0.02$). Additionally, VAS pain improvement was 49% in Group 1 and 13% in Group 2 ($p = 0.07$). WOMAC function change from baseline to 12 months was 55% in Group 1 and 45% in Group 2 ($p = 0.38$). The safety profile was also positive, with no significant differences in frequency, severity, or relatedness of AEs between groups. No procedure- or device-related SAEs were reported.

This pilot study provides evidence to support the safety and clinical effectiveness of a single intra-articular injection of this novel autologous therapy. Long-term follow-up is ongoing, and this positive results obtained against saline has been used to plan this confirmatory trial that will be conducted to further substantiate these findings against those offered by other treatments for knee OA.

Several other studies are ongoing to evaluate clinical outcomes of nSTRIDE APS.

Study objective

Primary Objective
The primary objective of this study is to determine whether nSTRIDE APS is superior to HA in mean Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) LK 3.1 pain score (change from baseline to 12 months post-injection).

Secondary Objectives
Secondary objectives of this study include determining whether nSTRIDE APS is superior to HA in improving patient reported outcomes including pain, function, stiffness, and quality of life in subjects with early to moderate symptomatic OA.
A long-term follow-up phase (LTFU) will examine the superiority of nSTRIDE APS in the duration of the treatment effect, injection frequency, patient preferences, healthcare resource utilization, and associated costs.
Safety of nSTRIDE APS will be compared to HA following intra-articular knee injections in subjects with early to moderate symptomatic OA.

Study design

The study will compare the efficacy of nSTRIDE APS injection to HA in patients with symptomatic OA in one knee, who have failed at least one prior conservative OA therapy (e.g. physiotherapy, simple analgesics). This will be done using a double-blind, multicenter, Randomized Controlled Trial (RCT) with study subjects receiving either a single injection of nSTRIDE APS or HA. The primary efficacy measure will be pain as measured utilizing the WOMAC LK 3.1 scale; other measures of efficacy will include function, stiffness, and quality of life. In addition to clinical efficacy measures, safety will be assessed by tracking adverse events (AEs).

Anatomical changes will be evaluated by radiographs (X-ray). In the LTFU (12 - 60 months), the study will evaluate treatment durability, patient preferences, and treatment cost effectiveness over time. During the LTFU, safety will be assessed by tracking the occurrence of AEs of interest (only).

Patients will be followed-up at 1, 3, 6, and 12 months after the initial injection, and thereafter LTFU will happen bi-annually until 36 months after injection and shift to annually until 60 months post initial injection. After each subject completes the 12 months follow-up visit, only subjects will be blinded to the treatment allocation, resulting in a single-blinded design. At that time, if the subject experienced no major safety event due to the first injection, as determined by the investigator, the subject may choose to enter the LTFU and request additional injections of their assigned treatment as frequently as needed.

During the LTFU, subjects may also elect to cross over to the other treatment arm and receive an injection of APS or HA, depending on their original randomization allocation. Subjects may only cross over from their originally assigned treatment group to the other treatment group one time during the study.

Intervention

Intra-articular injections of nSTRIDE APS or Synvisc One (Hyaluronic Acid

Study burden and risks

Benefits
The potential benefit of nSTRIDE APS in the treatment of knee OA includes symptomatic pain relief, knee function restoration, and anatomical improvement within the joint.
The potential benefit of HA in the treatment of knee OA includes symptomatic pain relief within the joint. In addition, the study could provide useful information for the future that may help researchers come up with a new treatment for OA of the knee.
The potential benefits for a subject depend on the study randomization and the

subject*s choice to cross over between treatment groups.

Risks
Blood Draw
The possible risks of drawing blood from the patient*s arm include pain, bleeding, bruising, blood clots and complications from blood clots such as the clot moving to a different part of the body causing harm. Other possible risks include infection at the injection site, fainting, scar tissue formation, or nerve/nervous system damage. These risks are not unique to this study and may occur with any blood draw procedure.

Knee Injection
The possible risks with the knee injection include worsening of pain and/or knee function, effusion (fluid buildup in the knee joint), and infection. These risks are not unique to this study and may occur with any knee injection procedure. There are no known specific risks of the investigational device itself. Mixing up blood and/or APS samples from multiple donors presents a risk of injecting the APS produced from one patient into another patient. This would be associated with a possible inflammatory reaction or disease transmission to the patient receiving the injection.
The most common side effects observed with Synvisc One injections are pain, swelling, heat, redness and/or fluid build-up around the knee. In a medical study less than 6% of patients experienced these side effects, which were generally mild and did not last long. The patients need to tell the doctor if they have had an allergic reaction, such as swelling of the face, tongue or throat, respiratory difficulty, rash, itching or hives to Synvisc or any hyaluronan-based products. Allergic reactions, some which can be potentially severe, have been reported during the use of Synvisc-One.

X-ray
There will be exposure to radiation from the X-rays that need to be taken for the screening and during some of the follow-up visits. The radiation used during the study may lead to damage to the patients health. However, this risk is small.

MRI
The magnetic field used by MRI scanners may cause implanted medical devices that contain metal to malfunction or heat up during the exam. Any loose metal object may cause damage or injury if it gets pulled toward the magnet. Dyes from tattoos can cause skin irritation. Medication patches can cause skin burns. Prolonged exposure to radio waves during the scan could lead to slight warming of the body. Patients may have some anxiety due to being in a confined space. The MRI technician will direct patients to reduce the possibility of these risks.

Questionnaires
There is a risk for the patients of being uncomfortable answering questions.

While completing the questionnaires, they may tell the research staff that they feel uncomfortable or do not wish to answer a particular question.

Confidentiality
There is a risk of loss of confidentiality.

Other Risks
There may be unforeseen risks that cannot be predicted.

The patient is asked to report to the doctor any illnesses or change in their health, even if they do not think it is related to the injection. The patient will be informed as soon as possible about any new information relating to the procedures involved in this study.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Male or female at least 18 years of age at time of screening.
2. Willingness and ability to comply with study procedures and visit schedules and able to follow oral and written instructions.
3. A standing knee radiograph showing a K-L grade of 2 to 4 and an absence of severe osteoarthritis (defined as advanced stage osteoarthritis, including large osteophytes, chronic fractures or bone remodeling, severe deformity or bone attrition, and/or bone-on-bone contact indicative of severe osteoarthritis/full thickness cartilage loss), as confirmed by the central imaging laboratory.
4. Body mass index <= 40 kg/m2.
5. A WOMAC LK 3.1 pain subscale total score >= 9 and <= 19.
6. Has undergone at least one prior conservative OA treatment (e.g. physical therapy, simple analgesics).
7. Signed an ethics committee-reviewed and approved informed consent form.

Exclusion criteria

1. Presence of clinically observed active infection or severe inflammation in the index knee joint or skin disease/breakdown or infection in the area of the planned injection site of the index knee.
2. Presence of symptomatic OA in the non-study knee at screening; if unclear then the WOMAC LK 3.1 pain sub-scale for the non-index knee must be <= 5.0.
3. Diagnosed with rheumatoid arthritis, Reiter*s syndrome, psoriatic arthritis, gout, ankylosing spondylitis, or arthritis secondary to other inflammatory diseases; Human Immunodeficiency Virus (HIV), viral hepatitis; chondrocalcinosis, Paget*s disease, or villonodular synovitis.
4. Diagnosed with leukemia, known presence of metastatic malignant cells, or ongoing or planned chemotherapeutic treatment.
5. Disease of spine, hip or other lower extremity joints judged by the investigator to be contributing to the pain in the index knee (e.g. sciatica, nerve pain, hip OA). Note: Patients with contra-lateral knee replacement, or hip replacement in either hip, may be enrolled provided there is sufficient pain relief after knee replacement or hip replacement that analgesics are not required.
6. Untreated symptomatic injury of the index knee (e.g., acute traumatic injury, anterior cruciate ligament injury, clinically symptomatic meniscus injury characterized by mechanical issue such as locking or catching).
7. Presence of surgical hardware or other foreign body intended to treat arthritis or cartilage-related pathology in the index knee. Note: this does not include small hardware (e.g. screws).
8. Presence of venous or lymphatic stasis in the index leg.
9. Orally administered systemic steroid use within 2 weeks prior to screening.

10. Planned/anticipated surgery of the index knee during the study period.
11. Major surgery (e.g. osteotomy) of the index knee within 12 months prior to screening.
12. Minor surgery (e.g. shaving or arthroscopy) of the index knee within 6 months prior to screening.
13. A history of local anesthetic allergy.
14. Use of systemic immunosuppressants within 6 weeks prior to screening.
15. Currently on anticoagulant therapy, such as Warfarin, vitamin K antagonists, direct thrombin inhibitors, or factor Xa inhibitors or on potent anti-platelet therapy, such as GPIIb-IIIa antagonists, Par-1 antagonists or dual anti-platelet therapy; i.e. an ADP receptor antagonist in combination with aspirin.
16. Any documented clinically significant degree of cognitive impairment or other condition, finding, or psychiatric illness at screening which, in the opinion of the investigator, could compromise patient safety or interfere with the assessment of the safety and treatment effects of the study injection.
17. Pregnant or nursing mothers or women planning to become pregnant during the time they will be participating in the study.
18. Known hypersensitivity (allergy) to hyaluronan (sodium hyaluronate) preparations.
19. Previously documented failed treatment with nSTRIDE APS or Synvisc One.
20. Known drug or alcohol dependence currently or within the last year.
21. Use of any investigational drug or device within 30 days prior to screening.
22. Use of any investigational biologics within 60 days prior to screening.

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Single blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	15-03-2018

Enrollment:	15
Type:	Actual

Medical products/devices used

Generic name:	nSTRIDE APS Kit
Registration:	Yes - CE intended use

Ethics review

Approved WMO Date:	24-11-2017
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	08-05-2019
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	20-11-2019
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
ClinicalTrials.gov	NCT03182374
CCMO	NL61346.068.17