The Effectiveness and Safety of Triple 2ml Hyaluronic Acid Intra-articular Injection (Suplasyn®) in Managing Symptomatic Primary Osteoarthritis of the Knee in Real-life Practice: ESTIK Survey.

STUDY PROTOCOL

Main Investigator:

Pavel Martinek, MD

SUMMARY

Official Title

The Effectiveness and Safety of Triple 2ml Hyaluronic Acid Intra-articular Injection (Suplasyn®) in Managing Symptomatic Primary Osteoarthritis of the Knee in Real-life Practice: ESTIK Survey.

Responsible Party/Sponsor

Mylan Institutional International
Thurgauerstrasse 40
8050 Zürich, Switzerland

Main investigator/Study Coordinator

Pavel Martinek, MD

Krnov Hospital (Czech Republic)

Study Officials/Investigators

Orthopeadists/Traumatologists

Review Board

All study materials have been approved by the Ethical Committee for Clinical Investigation of the Krnov Hospital (The Czech Republic).

Primary Outcome

To assess changes in clinical outcome of patients with OA recommended with a triple Suplasyn® 2ml injection for viscosupplementation.

Intended Intervention:

Suplasyn® 2ml during 3 weeks for the viscosupplementation of the knee.

Study Type:

Observational, non-interventional, international and multicenter study.

Study Design

Observational Model: Case-Only; Time Perspective: Prospective study

Condition for Study

Osteoarthritis of the Knee.

Study sample

Patients over 18 years old with Primary Knee Osteoarthritis (Kellgren's grades I to III) without effusion.

Data Monitoring

Clever Instruments S.L. will be in charge of logistic and clinical trial monitoring.

Calendar

Study Start Date: June, 2014 – September, 2014

Study Completion Date: December, 2014 - March, 2015

Overall study period will be of 6 months, approximately.

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1 GENERAL INFORMATION

Official Title

The Effectiveness and Safety of Triple 2ml Hyaluronic Acid Intra-articular Injection (Suplasyn®) in Managing Symptomatic Primary Osteoarthritis of the Knee in Real-life Practice: **ESTIK Survey**.

Responsible Party/Sponsor

Mylan Institutional International
Thurgauerstrasse 40
8050 Zürich, Switzerland

Main investigator

Pavel Martinek, MD
Krnov Hospital (Czech Republic)

Study Officials/Investigators

Orthopeadists/Traumatologists

Duration of the Study

Intended duration: 6-9 months

Data will be provided by investigators from retrospectively results observed in patients who were previously recommended with viscosupplementation with Suplasyn® between June-September 2014 and December2014-March 2015.

The assignment of the patient to a particular therapeutic strategy should not be decided in advance by this protocol but falls within current practice and the use Suplasyn® was clearly separated from the decision to include the patient's data in this study.

2 BACKGROUND

Osteoarthritis (OA) of the knee is a painful and disabling condition that is becoming more prevalent in patients over 50 years of age that results in symptoms in 10% of people older than 55 years which severely impair up to a quarter overall these patients. (1)

OA is generally treated using conservative measures at initial phases of the disease (2), more frequently with analgesics, topical and oral non-steroidal anti-inflammatory drugs (NSAIDs). However, their long-term use of these agents might different organic risks such as complications in hepatic, cardiovascular, gastrointestinal or renal systems.

In recent years, viscosupplementation has been more often used as a therapeutic modality for the management of knee OA (3,4). Intra-articular injections of Hyaluronic Acid (HA) have shown good safety profiles and efficacy for treating knee OA pain. Recent clinical data have demonstrated that anti-inflammatory and chondroprotective effects of HA viscosupplementation are associated with a significant and maintained reduction on pain up to 14-26 weeks after injection while improving patients' function (5-7), results which show a clear difference compared to the short-term effect of other interventions such as pharmacological treatment with NSAIDs and/or corticosteroid injections.

Viscosupplementation

Viscosupplementation is intended as an alternative of HA's degradation in the synovial fluid of patients affected with knee osteoarthritis by the administration of exogenous HA through intra-articular injection. Viscosupplementation is recommended (6) for the treatment of knee OA by the current Osteoarthritis Research Society International (OARSI) Guidelines and previous practice guidelines (4,8-11) and despite that in other reference documents such as current Clinical Practice Guidelines (CPG) of the American Academy of Orthopaedic Surgeons (AAOS) is not included as a main recommendation(12), this makes reference to published evidence reporting significant improvements on OA symptoms after viscosupplementation. Because of the lack of evidence and the possible discrepancies across studies, conclusion should be as that viscosupplementation may be of significant benefit for *some* patients (13).

Administration of an exogenous HA cannot explain long-term reduction of symptoms, considering that HA has short half-life. HA has biological effects on the inflammatory cells and

stimulates HA production by synovial cells. Its key molecular role in joints' biomechanics explains how a reduction in its concentration and molecular weight greatly alters the properties of synovial fluid, causing cartilage damage and worsening osteoarthritis symptoms (14). Treatment with exogenous HA attempts to restore the elasticity and viscosity of synovial fluid to normal levels, resulting in pain reduction and functional improvement. Different studies have also confirmed that HA interacts with mediators of inflammation and matrix turnover in joint cells. HA has also a biosynthetic chondroprotective effect (15-20).

Identification of CD44, a glycoprotein expressed on the cell surface of chondrocytes, may explain HA interaction with chondrocytes since CD44 is considered a HA's receptor at the chondrocyte cell surface so the provision of exogenous HA into articular cartilage is facilitated through this receptors (21,22).

Triple versus Single Injection

Study assessing five different dosing regimens of viscosupplementation suggests that 3 x 2ml injections one week apart are efficacious and well tolerated (25). Multidosage viscosupplementation (3-6 injections) still remains a golden standard if choosing the viscosupplementation as a treatment for knee OA.

The single injection represents a new alternative to the three injections treatment regimen with documented statistically and clinically significant improvements (30) both in pain and physical function in patients with knee OA (23), however its efficacy, safety and long-term effect should be studied in order to establish if this newly introduced approach is comparable with the proven triple injections regimen (26).

Suplasyn® 2ml and 1-shot (6ml)

Suplasyn® is a low-intermediate molecular weight HA (500-1000 kDa) product which is safe and well tolerated (24). Suplasyn® is a CE marked Medical Device (CE0473) and is approved by in several countries for the treatment of pain associated with knee osteoarthritis. The recommended treatment regimen for the treatment of knee osteoarthritis pain is one 2 ml intra-articular injection per week for three consecutive weeks (28) or a single injection of 6ml (33,34).

Both presentations are supplied as pre-filled syringes containing 20mg/2ml of sodium hyaluronate which is administered according to a dosing regimen of one injection per week for three to six consecutive weeks.

Suplasyn® has shown to be more effective than placebo on pain and function in knee osteoarthritis (24) with similar efficacy when compared to NSAIDs (27) and with maintained effects over the long term (28). These studies also demonstrated its excellent safety profile.

Suplasyn® has also demonstrated useful health economic benefits with a reduction in the costs of management of knee OA during the 26-weeks following the course of viscosupplementation (29).

Study Rationale

The current study is designed to assess the effectiveness and safety of Suplasyn® 2ml injections in a 26-week, international, multicenter, non-interventional observational study of patients recommended with one 2 ml intra-articular injection of Suplasyn® per week for three consecutive weeks with for the treatment of knee osteoarthritis. The intention is to assess the efficacy and safety of the treatment in real-life practice. Our primary target is to obtain and verify long-term outcomes from a naturalistic primary care experience.

Rationale for using viscosupplementation is to restore the protective viscoelasticity of synovial hyaluronic acid, decrease pain and improve mobility. Immediate benefit of viscosupplementation is the relief of pain while long-term benefits results are believed to include the return of joint mobility by the restoration of trans-synovial flow and the metabolic and rheological homeostasis of the joint (31). Short duration of HA within the joint does not fully explain the indisputable long-term clinical efficacy seen in practice (32).

In this case, it is appropriate to evaluate, under real-life conditions, the short-term and long-term effectiveness of triple Suplasyn® 2ml intra-articular injections and to how the extended treatment regime may impact patient satisfaction or treatment safety.

3 OBJECTIVES

3.1 Main Objective

To assess changes in clinical outcome of patients with OA recommended with a triple Suplasyn® 2ml injection for viscosupplementation.

3.2 Secondary Objectives

- To evaluate the safety profile and adverse events (AEs) of Suplasyn® 2ml injections.
- To evaluate the concomitant consumption of permitted rescue medications (analgesics, NSAIDS) throughout the study.
- To evaluate characteristics of the beneficiary population (Intended to treat).

4 SOURCE OF INFORMATION

All data will be provided by the researcher and by the patients who assist to the orthopedist/traumatologist with a symptomatic knee OA and according to physician criteria could be recommended with viscosupplementation with Suplasyn®.

5 STUDY DESIGN

5.1 Study Type:

Observational, non-interventional, international and multicenter study.

5.2 Study Design

Observational Model: Case-Only; Time Perspective: Prospective study

5.3 Study population

Main Selection Criteria:

Patients consulting to the orthopedist/traumatologist to primary care centers and according to specialist evaluation are susceptible of been recommended with viscosupplementation through a intraarticular

injection of Hyaluronic Acid (Suplasyn®) once per week during a 3 three weeks period. All patients who received the specific recommendation are includable for study.

Eligible patients:

- Ages: 18 years to 85 years
- Genders: Both
- Accepts Healthy Volunteers: No
- Study Population: Patients with symptomatic primary knee OA, with radiological grades I to III (according Kellgren-Lawrence Score) and without clinical effusion at time of inclusion.

All patients whose data will be recorded should have been informed by the researcher of the nature of the study and that his/her participation is voluntary. Registration of their data has to be started as long as he/she has signed the consent form and has clearly understood all the study procedures. Consent form could be obtained orally as long as the researcher asks for a witness to sign (i.e. nurse or patients' relative).

Inclusion Criteria:

- Age between 18 and 85 years old
- Primary osteoarthritic degeneration of the knee (patients with documented knee osteoarthritis)
- Patients fulfilling criteria for primary knee osteoarthritis, radiological grades I–III (Kellgren–Lawrence) (35) and joint space width ≥2 mm
- Patients without clinical effusion at baseline
- Fully aware of study procedures
- Willing to participate in all study processes and assessments

Exclusion Criteria:

- Allergic reactivity to hyaluronic acid
- Current knee infection, infection around injection site or any skin disease
- Pregnancy or lactation
- Participating in other clinical trial
- Any reason that may jeopardize the collection of data (patient likely to be lost-to-follow up)

5.4 Duration of Study Period and Follow-up

All patients will be followed during 26 weeks after the first injection with Suplasyn®. The study end date will be considered when the last patient has completed the observation period.

5.5 Intended Intervention

- 2ml of Hyaluronic Acid Intra-articular Injection (Suplasyn®) on the affected knee at baseline (Day 1), one week (Week1) and two weeks (Week 2) after initiation of the viscosupplementation VS treatment.
- Paracetamol, NSAID or analgesics are allowed as a rescue medication if unbearable pain had not improved after at least 1 hour rest.
- Glucosamines and chondroitines or other slow-acting drugs for osteoarthritis (i.e. diacerhein or avocado/soybean unsaponifiables) are allowed if at a stable dosage for 3 months or more. Consumption of rescue or other medication is recorded in a patients data form.

5.6 Sample size calculation

As it is an observational study of descriptive nature, a minimum margin to obtain statistical significance has not been settled. An estimated sample of 300 patients that have could be recommended during the established period for inclusion of data is considered.

6 MAIN VARIABLES

6.1 Main Variables for Evaluation

- Knee pain symptoms
- Physical function
- Quality of Life (QoL)
- Safety (Adverse Events)
- Compliance with treatment

6.2 Measures

The quality-of-life questionnaires that are completed by the patient with no input from the healthcare personnel may be more objective, because they more faithfully reflect the experience of the patient. In

knee osteoarthritis treatment, the self-assessed Oxford Knee Score (OKS) and Visual Analog Scale (VAS) are widely used.

☑ **Patients Outcome assessed with the Oxford Knee Score (OKS)** (39): Describes any changes from baseline over a period of 6 months; the study subjects will complete personally the (OKS) questionnaire at baseline, 1 and 6 months following the viscosupplementation of the knee.

This is a "self-administered" questionnaire. It has 12 items on daily activities, which the patient must answer without help from healthcare personnel. Each item is scored from 1 (normal function) to 5 (extreme difficulty). The global score is the sum of the 12 item scores. Therefore, the best possible score is 12 and the worst possible score is 60. Partial scores have also been defined, for pain (questions 1, 4, 5, 8 and 9) (5–25 points), range of motion (questions 2, 3, 7 and 12) (4 – 20 points) and walking (questions 4, 6, 9, 10 and 11) (5–25 points).

The OKS is a disease-specific, purpose built, high performance instrument for evaluative research in knee osteoarthritis clinical trials. It assesses the outcome, as judged by the patient. This is of value in the large multicenter trials. (40-42) **The OKS** questionnaire may be compared with others that have been successfully applied to the treatment of osteoarthritis, but it has the advantage over assessments such as the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and the Arthritis Impact Measurement Scales (AIMS), in that it is intended specifically for use with knee surgery and knee OA treatment alone, and is simpler and quicker to process (37,38).

☑ **Pain evaluated with the Visual Analog Scale (VAS**)

The (VAS) will describe the change in the level of knee pain from baseline following viscosupplementation of the knee. (Time Frame: The study subjects will complete the (VAS) at baseline, 1 and 6 months following the viscosupplementation of the knee.)

The (VAS) responses are expressed on a 100 mm line, with 0 representing no pain and 100 mm representing the worst pain possible. (43,44) The patient places a mark across the line representing where their perceived pain lies, from no pain to severe pain; measured at rest (night) and during daily activities.

☑ **Safety assessment**

Adverse events observed by the doctors or reported by the patients spontaneously or following a non-leading questions, will be collected on patient data form. Particular attention will be paid to local painful

reactions at the injection site, post-injection reactions (i.e. effusion, skin rush, swelling, warmth) and acute pseudoseptic arthritis (36).

☑ **Compliance** will considered based on the a posteriori analysis of the number of visits and number of doses applied for each patient. A discontinuation is defined as an interruption of recommended regimen of three weekly doses at any point of that period.

7 STATISTICAL ANALYSIS

All data will be analyzed with the statistical software SPSS-Windows.

7.1 Descriptive Statistics

All variables recorded will be descriptively analyzed. Categorical variables will be presented as frequencies and proportions. Quantitative factors (continuous/ordinals) will be also presented as central tendencies indexes (mean, median) and dispersion measures (standard deviation, minimum and maximum values).

7.2 Study Objectives

Primary outcome is to assess in real-life practice the effectiveness of viscosupplementation treatment using triple Suplasyn® 2ml injections (20 mg/2ml sodium hyaluronate, 500-1000kDa MW). The primary efficacy endpoint is the change from baseline in the Oxford knee score assessing the **function** of the OA knee at 4 and 26 weeks and the change from baseline in the patient-rated knee OA **pain** assessment (100 mm visual analogue scale/VAS) at 4 and 26 weeks.

Both scores obtained with the Oxford Knee Score and Pain VAS will be registered at 1 and 6 months following viscosupplementation of the knee.

Secondary objectives correspond to the evaluation of the **safety profile and adverse events** (AEs) of Suplasyn® 2ml injections, assessment of **concomitant consumption of permitted rescue medications** (analgesics, NSAIDs) throughout the study and the known the **characteristics of the beneficiary population** (intend-to-treat).

Continuous variables will be expressed as mean ± Standard Deviation (SD) while categorical binary variables will be presented as percentages.

Both primary and secondary objectives will be analyzed with tests for repeated measures to determinate the evolution of the variables throughout study visits. P values <0.05 will be considered as statistically significant.

7.3 Sample stratification

Sample could be stratified based on factors such as patients' characteristics (gender, age), Knee OA radiological characteristics, use of conventional medication (NSAIDS, corticosteroid injections), history of interventional treatment in the affected knee (open surgery, arthroscopy, arthrocentesis) and impairment associated with the perceived pain caused by the OA. These variables will be analyzed through statistic tests for independent measures.

8 ETHICAL CONSIDERATIONS

8.1 General Considerations

The present protocol will be conducted in full concordance with principles of the "Declaration of Helsinki" (Helsinki, 1964) amended by the 64th World Medical Assembly (Fortaleza, 2013), the Good Clinical Practice.

The ESTIK survey correspond to Post-Market Clinical Follow-up (PMCF) studies conducted using CE marked devices according to the Council Directive 93/42/EEC concerning Medical Devices (June 14th, 1993, last amended by Directive 2007/47/EC of the European Parliament and of the Council of on September 5th, 2007) which represents that Suplasyn® should be recommended following the Good Clinical Practice principles, thus to be use in the usual manner in accordance with the instructions for use (leaflet) supplied with the marketed products.

8.2 Evaluation of benefit-risk for patients during study

The participation in this study does not involve or represent an increased risk for patients and does not modify the usual therapeutic practices. Participants will be not subjected to additional or extraordinary diagnostic tests other than those normally indicated for these patients.

8.3 Safety Assessment

Adverse events observed by the doctors or reported by the patients spontaneously or following a non-leading questions, will be collected on patient data form. Particular attention will be paid to local painful reactions at the injection site, post-injection reactions (i.e. effusion, skin rush, swelling, warmth) and acute pseudoseptic arthritis. (36)

8.4 Patients Information Sheet and Consent Form

All patients will receive an information sheet with a description of the study and its procedures as well as a consent form to be signed. It is important to remark that all patients whose data will be recorded should be informed of the nature of the study and have to give their informed consent (or oral consent with signature of a witness, i.e. nurse or relative) for the collection of their data, since this project is an observational study thus the decision to include a patients in it must be considered after the recommendation of Suplasyn®.

8.5 Ethical Committee Evaluation

All study materials, including protocols and surveys, have been developed by Dr. Martinek, and have been approved by the Ethics Committee for Clinical Research of the Krnov Hospital (Czech Republic).

8.6 Data Protection

Researchers will guarantee the anonymity of each patients participating in the study and will protect his/her identity from third-parties or non-authorized figures.
No personal information which may allow identifying patients will be recorded. Patients' identity will be codified in the CRFs and only each researcher will have access to this data in cases of verification or clarifications.
All the data recorded in the surveys will be hosted in secured servers with restricted access, which are also subjected to Spanish Data Protection laws (database files are notified and registered at the Spanish Data Protection Agency) according the "Ley Orgánica 15/1999, 13 de diciembre de 1999".

8.7 Interference with researcher prescription habits

Suplasyn® should be recommended following the Good Clinical Practice principles, thus to be use in the usual manner in accordance with the instructions for use (leaflet) supplied with the marketed products.

The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the use of the medical device is clearly separated from the decision to include the patient in the study.

No additional diagnostic or monitoring procedures shall be applied to the patients and epidemiological methods shall be used for the analysis of collected data.

9 PRACTICAL CONSIDERATIONS

9.1 Work plan

All researches will have to register to be assigned with a personal id and password for access to study online surveys. Once the researcher has signed the *researcher commitment form* and have received a confirmation of his/her registration can proceed to the inclusion of data.

Patients will be selected from those who accomplish inclusion criteria, based on the consecutive sampling technique. Researcher will proceed to explain patient about the study and ask for a signature on the *consent form* prior to the inclusion.

It is important to keep in mind that the recommendation with Suplasyn® for the viscosupplementation of the affected knee is not conditioned to the development of the study or the inclusion of a specific patient in this study.

Data will be recorded by the researcher in an online electronic Case Report Form (eCRF) to which will access with their id and password. The online platform will assign to each patient an automatic and unique code which will allow registering his/her clinical information throughout all study visits for the later generation of a database and an analysis of the final results. The eCRF does not contain any patients' personal information and the researcher is committed to keep the access information and the content of the eCRFs in complete anonymity, besides the obligation to accomplish with the principles and laws applicable in his/her local context, being fully responsible for the truthful of the provided data.

- On **visit 1 (baseline)** patient will receive the first intraarticular injection of 2ml of Hyaluronic Acid - Suplasyn® in the affected knee following the product instructions leaflet and according to standard measures for these types of procedures. In this visit, patient will also have to complete the Patient eCRF which includes the OKS.
- On **visit 2 (administration of the second HA injection, one week after first injection)** and **Visit 3 (administration of the third HA injection, one week after second injection)** adverse events should be investigated. In case the researcher obtains as a response to the question

"How did you feel since your last visit" any adverse event since prior visit, the *Adverse Event Form* should be completed and sent to the study coordinator.

- **Visit 4 (1 month after injection):** Researcher will complete the eCRF corresponding to that visit by recording data on patient's consumption of any pharmacological treatment for pain during the previous month, recording data on frequency, dose and type of drug used. In this visit patient will have to assess his/her perceived pain with the VAS, grading the intensity of this symptom "during daily activities" and "at rest/at night".
- **Visit 5 (6 months after injection):** The procedure will be the same that on visit 4.

9.2 Interim and Final Reports

A final report will be developed based on the final results.

9.3 Dissemination of results

All data collected during this study will be used globally and not individually. Researchers who participated in the project will receive a copy of the final study report with the results obtained and this document shall be confidential.

Scientific publications and/or materials including conference presentations will be considered, always making explicit reference to the study.

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