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PILOT, OPEN NON-CONTROLLED TRIAL TO ASSESS THE FEASIBILITY OF IMPLEMENTING OBJECTIVE PARAMETERS AS PRIMARY ENDPOINTS IN A CLINICAL TRIAL WITH PATIENTS AFFECTED BY KNEE OSTEOARTHRITIS.

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ABSTRACT

Osteoarthritis (OA) is a disabling condition affecting more than one-third of people over 65 years of age. Studies on oral hyaluronic acid used to treat OA generally measure subjective parameters, such as visual analogue scales or quality of life questionnaires. As a result, objective measures are missing, and data validity is generally impaired.
Aim of this pilot study (performed in knee OA patients aged 50-70 years of both sexes) is to evaluate the feasibility of using objective tools as outcomes to evaluate improvements in knee mobility after a treatment with hyaluronic acid used by oral route.
Ultrasound and Range Of Motion measurements, objectively correlating changes in joint mobility with pain reduction, are proposed as primary objectives. Secondary objectives are focused on collecting data estimating the time and budget necessary to perform the main double-blind study randomized trial. These data may be both quantitative (such as enrolment rate per month, number of screening failures, and new potential outcomes) and qualitative (site logistical issues, patient reluctance to enrol, and interpersonal difficulties for investigators).Moreover, the pilot study should provide preliminary information on the efficacy of the investigational product.

Synopsis

Title: Pilot, open non-controlled trial to assess the feasibility of implementing objective parameters as primary endpoints in a clinical trial with patients affected by knee osteoarthritis.

Protocol code: Pilot OPRPH/0117/FS
Version: 1.0 (final) - 05/12/2017
Registry: www.ClinicalTrials.govNCT03421054

Acronym: :SMILE: **S**yalox, **M**ult**I**center, tria**L** to **E**valuate knee osteoarthritis
Logo:

Type: Interventional pilot study

Sponsor: RIVER PHARMA Srl
Viale Stazione, 6 – 26863 Orio Litta - Lodi (Italy)

CRO: OPERA CRO Srl
10 Cozia, 300209 Timisoara (Romania)

Rationale andResearch Hypothesis :

On 2014 the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) has suggested[8] as first step of pharmacological treatment for knee osteoarthritis (OA) a background therapy with chronic symptomatic slow-acting drugs for osteoarthritis (SYSADOAs). In this class[10-11] of natural compounds, hyaluronic acid (HA) has evidenced its efficacy after intra-articular (IA) administration in patient with mild to moderate knee OA with more than 137 studies reported in a recent meta-analysis[12]. On the other hand, the few studies regarding the oral administration of HA have demonstrated its efficacy in relieving knee pain but present several inconsistencies. We have recently updated the last published review[21] on efficacy and safety of HA oralformulation in knee OA until December 2017[22]. The critical issues emerging from this analysis are the following: different efficacy, end points, dosages and molecular weights between the studies; generally lowsample size population and short duration therapy (ESCEO recommend a chronic background therapy); prevalent use of subjective parameters (VAS, JKOM and JOA); symptoms measurement using an objective tool was performed in very few trials[28, 32-34] and was limited to ultrasound (US) and isokinetic dynamometer, often with ambiguous results and possible bias; no study has used actigraphy[41-42] to evaluate the composite measurement of pain and basic activities like walking or performing daily activities[43-33] or range of motion (ROM) to measure with a simple goniometer the knee joint movement amplitude[45]. We have planned to test in a new clinical trial the hypothesis that the oral administration of HMWHA for a period of 4 months would: i) reduce the pain in the affected knee at the end of the study period; ii) evidence a statistically significant difference versus a control population treated with placebo; iii) evidence the above mentioned improvement by both subjective measurements (VAS, QoL) and objective measurements (US, actigraphy and ROM). After the conclusion of the study period the patient should have the opportunity (even not mandatory) to enter in a follow up of 8 additional months. To test the above-mentioned hypothesis in a large randomized clinical trial (RCT) was extremely attractive from a scientific point of view, but can be a hazard (in terms of resources, money, time and management)[47] for our team of Investigators. For these reasons, we have asked for a grant by a pharma company producing the tested HMWHA and, on December 2018, we have planned to perform initially a pilot study in order to assess the feasibility of implementing US, actigraphy and ROM as objective measurements useful to correlate the improvement of the knee mobility with its pain reduction. In addition, the pilot study will assess the feasibility of the planned

recruitment monthly rate and the time and budget occurring, and it should give preliminary (but not exhaustive) efficacy data.

Objectives:

The primary objective is:

- to assess the feasibility of implementing Ultrasonography and Range of motion (ROM) as objective measurements to correlate the improvement of the knee mobility measured by these tools with the pain reduction of the affected knee evaluated using a subjective scale (VAS) in patients assuming nutraceutical containing HA.
- To evaluate the safety of the tested product

The secondary objectives of the trial are:

- to collect quantitative and qualitative data to assess the feasibility of the planned future main study for time and budget.
- to correlate the improvement of the US and ROM parameters and that evidenced by specific measurements of VAS (on moving and on pressing)

The explorative objectives of the trial are:·

Preliminary data on efficacy of the tested product.

- to assess the feasibility of implementing Actigraphy as objective measurements to correlate the improvement of the knee mobility with the pain reduction (optional).

Outcomes:

Primary efficacy outcome:

- Correlation between reduction in VAS (at rest) and ultrasonography parameters (i.e.. synovial effusion reduction)
- Correlation between reduction in VAS (at rest) and ROM improvement

Secondary efficacy outcomes:

- Correlation between reduction in VAS (on moving; on pressing) and US and ROM parameters.
- Number of enrolled patients per month, duration of enrolment, visit duration, measurement of end points, adherence to treatment.
- Information on patient reluctance to enrol, difficulty understanding the consent form, logistic issues at the site, interpersonal relationships among staff.
- QoL measured by the KOOS Questionnaire (Romanian version)
- Lequesne Algo-functional Index

Safety outcomes:

- AE/SAE (by asking to the patients during the visits and checking in the filled diary cards)

Explorative outcomes:

- Rescue medication use (paracetamol 500 mg). Correlation between reduction in VAS (at rest;

on moving; on pressing) and Actigraphy parameters

Design: Open non-controlled, single centre pilot study.

Disease: Knee osteoarthritis.

Inclusion criteria:

· Any gender and age from 50 to 70 years

· Symptomatic osteoarthritis (OA) of the knee with mild joint discomfort for at least 6 months prior to enrolment, following ACR criteria with history and physical examination[(44)]. Subjects diagnosed with
bilateral knee OA will be asked to specify the most affected knee at baseline, and this knee will be evaluated throughout the study period.

· Available confirmatory X-ray (performed within the previous 6 months) diagnosis (Kellgren/Lawrence score 2) at the evaluated knee joint[(45)].

· Subjects experienced pain for at least 15 of the 30 days prior to the start of the study.

· Signed informed consent
Compliance to all study requirements.

Exclusion criteria:

· Subjects who have any inflammatory arthritic condition (different from the OA of the knee), fibromyalgia,
multiple sclerosis or autoimmune disorder.

· Treatment with oral corticosteroids within 4 weeks before screening.

· Intra-articular injections of HA or corticosteroids in the target joint within 3 months before screening.

· Treatment with anti-inflammatory or chondroprotective drugs (chondroitin sulfate, glucosamine, methylsulfonylmethane, HA, diacerein) 2 weeks before the selection.

· HA-containing nutritional supplements or cosmetics during the month before the study.

· Previous surgical treatment of knee joint(s) or its necessity necessity for osteoarthritis (high tibial osteotomy, arthroplasty); complication(s) necessary for hospitalization
and surgical treatment.

· Significant injury to the target joint within the past 6 months prior to screening (identified from medical history).

· Subjects following an energy-restricted diet for weight loss.

· Pregnant women, nursing mothers, or women (only if childbearing potential) not using adequate
methods of contraception.

· Subjects with cardiovascular, hepatic, renal, respiratory, or hematologic illness, or other medical

or psychiatric condition that, in the opinion of the investigator, would compromise participation or be likely to lead to hospitalization during the course of the study.
· Participation in an interventional clinical study in the previous 30 days.
Presence of any clinically significant medical condition judged by the investigator to preclude the patient's inclusion in the study.

Number of patients: 8 evaluable patients

Sample size calculation: Usually, the sample size calculation is not requested in a pilot trial. Literature recommends about 10% of the number required for the main future RCT. Considering that the sample size of the main study will be 80 patients and given the exploratory nature of this clinical trial, Investigators have agreed to enrol just 8 subjects.

Number of Centres: 1 Center (located in Romania)

Not allowed concomitant treatment: Diuretics and any medication mentioned in exclusion criteria; routine intake of antiresorptive drugs, including bisphosphonates or oestrogen; alcohol, drug abuse.

Active Administration: High-molecular-weight HA 300 mg + AKBA 10 mg (SIALOX 300 PLUS) 1 tablet/day for 8 weeks (oral administration)

Administration duration: 8 weeks.

Chronogram of visits:
The study foresees 3 visits per patient:
· Visit 1 day -14 to day 0: Screening & Baseline visit
· Visit 2 week 4 (± 2 days): Follow-up visit (Phone call Visit and *optional* Site Visit)
Visit 3 week 8 (± 4 days): End of study visit

Procedures:
a) Visit 1: Screening & Baseline assessment (day -14 to day 0)
· Informed consent
· Inclusion/Exclusion Criteria
· Demographics and Medical History
· Physical examination and Vital signs
· Orthopaedic assessment
· Ultrasonography
· Start of measurement (24/24hrs) using Actigraph, for 7 days prior nutraceutical product administration (optional); The actigraph was placed by the Investigator below the patient knee 7 days before BL visit and was returned at BL.

· KOOS Questionnaire
· VAS
· ROM of knee joint measured by goniometer (active and passive knee flexion, active and passive knee extension)
· Nutraceutical product delivery
· Accountability card for rescue medication delivery
· Rescue medication (paracetamol 500 mg) delivery
· Safety assessment

b)Visit 2: Follow-up assessment (week4 ± 2 days by Phone call assessment and optional Visit at site)
· Orthopaedic assessment
· KOOS Questionnaire
· VAS
· ROM of the knee joint measured by goniometer
· Accountability for rescue medication
· Safety assessment

c) Visit 3: Final assessment (week 8 ± 4 days)
· Physical examination and Vital signs
· Orthopaedic assessment
· Ultrasonography
· Start of measurement (24/24hrs) using actigraph, for 7 days during the week prior to the Final assessment (optional); The actigraph was placed by the Investigator below the patient knee 7 days before visit 3 and was returned at visit 3.
· KOOS Questionnaire
· VAS
· ROM of the knee joint measured by goniometer
· Nutraceutical product return and final accountability
· Rescue medication (paracetamol 500 mg) return
· Final accountability for rescue medication return
Safety assessment

Statistical analysis: Quantitative variables (i.e. demographic) if normally distributed will be described through media, standard deviation (SD); variables with normal distribution are described using median and range of interquartile. The Student's t-test and the Mann-Whitney U will be employed to perform comparative analysis in accordance to the distribution of these variables. Factorial variance analysis can also be used to evaluate any interactions between quantitative variables and linear progression models
to relate possible confounding bias with independent variables. Categorical variables will be finally described using frequencies and percentages and comparative analysis will use

the chi^2 test. Spearman rank correlation is a non-parametric test that is used to measure the degree of association between two variables. The Spearman rank correlation test does not carry any assumptions about the distribution of the data and is the appropriate correlation analysis when the variables are measured on a scale that is at least ordinal (such is the case in the current study). In the population enrolled, applying the Spearman's rank correlation test, we are expecting to find a strong positive correlation (at least 0.7) between reduction in VAS (at rest) and ultrasonography parameters, and between reduction in VAS (at rest) and ROM improvement. The quality and completeness of the collected data will be evaluated preliminarily compared to data analysis. If a subject is missing information for one or more variables, even after the resolution of its query, the missing data will not be replaced. If a subject has been involved in violation of inclusion/exclusion criteria, the respective data will be excluded from the analysis.

Ethics Committee approval

Prior to the initiation of the trial, the Investigator must submit the clinical protocol, the Patient Information Sheet, the Patient Consent Form and any other documentation as required to the local centre's EC for review and approval.

Informed Consent and Patient Information

The Investigator is responsible for and must obtain the written informed consent (ICF) from each patient enrolled in the study, in accordance with the ICH-GCP Guidelines and the current version of the Declaration of Helsinki. The patients must be given a document in local (Romanian) language written in clear concise lay language for review and consideration (Patient Information Sheet). These documents (ICF an PIS) must previously approved by relevant EC and may further be updated as new important information that may affect patient's willingness to participate or continue in the trial becomes available.

Timing:

Start of enrolment (First patient in): February 2018
End of enrolment (Last patient in): April 2018
End of 1st month of IP administration: 30 April 2018
End of IP administration (Last patient out): 30 May 2018
Data Base Lock: 30 June 2018
Statistical Analysis: 30 July 2018

Flowchart:

A	B	C	D
	Visit 1	***Visit 2***	***Visit 3***
Days	***-14 to 0***	***28 (± 2)***	***56 (± 4)***
Weeks	***-2 to 0***	***4***	***8***
Informed consent	X		
Inclusion Criteria	X		
Exclusion Criteria	X	X	X
Demographics and Medical history	X		
Physical examination and Vital signs	X		
Othopaedic assessment	X		X
Concomitant treatments	X	X	X
Actigraphy - sensor delivery 1 week before the visit (optional)	X		X
Actigraphy - sensor return (optional)	X		X
KOOS	X	X1	X
VAS	X	X1	X
ROM by goniometer	X	X1	X
Ultrasonography	X		X
Nutraceutical product delivery	X		
Nutraceutical product return			X
Rescue medication delivery	X		
Rescue medication return			X
Rescue medication accountability card delivery	X		
Rescue medication accountability card return			X

	A	B	C	D
	Adverse Events	X	X2	X

X1: Tests and examinations not mandatory if the visit is performed as telephone call
X2 Safety (AE/SAE checking) is mandatory in any case

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