Safety and performance of the intra-articular injection of animal-free chitosan biomaterial (viscosupplementation) in patients with symptomatic knee osteoarthritis: a pre-market study

Published: 05-09-2018
Last updated: 11-04-2024

Primary:- To evaluate short-term and long-term safety of the IMD at the different time points, including after two repeated injections at 3-month time interval.Performance:- To evaluate the single injection performance of the IMD on knee pain as...

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

Summary

ID

NL-OMON48771

Source
ToetsingOnline

Brief title
APROOVE

Condition

- Joint disorders

Synonym
Artrosis, Osteoarthritis

Research involving
Human

Sponsors and support

Primary sponsor: KiOmed PHARMA SA
Source(s) of monetary or material Support: KiOmed Pharma SA

Intervention

Keyword: Chitosan, K&L grade II-III, Osteoarthritis

Outcome measures

Primary outcome

Safety:

Safety of the IMD will be assessed at the different time points by recording the incidence, severity and causal relationship of (Serious) Adverse Events ([S]AEs), (Serious) Adverse Device Effects ([S]ADEs), Unanticipated Serious Adverse Device Effects (USADEs) and Device Deficiencies (DDs), in accordance with ISO 14155/MEDDEV2.7/3 definitions. All AEs and SAEs will be coded using the last version of the MedDRA. In certain circumstances, local effects are normal postoperative complications of the IA injection procedure. After each injection and at each visit, the occurrence of local effects will be assessed by the investigator with a 4-point numerical rating scale (NRS).

Performance:

The primary performance endpoint will be assessed as a change in pain at 3 months versus pre-injection baseline using the 5-graded Likert WOMAC pain score following a single intra articulair injection. This endpoint will be determined on the clinical data collected in the Stage 2 cohort based on a randomized controlled design.

Exploratory:

As part the exploratory endpoints in APROOVE, different questionnaires have been established to the patient*s satisfaction and health and well-being. Specifically the SF-12 health survey is used to measure participant's profile of functional health and well-being.

Secondary outcome

• Changes from baseline in total score, pain, stiffness, and physical functioning subscales of the treatment knee as measured using the 5-graded Likert WOMAC at the different time points over 6 months.

• Changes from baseline in patient*s pain and global assessment using an 11-point NRS from "very poor = 0" to "excellent = 10" at the different time points over 6 months.

• Response to treatment according to Osteoarthritis Research Society International (OARSI) Standing Committee for Clinical Trials Response Criteria Initiative and the Outcome Measures in Rheumatology (OMERACT) at the different time points over 6 months.

• Treatment responders with >40% improvement in pre-injection pain (WOMAC Likert) at the different time points over 6 months.

• Physician* usability with the device as assessed using Likert scales at Injection Visits.

Study description

Background summary

According to World Health Organization (Wittenauer 2013), OsteoArthritis (OA), the most common musculoskeletal condition, is a long-term chronic disease involving the thinning of cartilage in joints which results in bones rubbing together, creating stiffness, pain, and impaired movement. OA is related with age, but is associated with a variety of both modifiable and non modifiable risk factors, including obesity, lack exercise, genetic predisposition, bone density, occupational injury, trauma, and gender. OA is a major cause of disability in elderly populations around the globe, especially in developed countries. It ranks as the fifth highest cause of years lost to disability in the whole population in high-income countries. It accounts for 50% of the entire musculoskeletal diseases, which also includes rheumatoid arthritis and osteoporosis, and thus is considered the highest-burden condition within this group of diseases. Radiographic evidence of knee osteoarthritis is present in approximately 30% of men and women over the age of 65. Worldwide estimates are that 9.6% of men and 18.0% of women over the age of 60 years have symptomatic osteoarthritis. Approximately 80% of those with OA will have limitations in movement, and 25% cannot perform their major activities of daily life. The prevalence of OA is increasing and will continue to do so as the population increases, ages, and is subject to risk factors such as the obesity epidemic. As OA causes pain and impairs functionality of the patient, it places a major burden on individuals, communities, health systems, and social care systems.

KiOmed Pharma is developing an innovative biomaterial coded CHITOSAN VS (KIO014) based on chitosan intended for synovial fluid viscosupplementation. One key component is a soluble derivative of highly purified chitosan of non-animal origin, KiOmedine®. KiOmedine® chitosan is an exclusive natural linear glucosamine polysaccharide extracted from the edible white mushroom, Agaricus bisporus.

When formulated as a viscous biomaterial, the resulting device CHITOSAN VS (KIO014) is a viscosupplementation (VS) device indicated in the symptomatic treatment of knee OA and has the potential to show single-injection performance in patients with knee OA. It shows acceptable lubrication and anti-oxidant capability and is slowly bioresorbable in the joints, which are desirable attributes for its intended use.

Study objective

Primary:
- To evaluate short-term and long-term safety of the IMD at the different time points, including after two repeated injections at 3-month time interval.
Performance:
- To evaluate the single injection performance of the IMD on knee pain as measured by change from baseline using the 5-graded Likert WOMAC pain score at 3 months.

Secondary

• To evaluate the performance of the IMD on OA symptoms as measured by change from baseline in total score, pain, stiffness, and physical functioning subscales using the 5-graded Likert WOMAC at the different time points over 6 months.
• To evaluate patient*s pain and global assessments of a single injection of the IMD at the different time points over 6 months.
• To evaluate treatment responders according to Osteoarthritis Research Society International (OARSI) Standing Committee for Clinical Trials Response Criteria Initiative and the Outcome Measures in Rheumatology (OMERACT) at the different time points over 6 months.
• To evaluate treatment responders with >40% improvement in pre-injection pain (WOMAC Likert) at the different time points over 6 months.
• To evaluate the physician*s usability of the IMD during its intra-articular injection at the Injection Visits.

Exploratory:
• To evaluate the consumption of rescue medication at the different time points over 6 months.
• To evaluate the change from baseline in patient*s health and well-being using the Short Form-12 health survey (SF-12) at the different time points over 6 months.
• To evaluate patient* satisfaction and health status improvement at the different time points over 6 months.
• To evaluate the physician* satisfaction on a medical point of view at the different time points at the different time point over 6 months.

Study design

Pre-market, first-in-man, multicenter, prospective, interventional, Stage 1 / Stage 2 clinical study to support CE marking

Intervention

The IMD will be injected intra-articularly in the most painful knee. The intra-articular injection will be performed by the Investigator having experiences in knee IA injections and trained on the device. See also CIP section 1.8.

Study burden and risks

Based on the total experience with components of KIO014, no specific risks of toxicity or tissue incompatibility or infection related to chitosan, carboxymethyl chitosan or other components of KIO014 were found on the investigative device used as IA treatment of symptomatic knee OA either in published data, in toxicological assessment or in specific preclinical studies.

It has a good local tolerance when injected into the knee of rabbits and sheep, an absence of any systemic toxicity and a nonclinical performance profile in terms of lubrication, anti-oxidant capacity and articular residence duration supporting the belief that it will provide a significant improvement of pain and possibly other symptoms for 3 months and longer when administered as a single injection of 3 mL into the knee of patients suffering from OA.
Durolane® used as benchmark device is CE-marked and has a long market history. Its risk-to-benefit rational has been appropriately established in clinical trials.

Contacts

Public
KiOmed PHARMA SA

Rue Haute Claire 4
Herstal B-4040
BE
Scientific
KiOmed PHARMA SA

Rue Haute Claire 4
Herstal B-4040
BE

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

• Male or female with age >= 40 years and <= 85 years except in Stage 1 cohort where age

is limited to <= 70 years.
• Body mass index (BMI) <= 35 kg/m².
• Uni- or bilateral femorotibial knee OA associated or not with femoropatellar knee OA.
• Primary knee osteoarthritis responding to the clinical and radiological criteria of the American College of Rheumatology (ACR)
• Radiological Kellgren and Lawrence (K&L) grade II to III from a standing knee radiograph taken less than 6 months previously.
• Symptomatic pain at least 6 months in the treatment knee not or poorly responding to first line non-opioid analgesics and non-steroidal anti-inflammatory drug in oral uptake.
• Pain criteria assessed prior to injection at V1 on both knees using the 5-graded Likert WOMAC pain score after mandatory 48-hour wash-out:
o Treatment knee: 7-17 points of the 5-graded Likert WOMAC pain score and at least 2 points on the WOMAC pain subscore A1 in the most affected knee.
o Non-treatment knee: not more than 6 points of the 5-graded Likert WOMAC pain score in the contralateral knee.
• Fully ambulatory patient for functional evaluation
• Willing NOT to take any pain medication for 48 hours prior to study visit.
• For female NOT surgically sterile (tubal ligation or hysterectomy) or NOT postmenopausal for at least one year, must have an effective contraception (pill, patch, ring, diaphragm, implant and intrauterine device).
• Able to understand and follow the instructions of the study.
• Having signed a written informed consent.

Exclusion criteria

• Related to the OA pathology and related symptoms:
o Radiological K&L grade 0, I or IV from a standing knee radiograph taken less than 6 months previously.
o Exclusively patellofemoral osteoarthritis where the symptoms, including pain, are principally of patellofemoral origin (Patellar syndrome).
o Chondromatosis or villonodular synovitis of the knee.
o Clinically-apparent knee effusion, inflammation or flare-up of the knee or abnormal synovial fluid macroscopy or volume upon arthrocentesis on the day of injection.
o History of injury to the treatment knee during the 6 months before inclusion or recent trauma (<1 month) of the knee responsible of pain that is not directly related to OA symptoms.
o Significant clinically-assessed or radiographic varus or valgus deformation of the selected knee at the judgment of the investigator.
o Inflammatory disease, i.e., rheumatoid arthritis, psoriatic rheumatism, articular chondrocalcinosis, gouty arthritis, ankylosing spondylitis, lupus, acute calcium pyrophosphate arthritis, or infectious arthritis, and, articular disease resulting from articular dysplasia, aseptic osteonecrosis, acromegaly, Paget*s disease, hemophilia, hemochromatosis.
o Pathologies interfering with the evaluation of OA pain for the knee to be treated, i.e., homolateral coxarthrosis, radiculalgia, femoral or sciatic nerve root pain, venous or lymphatic stenosis, arteritis, tendinopathy (e.g. hip periarthritis). ;• Related to treatments:

o Contraindications: hypersensitivity or allergy to the product components of KIO014, including chitosan, sorbitol and/or other mushroom-derived products, or to hyaluronic acid-based products.
o Corticosteroids or PRP or cell-based therapy injection in the treatment knee in the last 3 months before injection.
o Hyaluronic acid injection in the treatment knee in the last 6 months before injection.
o Arthroscopy and surgery in the treatment knee in the last 6 months before injection.
o Oral corticotherapy >=5 mg/day (in prednisone equivalent) in the last 3 months before injection.
o Change in the dosage regimen of symptomatic slow-acting drugs (SYSAD) or dietary supplement, i.e., curcuma extract, chondroitin, glucosamine, diacerein or avocado-soya unsaponifiables in the last 3 months before injection.
o Change in physiotherapy of the treatment knee in the last 3 months.
o Anticipated need for any surgical or other invasive procedure during the trial including prosthesis in the treatment knee.
o Anticipated need for any forbidden OA treatments during the trial except for rescue treatment as defined in the study protocol.
o Anticoagulants: coumarin-based compounds or heparin. ;• Related to associated diseases:
o Any Investigator-assessed clinically significant condition that may represent a substantial risk to the patient or may have an impact on the study assessments.
o History of recurrent bacterial infection, defined as at least 3 major infections resulting in hospitalization and/or requiring intravenous antibiotic treatment within the past 2 years or history of synovial infection or infections or skin diseases in the area of the injection site.
o History of symptomatic hip OA
o History of autoimmune disease.
o Severe, ongoing and uncontrolled diseases such as malignancy or history of malignancy, type I diabetes, liver failure, renal failure, lung/heart disease, neoplasia, malignant blood disease, tumor, HIV, or other major disease (e.g. systemic fungal infection), or other severe uncontrolled conditions.
o Subject addicted to alcohol (for example, more than 2 glasses/day of strong alcohol) or drugs or ongoing or recently recovered (<6 months) depression or psychiatric disorders or any other disorder and/or that may pose a health risk to the subject in the study and/or may have an impact on the study assessments.
o Severe alteration of mobility preventing any functional evaluation.
o High risk of hemorrhage.;• Related to patients:
o Participation in a therapeutic clinical trial in the last 3 months before injection.
o Patient under guardianship or judicial protection.
o Pregnancy, breastfeeding, planned conception, or premenopausal women without effective contraception (pill, patch, ring, diaphragm, implant and intrauterine device), tubal ligation or hysterectomy.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	04-12-2018
Enrollment:	35
Type:	Actual

Medical products/devices used

Generic name:	CHITOSAN VS (KIO014)
Registration:	No

Ethics review

Approved WMO Date:	05-09-2018
Application type:	First submission
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	22-01-2019
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	11-03-2019
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	14-06-2019

Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)

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
CCMO	NL66642.048.18