A randomized, placebo-controlled, patient and investigator blinded study investigating the safety, tolerability and preliminary efficacy of 8-week treatment with intra-articular LRX712 to regenerate articular cartilage in patients with mild/moderate knee osteoarthritis

Published: 09-10-2019
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Primary objective - To assess the efficacy of q4w x3 i.a. injections of LRX712 in restoring the morphometrics of articular cartilage in the medial femoral condyleSecondary objectives- To evaluate LRX712 and metabolite MAE344 pharmacokinetics in...

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

Summary

ID

NL-OMON52598

Source
ToetsingOnline

Brief title
Proof of Mechanism Study of LRX712 in patients with mild/moderate knee OA

Condition

- Joint disorders

Synonym
Osteoarthritis

Research involving
Human

Sponsors and support

Primary sponsor: Novartis
Source(s) of monetary or material Support: Pharmaceutical industry

Intervention

Keyword: Chondro anabolic drug, Knee osteoarthritis, MRI, PRO

Outcome measures

Primary outcome

Change in the medial femoral condyle cartilage volume in the index region measured by 7T MRI from baseline to week 28 in LRX712- vs. placebo-treated patients

Secondary outcome

- PK parameters in plasma : Tmax, Cmax, Cmin in plasma

- PK parameter in synovial fluid : Concentration at Day 1, Week 4, Week 8 post dosing

- Vital signs (blood pressure, heart rate, temperature) as per assessment schedule

- Hematology, blood chemistry and urinalysis as per assessment schedule

- Local and Systemic Adverse Events

- ECG parameters (PR, QRS, heart rate, RR, QT, QTc) as per assessment schedule

- Change in articular cartilage [23Na] content from baseline compared to placebo measured with 7T MRI at Week 16, 28 and 52 in LRX712- vs. placebo-treated patients

- Change in the medial femoral condyle cartilage (volume) measured by 7T MRI

from baseline to Weeks16 and 52.

Study description

Background summary

There are currently no approved therapeutics or surgical procedures which restore damaged articular cartilage damage to its native, hyaline state. Previous compounds that failed to show efficacy have targeted catabolic mechanisms in cartilage degeneration (e.g., with inhibitors of matrix metalloproteinases and aggrecanases), where no preservation or improvement of the cartilage was demonstrated and multiple adverse events were reported. Surgical options exist, but healing often leads to fibrous and/or calcified cartilage, which is not capable to withstand the biomechanical forces acting in the joint. In fact, the vast majority of patients, do not benefit on a long term follow-up from these surgical techniques. Clinical evidence has also shown that focal defects may lead to osteoarthritis (OA), with the need for joint replacement later in life. There is, therefore, a high unmet medical need for earlier interventions capable to regenerate hyaline cartilage, in order to restore the articular surface and prevent the onset of OA. LRX712 is a synthetic, small molecular entity identified via phenotypic screening and intended for intra-articular (i.a.) administration. The direct molecular target of LRX712 has not yet been identified. However LRX712 drives cartilage stem/progenitor cells (CSPCs) to undergo differentiation into chondrocytes and facilitate hyaline articular cartilage repair, while not inducing molecules involved in fibrosis and hypertrophy/ossification. LRX712 induces restoration of hyaline articular cartilage in the efficacy models evaluated. While most of the current approaches aim to improve surgical outcomes after cartilage injury, treatment with LRX712 allows avoiding surgical intervention by promoting hyaline cartilage regeneration upon i.a. administration.

Study objective

Primary objective
- To assess the efficacy of q4w x3 i.a. injections of LRX712 in restoring the morphometrics of articular cartilage in the medial femoral condyle

Secondary objectives
- To evaluate LRX712 and metabolite MAE344 pharmacokinetics in plasma and synovial fluid
- To assess safety and local tolerability of multiple i.a. injections of LRX712
- To assess the efficacy of q4w x3 i.a. injections of LRX712 in regenerating the articular hyaline cartilage composition in the medial femoral condyle

Study design

This is a 52 week, randomized, double-blind, placebo-controlled, parallel-group, clinical study

Intervention

Three treatment arms are planned to test repeated dosing with three consecutive i.a. injections of either LRX712 15 mg, LRX712 25 mg or placebo.

Study burden and risks

Given that study participants will have mild/moderate osteoarthritis and LRX712 have shown promising chondrogenic effects in preclinical studies, it is possible that the 3 consecutive doses of the drug may elicit beneficial effects on structural lesions in the articular cartilage with potential implications for joint pain and function. Occasional and transient local tolerability findings upon intra-articular injection are expected.

Contacts

Public
Novartis

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Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Patient must be between 35 and 75 years old at screening
- Patient must weigh at least 50 kg to participate in the study, and must have a body mass index (BMI) within the range of 18 - 35 kg/m2 at screening. BMI = Body weight (kg) / [Height (m)]2 at screening
- Patient must have knee osteoarthritis (OA) at screening. Structural signs of Radiographic OA need to be confirmed by radiography taken in standing weight-bearing fixed flexion position and PA view, indicating Kellgren-Lawrence grade 2 or 3 in the index knee
- Patient must have symptomatic disease predominantly in one (the index) knee, with minimal or no symptoms in the contralateral knee. Symptomatic disease is defined as having pain in the knee >= 4 days of the week for at least 3 months at screening.
- Patient must have radiographic confirmation of a medial joint space width of 1.5 to 3.5 mm for females, or 2 to 4 mm for males, measured at the X=0.225 fixed point location within the medial tibio-femoral compartment of the index knee, at screening.
- Patients must be ambulatory at screening (walk without aid)

Exclusion criteria

- Patient has a known autoimmune disease, inflammatory or chronic arthropathy other than OA (including but not limited to rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, SLE, (systemic lupus erythematosus), CPPD (calcium pyrophosphate dihydrate crystal deposition disease),, gout and fibromyalgia), active acute or chronic infection of the joint, Lyme disease involving the knee, systemic cartilage disorder, or a known systemic connective tissue disease
- Subject has had surgical treatment of the target knee using mosaicplasty, microfracture, or resecting more than 50% of meniscal tissue
- Subject has symptomatic, isolated patello-femoral pain in the index knee as per the Investigator's examination
- Subject has malalignment (valgus- or varus-deformity) in the index knee >= 7.5° as per anatomic PA axis measured by weight-bearing short knee radiography.
- Effusion in the index knee that clinically requireding aspiration in the past 12 weeks prior to screening, or that is clinically relevant in the index knee as per physical examination (bulge sign, patellar tap) at screening or Day 1

- Any local i.a. treatment to the knee, including but not restricted to viscosupplementation and corticosteroids, within 12 weeks prior to screening
- Signs or symptoms, in the judgment of the investigator, of a clinically significant systemic
viral, bacterial or fungal infection within 30 days prior to screening;
COVID-19 specific: It is highly recommended that PCR or antigen testing for COVID-19 be completed within 1 week prior to first dosing. If testing is performed, negative test results are required prior to enrollment into the study. Additional testing may occur at the discretion of the investigating physician. This requirement may be ignored if the pandemic is declared ended by the country where the site is located, and resumed if the pandemic recurs.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	20-07-2020
Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	LRX712
Generic name:	na

Ethics review

Approved WMO Date:	09-10-2019
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	05-02-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	24-02-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-07-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-07-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-08-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	24-12-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO	

Date:	07-01-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-03-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-08-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-08-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	28-01-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-02-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	16-05-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	07-06-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek

	(Assen)
Approved WMO Date:	01-11-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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
EudraCT	EUCTR2019-002963-92-NL
ClinicalTrials.gov	NCT04097379
CCMO	NL71327.056.19