A randomized, placebo controlled, subject and investigator blinded, first-in-human, single ascending dose study to evaluate the safety, tolerability, and pharmacokinetics after intra-articular injection of LRX712 into the knee of osteoarthritic patients.

Published: 16-10-2017
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Primary objective:- To evaluate safety and tolerability of LRX712 after a single i.a. injection in OA patients.Secondary objective: - To evaluate LRX712 and metabolite MAE344 pharmacokinetics in plasma.Exploratory objectives:- To evaluate LRX712 and...

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

Summary

ID

NL-OMON46705

Source
ToetsingOnline

Brief title
Safety, tolerability, and pharmacokinetics of LRX712

Condition

- Joint disorders

Synonym
osteoarthitis

Research involving
Human

Sponsors and support

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

Intervention

Keyword: intra-articular injection, LRX712, osteoarthritis

Outcome measures

Primary outcome

- Adverse Events (CTC-AE v 4.03)

- 24 Hour Holter Monitoring

- ECG parameters (PR, QRS, heart rate, RR, QT, QTcF)

- Vital signs

- Hematology, blood chemistry, urinalysis

Secondary outcome

- PK parameters in plasma : Tmax, Cmax, AUClast, AUCinf, T1/2, CL/F, Vz/F

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 evaluate safety and tolerability of LRX712 after a single i.a. injection in OA patients.

Secondary objective:
- To evaluate LRX712 and metabolite MAE344 pharmacokinetics in plasma.

Exploratory objectives:
- To evaluate LRX712 and metabolite MAE344 exposure in the synovial fluid.
- To perform exploratory biomarker assessment to characterize the mechanism of action of the drug, identify early efficacy/disease markers or potential markers associated with response to treatment with LRX712.
- To perform exploratory DNA assessments to examine whether individual genetic variation in genes relating to drug metabolism, transporters, cartilage repair, the drug target pathway, or other relevant genetic pathways confer differential response to investigational drug LRX712.

Study design

This is a subject and investigator blinded, randomized, placebo-controlled, non-confirmatory, first-in-human, i.a., SAD study.

Intervention

A single administration with ascending doses of lRX712 in the target knee joint.

Study burden and risks

The risks of the study treatment are related to intravenous- and intraarticular puncture and are considered to be either rare (septic arthritis) or mild (faining, bruising). The burden of the study is considered moderate because it requires a considerable time investment.

Contacts

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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

Moderate knee OA patients eligible for inclusion in this study must fulfill all of the following criteria:
1. Subjects must sign a written informed consent before any assessment is performed.

2. Male and female patients 35 to 65 years of age inclusive, and in good health as determined by past medical history, physical examination, vital signs, electrocardiogram, and laboratory tests at screening.
3. At screening, and at baseline vital signs (systolic and diastolic blood pressure and pulse rate) will be assessed in the sitting position after the subject has rested for at least three minutes, and again (when required) after three minutes in the standing position as outlined in the SOM. Sitting vital signs should be guided by the following ranges: Oral body temperature between 35.0-37.5 °C, systolic blood pressure 90-139 mm Hg, diastolic blood pressure 50-89 mm Hg, pulse rate 40 - 90 bpm
4. Subjects must weigh at least 50 kg to participate in the study, and must have a body mass index (BMI) within the range of 18 - 32 kg/m2. BMI <= Body weight (kg) / [Height (m)]
5. Able to communicate well with the investigator, to understand and comply with the requirements of the study.
6. Patient has radiologically apparent moderate degenerative joint disease in the target knee as determined by Kellgren and Lawrence grade 1- 3 based on X-ray evaluation performed within 6 months from screening.

Exclusion criteria

Moderate knee OA patients fulfilling any of the following criteria are not eligible for inclusion in this study:
1. Use of other investigational drugs at the time of enrollment, or within 5 half-lives of enrollment, or within 30 days, whichever is longer; or longer if required by local regulations.
2. History of hypersensitivity to any of the study treatments or excipients or to drugs of similar chemical classes.
3. A history of clinically significant ECG abnormalities, or any of the following ECG abnormalities at screening and baseline:
* PR > 200 msec
* QRS complex > 120 msec
* QTcF > 450 msec (males)
* QTcF > 460 msec (females)
4. Known family history or known presence of long QT syndrome.
5. Known history or current clinically significant arrhythmias.
6. Concomitant use of agents known to prolong the QT interval unless they can be permanently discontinued for the duration of study.
7. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases.
8. Pregnant or nursing (lactating) women.
9. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant. Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the

reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.
10. Sexually active males unwilling to use a condom during intercourse for five times the T* of LRX712 after drug administration. A condom is required for all sexually active male participants to prevent them from fathering a child AND to prevent delivery of the investigational drug via seminal fluid to their partner. In addition, male participants should not donate sperm for the time period specified above.
11. Use of any strong CYP3A4 inhibitors or inducers from screening to end of study. These drugs can be used if they are the only appropriate treatment in case of urgent medical intervention, and must be documented in the Concomitant medications / Significant non-drug therapies page of the CRF.
12. Donation or loss of 450 mL or more of blood within eight weeks prior to initial dosing, or longer if required by local regulation.
13. Hemoglobin levels below 12.0 g/dL at screening or baseline.
14. Significant illness which has not resolved within two (2) weeks prior to initial dosing.
15. Recent (within the last three years) and/or recurrent history of autonomic dysfunction (e.g., recurrent episodes of fainting, palpitations, etc.).
16. Recent (within the last three years) and/or recurrent history of acute or chronic bronchospastic disease (including asthma and chronic obstructive pulmonary disease, treated or not treated).
17. History of multiple and recurring allergies or allergy to the investigational compound/compound class being used in this study.
18. History of immunodeficiency diseases, or a positive HIV (ELISA and Western blot) test result.
19. Chronic infection with Hepatitis B (HBV) or Hepatitis C (HCV). Positive HBV surface antigens (HBsAg) test, or if standard local practice, a positive HBV core antigen test, excludes a subject. Patients with a positive HCV antibody test should have HCV RNA levels measured. Patients with positive (detectable) HCV RNA should be excluded.
20. History of drug abuse or unhealthy alcohol use# within the 12 months prior to dosing, or evidence of such abuse as indicated by the laboratory assays conducted during screening baseline. #Unhealthy alcohol use is defined as a history of, or current alcohol misuse/abuse, defined as: five or more drinks on the same occasion on each of 5 or more days in the past 30 days.
21. Smoker of more than 10 cigarettes per day prior to screening, or who use tobacco products equivalent to more than 10 cigarettes per day and unable to abstain from smoking whilst in the unit.
22. History of recreational cannabis use within four weeks prior to dosing, or evidence of such use as indicated by the laboratory assays conducted during screening and baseline. This exclusion criterion applies even if cannabis use is legalized where the site is located. Any prescribed, medicinal use of cannabis is to be handled according to the prescription drug usage criteria defined above.
23. Patient taking medications prohibited by the protocol: any local i.a. treatment into the knee, including but not restricted to viscosupplementation and corticosteroids within 12 weeks from screening; corticosteroid use by any route except topical within 4 weeks from screening; oral glucosamine, chondroitin sulfate, or any nutraceutical with potential activity on cartilage repair within 2 weeks from screening.
24. Patient has a known autoimmune disease, inflammatory arthropathy (including but not

limited to rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, calcium pyrophosphate dihydrate disease, gout), history of infection of the joint, active acute or chronic infection of the joint, Lyme's disease to the knee, systemic cartilage disorder, or a known systemic connective tissue disease.
No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	12-12-2017
Enrollment:	42
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	LRX712
Generic name:	n.a.

Ethics review

Approved WMO

Date:	16-10-2017
Application type:	First submission

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	20-10-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	06-11-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	07-11-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-11-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	05-01-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-01-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	26-01-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO	

Date:	26-03-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-10-2018
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	EUCTR2015-005530-21-NL
CCMO	NL62267.056.17