A phase 2b Study Evaluating the Efficacy of a Single Injection Autologous Adipose Derived Mesenchymal Stromal Cells in Patients with Knee Osteoarthritis

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To evaluate the efficacy of a single intra-articular injection of ASC in mild to moderate knee OA (KL 2-3) based on improvement of WOMAC pain and function subscore at 6 month, compared to placebo (vehic: 0.5% glucose in saline with 4.5% alb).The...

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

Summary

ID

NL-OMON47160

Source
ToetsingOnline

Brief title
ADIPOA-2

Condition

- Joint disorders

Synonym
damaged cartilage, Knee arthrosis

Research involving
Human

Sponsors and support

Primary sponsor: CHRU Montpellier

Source(s) of monetary or material Support: Europese Unie

Intervention

Keyword: Knee arthrosis

Outcome measures

Primary outcome

Primary Efficacy Analysis:

* Improvement from baseline to month 6 in WOMAC pain score of the index knee.

* Improvement from baseline to month 6 in WOMAC physical function score of the index knee.

The main objective is to evaluate the efficacy of a single intra-articular injection of ASC (either 2.106 or 10.106 ASC) in mild to moderate knee OA (KL 2-3) based on improvement of WOMAC pain and function subscore at 6 month, compared to placebo (vehicle: 0.5% glucose in saline with 4,5% human albumin)..

Secondary outcome

Secondary efficacy analysis:

* Changes from baseline to months 1, 3, 6, 12 and 24 in OARSI scores of the index knee.

* Changes from baseline to months 1, 3, 6, 12 and 24 in VAS pain scores of the index knee.

* Changes from baseline to months 1, 3, 6, 12 and 24 in WOMAC stiffness scores of the index knee

* Changes from baseline to months 1, 3, 6, 12 and 24 in WOMAC global scores of the index knee

* Changes from baseline to months 1, 3, 12 and 24 in WOMAC pain and function scores of the index knee

* Changes from baseline to months 1, 3, 6, 12 and 24 in KOOS scores of the index knee

* Changes from baseline to months 1, 3, 6, 12 and 24 in SAS scores of the index knee

* Changes from baseline to months 1, 3, 6, 12 and 24 in SF-36

* Changes from baseline to months 12 and 24 in cartilage volume/thickness of the index knee MRI (MOAKS score).

* Changes from baseline to months 12 and 24 in femorotibial joint space of the index knee on X-ray

Potential structural benefit

- Kellgren-Lawrence scores will be assessed on the basis of X-rays (conventional standing antero-posterior radiograph with fixed location JSW). Joint space width will be measured at baseline, one-year and 2-years post-injection as previously described (Kothari M, Guermazi A, von Ingersleben G, et al. Fixed-flexion radiography of the knee provides reproducible joint space width measurements in osteoarthritis. Eur Radiol 2004;14:1568*73). Concerning the X ray, a standardize procedure will be approved. We propose semiflexion and lateral view of knee joint, with similar distance and position at one year. For this, a device will be used. Joint space narrowing less than 0.5 mm will be considered as significant.

- Progression of affected knee joints by quantitative MRI will include volumetric measurement (cartilage volume, thickness, surface area, 3D shape) on T1 PDw FSE fat sat at baseline, months 12 and 24. Progression of affected knee joints by quantitative MRI will include volumetric measurement (cartilage volume, thickness, surface area, 3D shape) on T1 PDw FSE fat sat at baseline, months 12 and 24. Sequences for MOAKS semi-quantitative knee scoring will use proton density fat saturation in axial, coronal and sagittal planes and a T1-weighted coronal acquisition. Sequence for cartilage morphology analysis will use a 3D T1-weigthed gradient echo with fat saturation and sagittal plane reconstruction at 1.5 mm slice thickness: FLASH (Siemens), SPGR (GE) and FFE or WATSc (Philipps). Full protocol details are given in Appendix along with sample images. Cartilage will be assessed through MRI Osteoarthritis Knee score (MOAKS) (Hunter et al, Osteoarthritis & cartilage 2011) measured in T1 weighted images performed at 0, 12 and 24 months. The MOAKS instrument refines the scoring of BMLs (providing regional delineation and scoring across regions), cartilage (sub-regional assessment), and refines the elements of meniscal morphology (adding meniscal hypertrophy, partial maceration and progressive partial maceration) scoring. Every patient will be scanned three times: first before the start of the treatment, to define the initial state of joint, then at 12 and 24 months after the treatment to quantify the long term benefits/effects of the therapy, in particular absence of progression at 24 months post-treatment. Additional MRI scans can be performed.

- Disability and life quality (WOMAC, KOOS questionnaire, SAS questionnaire and Short Form (SF)-36 scores) measures will be assessed at 0, 1, 3, 6, 12 and 24

months. The secondary clinical outcomes will include: SAS score, WOMAC total score, and WOMAC stiffness subscores; patient and physician global assessments of disease activity; quality of life assessment (KOOS questionnaire and SF-36 scores).

- OARSI response will be assessed at month 1, 3, 6, 12 and 24. Patients will be classified as responders defined by improvements from baseline in at least 2 of the 3 next values (WOMAC pain, WOMAC function and VAS pain), as follows of at least 20%, together with an absolute change of 10 mm on a 0-100 scale.

- Paracetamol (Acetaminophen) medication: the drug consumption will be assessed throughout the study at each visit. A reduction in dose or frequency of administration of paracetamol is an indirect marker of the benefits of ASC therapy.

Study description

Background summary

Current standard treatment of knee OA is strictly symptomatic. No therapeutic option has been shown to influence the course of the disease. This obvious medical need would best be met by an effective, safe, well tolerated, local treatment with disease-modifying properties.
ASCs exhibit many properties that could be beneficial for the prevention of formation and repair of cartilage lesions. Moreover, ASCs have been demonstrated to exhibit immunosuppressive effects both in vitro and in vivo and may contribute to a reduction in local inflammation through the secretion of soluble factors of the Interleukin 6 (IL6) family (Hoogduijn MJ et al. 2007, Puissant et al. 2005, Wolbank S et al.2007, Yanez et al 2006). Through expression of Interleukin 1 receptor antagonist (IL1-RA), a potent IL1b antagonist, ASCs may also prevent tissue fibrosis in vivo and exhibit some anti-inflammatory effects, since IL1b is also a major pro-inflammatory cytokine. Adipose derived stem cells have been already used in clinical studies targeting non-life threatening diseases. A control phase III trial has been performed using allogenic adipose derived cells in Crohn disease and has shown a clinical

benefit as well as appropriated tolerance. More than 300 patients have been treated locally with this product with no significant side effects reported. ASC have been administered locally in 50 patients undergoing menisectomy to prevent OA, and no local side effects were reported (Garcia-Olmo D et al. 2009). The ASC proposed in this protocol have been approved by French regulatory agency in the ADIPOA trial (NCT), without any systemic or local side effects reported (Pers YM et al. 2015; submitted)

Study objective

To evaluate the efficacy of a single intra-articular injection of ASC in mild to moderate knee OA (KL 2-3) based on improvement of WOMAC pain and function subscore at 6 month, compared to placebo (vehic: 0.5% glucose in saline with 4.5% alb).

The objective of this clinical trial is to generate efficacy and safety data following a single injection of 2 doses of autologous ASCs when administered locally into a knee joint affected by mild to moderate OA after in vitro cell expansion. The objective of this study is to validate and optimize the concept of ASC in OA therapy.

Study design

This will be a phase IIb, multi-centre, prospective, randomized, double-blind study, comparing culture-expanded autologous ASC with placebo. This proposed design with a placebo arm and a double-blind methodology seems the most important design techniques to draw valid conclusions. We planned a sham lipoaspiration in the control group to mimic the procedure. It is essential because patients will notice otherwise. We considered the sham lipoaspiration ethically justifiable in order to obtain valid results. It is not possible to store the cells of the patients in the control group for subsequent treatment because characteristics and cell behaviour will change. Thereby, we decided not to remove adipose tissue in the control group.

Patients will be randomized in 3 arms to a total of 150 patients and followed up for 25 months (1 month before and 24 months after knee injection), with both two clinical endpoint (WOMAC pain and function subscore) at 6 month. Duration of recruitment for each centre: 12 months

Study burden and risks

Current standard treatment of knee OA is strictly symptomatic without disease-modifying properties. TKA, a highly invasive surgical intervention, is limited to cases of severe, end-stage knee OA when all conservative treatments have been exhausted. This clinical trial will exclusively enrol subjects with mild to moderate OA of the knee. Each subject will receive a single injection

into the knee joint affected by OA of either a placebo comparator (vehicle used to contain ASC), versus 2 different doses of ASCs (2x106 or 10x106 cells) which prior to in vitro expansion have been collected from subcutaneous abdominal adipose tissue of the same subject. The autologous nature of the study medication effectively excludes the risks of transmission of infectious agents, graft rejection, or GVHD (Le Blanc et al., 2008).
This proposal will progress beyond the current state of the art as it will be the first European clinical trial to reach significance in assessing ASCs for the treatment of OA. This study provides the first major step in determining subsequent clinical and commercial activity relating to stem cell therapy. It will definitively provide robust in patient regenerative medicine research that either supports or refutes the potential of intraarticular injection of ASCs for the treatment of mild-moderate OA. If successful, this will allow a new therapy to be taken to the next level of testing, taking the field closer to marketability and delivery, a key step that has eluded stem cell therapies to date.

Based on previous clinical experience with similar products reported in the literature, ASC is deemed to be effective and safe in various diseases (Garcia-Olmo et al., 2009, http://www.clinicaltrials.gov). Manufacturing of the study medication is performed according to GMP standards. The risk of local or systemic infection, bacteremia, or sepsis due to contamination of the cell preparation seems negligible. Pre-clinical in vitro and in vivo evaluations of the study medication did not show any hint of tumorigenic potential of the preparation or systemic migration of ASCs after IA injection. IA injection of corticosteroids is prohibited during the first 6-month of the clinical trial to minimize the risk of ectopic calcification. The risk associated with the fat tissue collection by liposuction of ASCs from subcutaneous abdominal adipose tissue seems low as long as standards of sterile sampling of tissue are observed. There is a low risk of systemic AEs occurring after the end of the observation period, but the sample size of this clinical trial implies a very low probability of detecting rare events anyway.

The benefit for patients with knee OA may be considerable, since ASCs might represent the first disease-modifying therapeutic option for this chronic and debilitating disease. This clinical trial will be accompanied by a Data and Safety Monitoring Board (DSMB), which will review safety data and provide recommendations to the Sponsor regarding the safety of subjects, the conduct of the study and potential premature termination. Furthermore, under certain pre-defined conditions, e.g. the occurrence of suspected unexpected serious adverse reactions (SUSARs), the Sponsor will suspend treatment of subjects until a decision whether to continue the clinical trial or not has been taken in accordance with the recommendations of the DSMB. In conclusion, subjects will be exposed to limited risks during their participation in this clinical trial. The efficacy for patients with knee OA may be considerable. A benefit on pain, on synovial inflammation and chondroprotection is anticipated. Therefore, the risk-benefit ratio for this clinical trial is anticipated to be favourable

and advocates its conduct in the selected group of subjects.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1) Male or female between the ages of 45 and 70, during screening.
2) BMI between 20 and 35 kg/m2
3) Symptomatic mild to moderate osteoarthritis (OA) of the index knee as defined at baseline by the American college of Rheumatology (ACR):
-History of pain in the index knee * 6 months, AND
-Kellgren and Lawrence (K-L) Grade 2 or 3 only, on plain radiographs of the index knee (including fixed flexion), AND
-Swelling of the index knee evaluated by the investigator
4) Must meet the following pain criteria at the time of baseline visit since at least half of the

days in the previous month:
-Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscores * 40 mm on the 0-100 normalised scale
-Visual analogis scale (VAS) pain rating of at least 40 on a 100-mm scale
-Subject*s global assessment of arthritis status must be fair, poor, or very poor
-Subject*s global assessment of the contralateral knee <20 mm by 100-mm using VAS*
5) NSAID washout of at least 2 days before screening and baseline
6) Written informed consent dated and signed prior to the beginning of any procedures related to the clinical trial

Exclusion criteria

1) Previous treatments acting on cartilage or bone metabolism (eg, oral or intravenous bisphosphonates <1 year previously, strontium ranelate or teriparatide or raloxifene <7 days prior to selection, and oral glucosamine *1500 mg/day and chondroitin sulphate <3 months previously)
2) Has had any trauma of the index knee in the previous 12 months prior to the screening visit
3) Has OA of the index knee that meets K-L classification criteria of grade 1 or 4
4) Osteoarthritis causing significant pain in any joint other than the identified knee, i.e., pain in hip, back, or contralateral knee (* 20 mm pain) as confirmed by a separate VAS at baseline for any other painful joint concerned
5) Prior to the screening visit, has received:
-Oral corticosteroid therapy within the previous 3 month, OR
-Intramuscular, intravenous or epidural corticosteroid therapy within the previous 6 months, OR
-Intra-articular injection of corticosteroids in the index within the previous 6 months, OR
-Intra-articular injection of hyaluronic acid in the index knee within the 6 months. OR
-Intra-articular injection of platelet rich plasma in the index knee within the 6 months.
-Tramadol or Opioids (alone or in combination products) therapy within the previous month
6) Inflammatory or other rheumatic diseases defined by clinical examination and previous serum markers (such as rheumatoid arthritis, autoimmune disorder, seronegative spondyloarthritis, gout or pseudogout (defined as acute episodic attacks of swollen, painful joint in a patient with X-ray chondrocalcinosis or CPPD crystals))
7) Severe misalignment of the knee (excessive varus or valgus * 8°) at physical examination, as confirmed by standard radiograph
8) Severe osteoporosis with previous fractures
9) History of joint replacement of the knee or hip within the previous 12 months
10) Serious systemic diseases or infectious/inflammatory skin diseases in the area of the affected knee
11) Positive serology for HIV, hepatitis B, C and syphilis
12) History of cancer or blood dyscrasias, or previous chemotherapy, radiotherapy or immunotherapy

Study design

Design

Study phase:	2
Study type:	Observational invasive
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):	01-02-2017
Enrollment:	15
Type:	Actual

Medical products/devices used

Product type:	Medicine
Generic name:	Somatic cells autologous

Ethics review

Approved WMO Date:	13-05-2016
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	29-11-2016
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO Date:	05-09-2018
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	10-09-2018
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	01-11-2018
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	26-04-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	23-05-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	19-08-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	04-11-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

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	EUCTR2015-002125 FR-NL
CCMO	NL55680.000.16