FGF-18 compound dosing regimen

Field of Invention

The present invention relates to the treatment of cartilage and cartilage/bone disorders, osteoarthritis and cartilage injury in particular. More particularly, it relates to an FGF-18 compound for use according to particular treatment regimens. Specifically, it concerns a treatment scheme comprising once every 2 weeks administration for three or four times of an FGF-18 compound per treatment cycle. The dosing regimen can further comprise the administration of a anti-inflammatory drug with effects on symptoms (pain and function), such as anakinra or diclofenac.

Background of the invention

Cartilage is composed of chondrocytes (cells derived from mesenchymal cells) which are dispersed in the matrix (a firm, gel-like ground substance). The cartilageneous matrix is produced by these cells and comprises mainly Type II collagen fibers (except fibrocartilage which also contains type I collagen fibers), proteoglycans, and elastin fibers. Cartilage is found among other places in the joints, the rib cage, the ear, the nose, in the throat, in the trachea and in the intervertebral disks. There are three main types of cartilage: hyaline, elastic and fibrocartilage, providing notably different functional properties according to their histological morphology. Articular cartilage, for instance, is a hyaline cartilage, having viscoelastic properties, covering the articular surfaces of bones. The main purpose of articular cartilage is to provide smooth surfaces in order to ensure nearly frictionless movement of articulating bones.

Cartilage disorders broadly refer to diseases characterized by degeneration / desintegration of cartilage and abnormalities in the connective tissues which are manifested by inflammation, pain, stiffness and limitation of motion of the affected body parts. These disorders can be due to a pathology or can be the result of trauma or injury. Mature cartilage has very limited ability to self repair, notably because mature chondrocytes have little potential for proliferation due to limited supply with nutrients linked to the absence of blood vessels in cartilage. Replacement of damaged cartilage, in particular articular cartilage, caused either by injury or disease, is a major challenge for physicians, and available surgical treatment procedures are considered unpredictable and effective for only a limited time in younger patients without osteoarthritic changes. Therefore, the majority of patients either do not seek treatment or are counseled to postpone treatment for as long as possible. When treatment is required, the standard procedure is age dependend and varies between total or partly joint replacement, transplantation of pieces of cartilage or chondrocytes or marrow stimulating technique (such as microfracture). Microfracture is a cheap and common procedure that involves penetration of the subchondral bone to stimulate cartilage deposition by bone marrow derived stem cells. However, it has been shown that this technique does not repair sufficiently the chondral defect and the new cartilage formed is mainly fibrocartilage, resulting in a short-lived repair tissue. Indeed, fibrocartilage does not have the same biomechanical properties as hyaline articular cartilage and lacks often proper

lateral integration into the surrounding cartilage. For this reason, the newly synthesized fibrocartilage may breakdown more easily (expected time frame: 5-10 years).

For patients with osteoarthritis (OA) all these cartilage repair techniques fail. The remaining non-surgical treatment consists notably of physical therapy, lifestyle modification (e.g. body weight reduction), supportive devices, oral drugs (e.g. non-steroidal anti-inflammatory drugs), injection of drugs(e.g. hyaluronic acid and corticoids), and food suplementation. All these treatments are unable to stop OA disease progression. If the pain therapy also fails, surgery, such as joint replacement or high tibial osteotomy for the knee joint, is the remaining option for the patients. Tibial or femoral osteotomies (cutting the bone to rebalance joint wear) may reduce symptoms, help to maintain an active lifestyle, and delay the need for total joint replacement. Total joint replacement can provide relief for the symptom of advanced osteoarthritis, but generally requires a significant change in a patient's lifestyle and/or activity level.

Current available drug treatments are mainly directed to pain relief. At this time, there is no commercially available treatment that restores the cartilage damages (see Lotz, 2010).

Interleukin-1 alpha (IL-1α]) and interleukin-1 beta (IL-1β) are naturally occurring agonists of the type I IL-1 receptor (IL-1RA). Overexpression of proinflammatory cytokines, such as IL-1, has been shown to play a major role in the pathogenesis of immunoinflammatory diseases such as rheumatoid arthritis (RA)(Bingham, 2002) or osteoarthritis (OA)(Lee *et al.,* 2013). The clinical application of antagonizing IL-1α and IL-1β in RA has been investigated with anakinera (Kineret™), a recombinant, non-glycoslyated from of human IL-1ra, The use of this therapeutic protein has led to a reduction in frequency and severity of joint damage in RA patients (Bresnihan, 2002; St. Clair, 2002), as well as to pain reduction (Mertens *et al.,* 2009). This molecule has been approved in 2001 in the treatment of some types of RA. Although IL-1 is also involved in OA, Anakinra therapy is not significantly associated with improvements in OA symptoms compared with placebo, although a tendency toward pain reduction with anakinra 150 mg versus placebo was noted (Chevalier *et al.,* 2009).

Fibroblast Growth factor 18 (FGF-18) is a member of the Fibroblast Growth Factor (FGF) family of proteins, closely related to FGF-8 and FGF-17. It has been shown that FGF-18 is a proliferative agent for chondrocytes and osteoblasts (Ellsworth et al., 2002; Shimoaka et al., 2002). FGF-18 has been proposed for the treatment of cartilage disorder such as osteoarthritis and cartilage injury either alone (WO2008/023063) or in combination with hyaluronic acid (WO2004/032849).

Various dosing regimen have been suggested for FGF18. For instance, Moore et al. (2005) disclosed administration twice weekly for 3 weeks, and WO2008/023063 taught administration once a week for 3 weeks. This last dosing regimen has been investigated in clinical trials (for more details see for instance NCT01033994, NCT00911469 and NCT01066871).

Although the dosing regimen described in WO2008023063 gives good results in articular cartilage repair, there is still a risk for acute synovitis. For this reason, there is a need of a method for decreasing risk for treatment related acute synovitis as well as increasing patient tolerance to intrarticular injection, while maintaining the efficacy for the treatment of cartilage disorder, via notably chondrocytes proliferation and subsequent cartilage repair. Such a method should not only allow articular cartilage

repair, possibly in absence of synovitis, but also allow reformation of new cartilage having good properties (i.e. mainly hyaline cartilage). Indeed, generation of said hyaline cartilage is valuable both as a therapeutic and as component for biological matrices (Getgood *et al.,* 2010). There is also a need of a method for decreasing pain/improving function, while maintaining the efficacy for the treatment of cartilage disorder. Indeed, pain is not only very often associated with cartilage disorders but represents the leading symptom for clinical detection of these disorders.

Summary of the invention

It is an object of the present invention to provide a method for treating a patient having a cartilage disorder comprising the administration of an FGF-18 compound wherein the FGF-18 compound is administered at least two times per treatment cycle, said administrations being separated by about 2 weeks, preferably by 2 weeks (bi-weekly administrations). In a preferred embodiment said administrations are separated by regular interval of about 2 weeks each. Preferably, the FGF-18 compound is administered in regular bi-weekly intervals .

The present invention further provides an FGF-18 compound for use in the treatment of a patient having a cartilage disorder wherein the FGF-18 compound is to be administered at least two times per treatment cycle, said administrations being separated by about 2 weeks, preferably by 2 weeks (bi-weekly administrations). In a preferred embodiment said administrations are separated by regular interval of about 2 weeks each. Preferably, the FGF-18 compound is administered in regular bi-weekly intervals.

Preferably, the FGF-18 compound to be administered is the FGF-18 fragment designated herein as trFGF-18 (or sprifermin) and the posology cycle is 3 to 300 µg per intra-articular injection, once every 2 weeks for 3 consecutive administrations (one treatment cycle).

In the context on the present invention as a whole, any treatment (or any method for treating) with an FGF-18 compound can further comprise the administration of an anti-inflammatory drug with effects on symptoms (pain and function), such as anakinra or diclofenac. Preferably, such administration is performed at the same time as the administration of the FGF-18 compound. If a anti-inflammatory drug is needed, it would therefore follow that said anti-inflammatory drug is to be administered concomitantly with the FGF-18 compound at least two times per treatment cycle, said administrations being separated by about 2 weeks, preferably by 2 weeks (bi-weekly administrations). Preferably the anti-inflammatory drug is anakinra or diclofenac and the posology cycle is 0.01 to 500 mg per administration, once every 2 weeks for 3 consecutive administrations (one treatment cycle).

In a preferred embodiment such a treatment cycle (i.e. FGF-18 compound alone or in combination with a anti-inflammatory drug with effects on symptoms (pain and function)) may be repeated several months after the last injection of the preceding treatment cycle, for instance after 2, 4 or 6 months or even after 1 year.

In preferred embodiments of the invention, the cartilage disorder to be treated is arthritis, such as osteoarthritis, or cartilage injury with or without surgical intervention such as microfracture. It has surprisingly been found that the methods and uses of the present invention improve notably cartilage

repair and stimulate proliferation of chondrocytes, and in the meantime, increase patient tolerance to intrarticular injection. It has further surprisingly been found that when anakinra or diclofenac is used together with FGF18, it is able to efficiently restore the proliferative activity of the FGF-18 compound. Another advantage of the present invention is that synovitis will be reduced compared to what is observed with other regimens.

Definitions

- The term “FGF-18 compound” or “FGF-18”, as used herein, is intended to be a protein maintaining at least one biological activity of the human FGF-18 protein. FGF-18 may be native, in its mature form, a recombinant form or a truncated form thereof. Biological activities of the human FGF-18 protein include notably the increase in chondrocyte or osteoblast proliferation (see WO98/16644) or in cartilage formation (see WO2008/023063). Native, or wild-type, human FGF-18 is a protein expressed by chondrocytes of articular cartilage. Human FGF-18 was first designated zFGF-5 and is fully described in WO98/16644. SEQ ID NO:1 corresponds to the amino acid sequence of the native human FGF-18, with a signal peptide consisting of amino acid residues 1(Met) to 27(Ala). The mature form of human FGF-18 corresponds to the amino acid sequence from residue 28(Glu) to residue 207(Ala) of SEQ ID NO: 1 (180 amino acids).

FGF-18, in the present invention, may be produced by recombinant method, such as taught by the application WO2006/063362. Depending on the expression systems and conditions, FGF-18 in the present invention is expressed in a recombinant host cell with a starting Methionine (Met) residue or with a signal sequence for secretion. When expressed in prokaryotic host, such as in E. coli, FGF-18 contains an additional Met residue in N-terminal of its sequence. For instance, the amino acid sequence of human FGF-18, when expressed in E.coli, starts with a Met residue in N-term (position 1) followed by residues 28 (Glu) to residue 207 (Ala) of SEQ ID NO: 1.

- The term “truncated form”of FGF18, as used herein, refers to a protein which comprises or consists of residues 28(Glu) to 196(Lys) of SEQ ID NO: 1. Preferably, the truncated form of FGF-18 protein is the polypeptide designated “trFGF-18” (170 amino acids; also known as rhFGF18 or sprifermin), which starts with a Met residue (in N-terminal) followed by amino acid residues 28 (Glu) -196 (Lys) of the wild-type human FGF-18. The amino acid sequence of trFGF-18 is shown in SEQ ID NO:2 (amino acid residues 2 to 170 of SEQ ID NO:2 correspond to amino acid residues 28 to 196 of SEQ ID NO:1). trFGF-18 is a recombinant truncated form of human FGF-18, produced in E.coli (see WO2006/063362). trFGF-18 has been shown to display similar activities as the mature human FGF-18, e.g. it increases chondrocyte proliferation and cartilage deposition leading to repair and reconstruction for a variety of cartilaginous tissues (see WO2008/023063).

- The terms “anti-inflammatory drug with effects on symptoms (pain and function)” or “anti-inflammatory drug” as used herein refer to an anti-inflammatory drug having effects on symptoms linked to the cartilage disorders to be treated such as pain and function. The preferred “anti-inflammatory drugs” to be used according to this invention are anakinra and diclofenac. Anakinra is a recombinant, nonglycosylated form of human interleukin-1 receptor antagonist (IL-1Ra). It is

commercialized under the name Kineret®. Its sequence corresponds to SEQ ID NO.3. Diclofenac (i.e. 2-(2,6-dichloranilino) phenylacetic acid) is a drug well known for reducing inflammation and as an analgesic reducing pain in certain conditions. It is commercialized under various trade names.

- The term “about” in “about 2 weeks” or “about every 2 weeks” encompasses administrations separated by 2 weeks (14 days), as well as administration separated by 2 weeks +/- few days (e.g. +/- 1, 2, 3 day(s)). Indeed, it should be understood that, notably for a practical point of view, the administration of the FGF-18 compound, for instance trFGF-18, cannot always be performed at exact intervals, *e.g.* exactly 2 weeks (14 days) day per day after the previous administration. Therefore, in the context of the invention, 2 weeks means 14 days, but may also be 11, 12, 13, 15, 16, or 17 days after the previous administration, for the conveniency of the patient. In the context of the present invention, the term “2 weeks” is similar to the terms “every 2 weeks”, “every other week” or “bi-weekly” and they can be used interchangeably (Figure 1). “2 weeks” can be used should one refers to “days” (e.g. 1st injection a Monday, following injection a Monday 2 weeks after) or should one refers to a “date” (e.g. 1st injection the 1st of August. Following injection the 15th of August).

- The term “treatment cycle” or “cycle” corresponds to the period wherein an FGF-18 compound is given every 2 weeks (consecutive administrations). As an example, a treatment cycle can consist of 3 injections at 2 weeks interval each. Such a “treatment cycle” can be repeated. For instance, a second “treatment cycle” can be performed 2, 3, 4, 5 or 6 months after the last injection of the previous cycle. Alternatively, a second cycle can also be performed 1 year or 2 years after the first injection in the first cycle. As an example, a first treatment cycle consisting of 3 injections at 2 weeks interval each can be followed, 3 months after the last injection of said cycle, by a second treatment cycle of 3 injections at 2 weeks interval each.

-The term “cartilage disorder”, as used herein, encompasses disorders resulting from damages due to injury, such as traumatic injury, chondropathy or arthritis. Examples of cartilage disorders that may be treated by the administration of the FGF-18 formulation described herein include but are not restricted to arthritis, such as osteoarthritis, and cartilage injury. Degenerative diseases/disorders of the cartilage or of the joint, such as chondrocalcinosis, polychondritis, relapsing polychondritis, ankylosing spondylitis or costochondritis are also encompassed by this wording. The International Cartilage Repair Society has proposed an arthroscopic grading system to assess the severity of the cartilage defect: grade 0: (normal) healthy cartilage, grade 1: the cartilage has a soft spot or blisters, grade 2: minor tears visible in the cartilage, grade 3: lesions have deep crevices (more than 50% of cartilage layer) and grade 4: the cartilage tear exposes the underlying (subchronal) bone. (see ICRS publication: http://www.cartilage.org/_files/contentmanagement/ICRS_evaluation.pdf, page 13).

- The term “arthritis” as used herein encompasses disorders such as osteoarthritis, rheumatoid arthritis, juvenile rheumatoid arthritis, infectious arthritis, psoriatic arthritis, Still's disease (onset of juvenile rheumatoid arthritis) or osteochondritis dissecan. It preferably includes diseases or disorders in which ones the cartilage is damaged.

- The term “Osteoarthritis”, or “OA”, is used to intend the most common form of arthritis. The term “osteoarthritis” encompasses both primary osteoarthritis and secondary osteoarthritis (see for instance

The Merck Manual, 17th edition, page 449). Osteoarthritis may be caused by the breakdown of cartilage. Bits of cartilage may break off and cause pain and swelling in the joint between bones. Over time, the cartilage may wear away entirely, and the bones will rub together. Osteoarthritis can affect any joint but usually concerns hands, shoulders and weight-bearing joints such as hips, knees, feet, and spine. In a preferred example, the osteoarthritis may be knee osteoarthritis or hip osteoarthritis. This wording encompasses notably the forms of osteoarthritis which are classified as stage 1 to stage 4 or grade 1 to grade 6 according to the OARSI classification system. The skilled person is fully aware of osteoarthritis classifications that are used in the art, in particular said OARSI assessment system (also named OOCHAS; see for instance Custers et al., 2007). Osteoarthritis is one of the preferred cartilage disorders that can be treated by administering the FGF-18 coumpounds according to the present invention.

- The term “cartilage injury” as used herein is a cartilage disorder or cartilage damage resulting notably from a trauma. Cartilage injuries can occur notably after traumatic mechanical destruction, notably further to an accident or surgery (for instance microfracture surgery). This term “cartilage injury” also includes chondral or osteochondral fracture and damage to meniscus. Also considered within this definition is sport-related injury or sport- related wear of tissues of the joint. The term also includes microdamage or blunt trauma, a chondral fracture, an osteochondral fracture or damage to meniscus.
- In the context of the present invention, the “efficacy” of a treatment can be measured based on changes in the thickness of the cartilage, for instance the thickness of the articular cartilage of the joint. This thickness can be assessed, for instance, through X-ray computed tomography, Magnetic Resonance Imaging (MRI) or ultrasonic measurments.

Detailed description of the invention

The present invention provides administration schemes for the treatment of various cartilage disorders, such as osteoarthritis and cartilage injury, with a FGF-18 compound. Preferably, said FGF-18 compound is trFGF-18 as defined above. In the context of the present invention it has been shown that FGF-18 compounds have optimal disease- or symptom-ameliorating effects on cartilage disorders when administered according to the methods and uses disclosed herein. It has been surprisingly found that the dosing regimens of the present invention (*i.e.* less frequent dosing schedules than once a week for three week per treatment cycle) cause reduced inflammation (*e.g.* acute synovitis) status during the next injection and therefore the full activity of FGF-18 compounds can be observed. This finding was not expected because of the rather short half-life of FGF-18 in the joint (less than 24 hours).

In the context on the present invention as a whole, any treatment (or any method for treating) with an FGF-18 compound can further comprise the administration of a anti-inflammatory drug with effects on symptoms (pain and function), such as anakinra or diclofenac. Preferably, such administration (or co-administration) is performed at the same time as (i.e. concomitantly with) the administration of the FGF-18 compound.

In one embodiment, the present invention provides a method for treating a patient having a cartilage disorder comprising the administration of an FGF-18 compound wherein the FGF-18 compound is administered at least two times per treatment cycle, said administrations being separated by about 2 weeks, preferably by 2 weeks (i.e. every 2 weeks, every other week or bi-weekly). The preferred FGF-18 compound is trFGF-18. In a preferred embodiment, FGF-18 compound can be administered 3 times per treatment cycle, in regular intervals of 2 weeks or of about 2 weeks (i.e. 3 times per treatment cycle, in regular intervals of 2 weeks or once every 2 weeks). Such treatment may comprise 1, 2 or 3 treatment cycles per year. A anti-inflammatory drug, such as anakinra or diclofenac, can be administered at the same time as the FGF-18 compound.

In another aspect of the present invention there is provided an FGF-18 compound for use in the treatment of a patient having a cartilage disorder wherein the FGF-18 compound is administered at least two times per treatment cycle, said administrations being separated by about 2 weeks, preferably by 2 weeks. The preferred FGF-18 compound is trFGF-18. In a preferred embodiment the FGF-18 compound is administered 3 times per treatment cycle, in regular intervals of 2 weeks or of about 2 weeks (i.e. 3 times per treatment cycle, in regular intervals of 2 weeks or once every 2 weeks). Such treatment may comprise 1, 2 or 3 treatment cycles per year. A anti-inflammatory drug with effects on symptoms (pain and function), such as anakinra or diclofenac, can be administered at the same time as the FGF-18 compound.

According to the present invention, the administration of the FGF-18 compound, either alone or in combination with a anti-inflammatory drug, such as anakinra or diclofenac, is to be performed at regular intervals, however slight variations of +/- few days are authorized (preferably no more than 3 days). For example, where administrations are separated by about 2 weeks, if the first administration of a cycle is given on a Tuesday, the second administration may be made the Tuesday, 2 weeks after the first administration (regular interval) or a few days after or before (for instance the Monday before or Thursday after. Similarly, if the first administration is given for instance the 1st of August (a Monday for instance), the second administration may be made the 15th of August (Monday), i.e. 2 weeks after the first administration (regular interval) or a few days after or before (for instance the Friday or Saturday before the 15th of August or the Tuesday or Wednesday following that 15th of August). Such a flexibility allows the dosing regimen to be notably less restricting and more convienient for the patient. Preferably, administrations are performed on a regular interval basis, e.g. every 2 weeks. In one preferred embodiment they are separated by 2 weeks (i.e. bi-weekly injection).

In the context of the present invention as a whole, the FGF-18 compound is administered at least two times per treatment cycle. It can also be administered, for instance, at least 3 times or at least 4 times per treatment cycle. Preferably, it is administered for 3 times or 4 times per treatment cycle.

In a preferred embodiment, the FGF-18 compound, either alone or in combination with a anti-inflammatory drug (such as anakinra or diclofenac), is to be administered for at least 2 consecutive times, at least 3 consecutive times or at least 4 consecutive times per treatment cycle. In a further preferred embodiment the FGF-18 compound, either alone or in combination with a anti-inflammatory drug (such as anakinra or diclofenac), is administered for 2 consecutive times, 3 consecutive times or

4 consecutive times per treatment cycle. In an even preferred embodiment, it is administered for 3 consecutive times.

In the context of the present invention as a whole, such treatment may comprise several treatment cycles per year, such as 1, 2 or 3 treatment cycles per year. In one preferred embodiment, such treatment comprises 2 cycles per year. As an alternative, the treatment comprises 1 cycle per year, repeated 1 year or 2 years after the beginning of the first treatment cycle. As an example, should a treatment comprising 1 cycle, said treatment may consist of 3 injections at 2 weeks interval each. As a further example, should a treatment comprising at least 2 cycles, a first treatment cycle consisting of 3 injections at 2 weeks interval each can be followed, several months after the last injection of said cycle, by a second treatment cycle of 3 injections at 2 weeks interval each.

The FGF-18 compound of the invention is preferably selected from the group consisting of a) a polypeptide comprising or consisting of the human FGF-18 mature form comprising residues 28-207 of SEQ ID NO:1, or b) a polypeptide comprising or consisting of FGF-18(170AA)(SEQ ID NO:2). Particularly, this compound is selected from human wildtype mature FGF-18 or trFGF-18. Said compound increases cartilage deposition and allows cartilage repair.

In a further preferred embodiment, the treatment comprises administration of the FGF-18 compound at a dose of 3-600 micrograms (µg or mcg), preferably 3-300 µg, or preferably 10-200 µg, or more preferably 30-150 µg, or even more preferably 30-120 µg per single intra-articular administration. In a preferred embodiment the treatment comprises administration at a dose of about 3, 10, 20, 30, 40, 50, 60, 90, 100, 120, 150, 180, 200, 240 or 300 µg per single intra-articular administration of the FGF-18 compound. Preferred doses include 10, 20, 30, 60, 90, 120, 180, 240 or 300 µg per single intra-articular administration of the FGF-18 compound. It should be understood that the dose of the FGF-18 compound to be administered will be different should the patient to be treated is a human or a non-human mammal. For instance, for dogs, the dose will be preferably 5-fold less important than for human. As an example, should the human dose being range from 30 to 120 µg per single intra-articular administration, the dose for a dog could be ranged from 5 to 20 µg per single intra-articular administration. Examples of dosing for rats and rabbits can be found in the examples sections.

In the context of the present invention as a whole, the FGF-18 compound can be used in combination with a anti-inflammatory drug with effects on symptoms (pain and function). The preferred anti-inflammatory drug is anakinra (see SEQ ID NO.3) or diclofenac. When any one of anakinra or diclofenac is administered, the treatment comprises administration at a dose of 0.01 – 500 milligrams (mg), preferably 0.1-250 mg, or more preferably 0.5-150 mg per single administration, either intraarticularly (preferable way for anakinra for instance) or orally (preferable way for diclofenac for instance). In a preferred embodiment the treatment comprises administration at a dose of about 0.03, 0.1, 0.25, 0.3, 0.5, 1, 1.5, 2, 5, 10, 15, 20, 30, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or 300 mg per single administration of the anti-inflammatory drug. Preferred doses include 0.5, 1, 5, 1.5, 10, 50, 100 and 150 mg per single administration. It should be understood that the dose of anti-inflammatory drug to be administered will be different should the patient to be treated is a human or a non-human mammal. For instance, for dogs, the dose will be preferably 6-fold less important than for human. As

an example, should the human dose of anakinra being 150 mg per single intra-articular administration, the dose for a dog could be 25 mg per single intra-articular administration. The physicist will adapt the dosing regimen for the anti-inflammatory drug case by case, depending on the patient and on the anti-inflammatory drug to be adminsitered. For instance, for diclofenac given orally, the dosing regimen can be 50 or 75 mg, two or three time a day.

FGF-18 compounds may be formulated as a pharmaceutical composition, i.e. together with a pharmaceutically acceptable carrier, excipients or the like. The definition of "pharmaceutically acceptable" is meant to encompass any carrier, excipients or the like, which does not interfere with effectiveness of the biological activity of the active ingredient and that is not toxic to the patient to which it is administered. For example, for parenteral administration, the active protein(s) may be formulated in a unit dosage form for injection in vehicles such as saline, dextrose solution, serum albumin and Ringer's solution. Formulations for intraarticular application will comply with most of the requirements that also apply to other injection formulations, i.e., they need to be sterile and compatible with the physiological conditions at the application site (e.g., knee joint, synovial fluid). The excipients used for intraarticular injection may also be present in other injection formulations, e.g., for intramuscular or subcutaneous application. Such formulations of FGF-18 compounds, including at least one further pharmaceutically acceptable carrier, excipients or the like, are herein also referred to as "FGF-18 compositions" or “FGF-18 formulations”. Said "FGF-18 compositions" or “FGF-18 formulations” are also useful in the context of the present invention.

If a anti-inflammatory drug, such as anakinra or diclofenac, is used together with an FGF-18 compound, it can be either added to the FGF-18 compound formulation before administration, or co-administered either using 2 different syringes/needles, or using 2 different syringes but preferably the same needle to increase patient convenience. Alternatively, the anti-inflammatory drug can be administered orally or by any other way of administering.

FGF-18 compounds, such as trFGF-18, and compositions containing FGF-18 compounds ("FGF-18 compositions") will be useful for treating cartilage disorders. In particular it can be useful for treating articular cartilage defects in synovial joints that are, for instance, due to superficial fibrillation (early osteoarthritis), cartilage degeneration due to osteoarthritis, and chondral or osteochondral defects due to injury or disease. FGF-18 compounds and compositions may also be useful for treating joint disease caused by osteochondritis dissecans and degenerative joint diseases. In the field of reconstructive and plastic surgery, FGF-18 compounds and compositions will be useful for autogenous or allogenic cartilage expansion and transfer for reconstruction of extensive tissue defects. FGF-18 compositions can be used to repair cartilage damage in conjunction with lavage of the joint, stimulation of bone marrow, abrasion arthroplasty, subchondral drilling, or microfracture of the subchondral bone. The optional co-administration with a anti-inflammatory drug with effects on symptoms (pain and function), such as anakinra or diclofenac, would decrease pain associated with the cartilage disorder to be treated.

In a preferred embodiment, the cartilage disorder to be treated according to the invention is osteoarthritis, such as knee osteoarthritis or hip osteoarthritis. The osteoarthritis to be treated can be,

for example, and not limited to, primary osteoarthritis or secondary osteoarthritis, as well as osteoarthritis which is classified as stage 1 to stage 4 or grade 1 to grade 6 according to the OARSI classification system.

In an other preferred embodiment, the cartilage disorder to be treated according to the invention is cartilage injury with and without surgical interventions, such as microfractures. Additionally, after the growth of cartilage due to the administration of the FGF-18 composition (administered either alone or together with a anti-inflammatory drug, such as anakinra or diclofenac), a surgical treatment may be necessary to suitably contour the newly formed cartilage surface.

In a preferred embodiment, the treatment comprises intra-articular administration of the FGF-18 compound or FGF-18 composition, either alone or together with a anti-inflammatory drug with effects on symptoms (pain and function), such as anakinra or diclofenac. FGF-18 compounds or FGF-18 compositions can be applied, either alone or together with a anti-inflammatory drug, such as anakinra or diclofenac, by direct injection into the synovial fluid of the joint or directly into the defect, either alone or complexed with a suitable carrier for extended release of protein (e.g. sustained-release formulations) or restricted local release. Preferably, the mode of administration of the FGF-18 compound, either alone or together with a anti-inflammatory drug, such as anakinra or diclofenac described herein is selected from the group consisting of: peri-synovial administration, intra-synovial administration, peri-articular administration and intra-articular administration. In a preferred embodiment, the FGF-18 compound described herein is administered, either alone or together with a anti-inflammatory drug, such as anakinra or diclofenac, preferably intrarticularly (administration within a joint). The anti-inflammatory drug is administered preferably intrarticularly (preferable way for anakinra) or orally (preferable way for diclofenac). The intraarticular administration is done in a joint selected from joint of the hip, knee, elbow, wrist, ankle, spine, feet, finger, toe, hand, shoulder, ribs, shoulder blades, thighs, shins, heels and along the bony points of the spine. In yet another preferred embodiment the intraarticular administration is done in a the joint of the hip or the knee.

Description of the figures:

Figure 1: Treatment schedule outline. Figure 1a: once weekly dosing regimen; Figure 1b: once monthly (or every 4 weeks) dosing regimen; Figure 1c: once monthly (or every 4 weeks) dosing regimen +/- few days of variations accepted for the convenience of the patient.

Figure 2: FGF-18 componds evoke dose dependent articular matrix deposition in an rat OA model illustrated by quantification of Safranin-O staining

Figure 3: Total Joint Score Without Femur

Figure 4: Total Joint Score

Figure 5: Substantial Tibial Cartilage Degeneration Width

Figure 6: Cell concentration after 8 days of culture of porcine chondrocytes stimulated or not with IL1α stimulated or not with IL1 days of culture (A) or after a 6 hours delay (B) with rhFGF18 100 ng/mL and/or Anakinra 100 ng/mL. N=4 for (A) and N=6 for (B).

Figure 7: Serum α2MG Levels Over Time

Figure 8: AUC (area under the curve) of joint diameter difference between target knee (OA joint) and the contralateral joint (healthy knee) over time

Figure 9: cartilage volume (in mm^3) on medial tibia

Description of the sequences:

SEQ ID NO.1: Amino acid sequence of the native human FGF-18.

SEQ ID NO.2: Amino acid sequence of the recombinant truncated FGF-18 (trFGF-18).

SEQ ID NO.3: Amino acid sequence of the recombinant human iIL-1 receptor antagonist (anakinra)

Examples

Material

The recombinant truncated FGF-18 (trFGF-18) of the present examples has been prepared by expression in E.coli, according to the technique described in the application WO2006/063362. In the following examples, trFGF-18 and FGF-18 are used interchangeably.

The recombinant human interleukin-1 receptor antagonist (anakinra) has been obtained via Pharmacia.

Scoring of joints

After the sacrifice, the right knee was removed and decalcified in 5% formic acid for 4–6 d before cutting in half in the frontal plane and embedding in paraffin wax. Three sections were cut in 200 µm steps, stained with toluidine blue, and analyzed using ImagePro Plus™ software (Media Cybernetics). In scoring the three sections of the joint, the worst-case scenario for the two halves on each slide was determined for the cartilage lesion as the cartilage degeneration width (µm). This reflects the areas of tibial cartilage lesion in which both chondrocyte and proteoglycan loss extend ≥50% of the cartilage thickness. The measurement was taken over the area of greatest lesion severity in each of the three zones across the tibial surface.

A treatment group Mean±SE for each score and measurement was determined.

Data was analyzed using a one-way analysis of variance (1-way ANOVA) or Kruskal- Wallis test (non-parametric), along with an appropriate multiple comparison post-test. Right knee caliper measurements were compared to lefts using a student's t-test. Unless indicated, Bolder BioPATH, Inc. performs statistical analysis on raw (untransformed) data only. Statistical tests make certain assumptions regarding the data's normality and homogeneity of variance, and further analysis may be required if testing resulted in violations of these assumptions. Significance for all tests was set at $p \leq 0.05$. Comparisons were made between each group and the vehicle control group, as well as between pairs

Example 1

Method: The anterior cruciate ligament transection with resection of the medial meniscus (ACLT+tMx) model of instability induced OA was performed in male Lewis rats 10-15 weeks of age. Briefly, under

anesthetizis with Isoflurane, the joint capsule of the right knee of each rat was opened, the anterior cruciate and the meniscus fixating ligaments were sharply transected, the meniscus was removed and the capsule, muscles and skin closed by sutures. Animals were randomly allocated into 10 groups of n=10 each. Following dosages were investigated 0, 0.3, 1, 3 and 10µg per intraarticular injection. Groups 1-5 received one cycle of three single injections in weekly intervals, group 6-10 three single injections in monthly intervals. Intraarticular treatment was started three weeks post surgery. At this time pathophysiological changes are alredy mainifest eg cartilage matrix loss. Animals were euthanized 17 weeks after surgery and joints were investigated.

Results: trFGF-18 induced dose-dependent neo-formation of cartilaginous tissue which became significant in the lateral tibia with 1 µg/joint independently of the injection regime (see Figure 2a). trFGF-18 induced dose-dependent neo-formation of cartilaginous tissue which became significant in the medial tibia with 1 µg/joint according to the one weekly regimen and with 0.3 µg/joint according to the one monthly regimen (see Figure 2b)

Example 2

Method: Male Lewis rats underwent surgery (under anesthetizis with Isoflurane) to induce a medial meniscal tear in the right knee joint. Animals were dosed IA with vehicle or FGF-18 on one of two different regimens (see table below), then terminated on day 105. Knees had caliper measurements taken at baseline and days 21, 42, 56, 84, and 105. Serum was evaluated for α2macroglobulin levels at baseline and on days 21, and 105, as well as one week after the final dose (day 42 or 84). Right knees were collected for histopathology evaluation.

Table 1: treatment groups

Group	Number of rats	Treatment (10 µg in 50 µl)
1	10	Normal+vehicle d21,35,49
2	10	surgery+vehicle d21,35,49
3	10	Surgery+FGF-18 d21,28,35 (weekly treatment)
4	10	surgery+FGF-18 d21,35,49 (bi-weekly)
5	10	Surgery+FGF-18 d21,49,77 (monthly treatment)
6	10	Surgery+FGF18 d21,35
7	10	Surgery+ FGF18 d21,77

Results and conclusions:

All animals resumed weight bearing immediately post surgery upon recovery from anesthesia. All animals gained weight over the course of the study and there were no significant differences in body weight change between groups.

Knee diameters, measured by caliper measurement and serum levels of a2MG increased after FGF-18 injections but a clear benefit of one specific treatment regime over another was not demonstrated

in this study using these parameters. In contrast the structural benefit was highest with monthly injection scheme (Figures 3, 4, 5). The bi-weekly injection scheme is also promising and provide interesting structural benefits.

Overall, results of this study indicate that treatment with FGF-18, regardless of regimen, significantly increased swelling in the treated knee after the first injection. Histopathology evaluation indicated that treatment generally increased the extent of injury over the tibial surface, particularly in terms of collagen damage, while reducing its severity. This effect was most evident in the treatment groups that received three doses rather than two, and in groups that received their final dose at the latest time point (day 77). Several other side effects of treatment were seen, including cartilage hypertrophy, synovitis, and synovial fibrosis. These changes were most evident and severe in animals that received three doses in rapid succession (Groups 3 and 4), while animals that received only two doses (Groups 6 and 7) or received their doses over a greater timeframe (Group 5) had slightly less severe changes. The treatment regimen that resutled in the best overall morphology was the three injections, once monthly (Group 5; injections at days 21, 49, and 77), indicating that some recovery time between doses was beneficial. Alternatively, the treatment regimen three injections, once every 2 weeks (Group 4; injections at days 21, 35 and 49), resulted in good overall morphology.

Example 3

Methods:

60 adult male, naïve, New Zealand White rabbits were used for this study. Animals were approximately 3-4 months of age Rabbits underwent for creation of the cartilage defect right knee. A 2 mm by 6 mm fullthickness defect was made in the articular cartilage of the trochlear groove. The microfracture was created using 18 gauge needles, two 3 mm deep micro fractures were made through the subchondral bone at the base of the defect, one proximally and one distally. Each micro fracture hole was approximately 1.5 mm in diameter and the holes separated by 2 mm.

The experiment consisted of the following six treatment groups, with 10 animals in each group for a total of 60 rabbits (Table 2). Rabbits in Groups 3, 4, 5 and 6 were treated with intra-articular rhFGF18 in either one cycle of three weekly injections of 100µg of rhFGF18 (Group 3 and 5) or one cycle of three monthly injections 100µg of rhFGF18 (Group 4 and 6). All animals were euthanized and necropsied 6 months after surgery.

Table 2: treatment groups

Group # (n=10)	Cartilage defect	Micro-fracture	Test article & treatment schedule	Dose µg/injection (trFGF-18)	trFGF-18 concentration (µg/ml)	Volume (ml/joint)	Day of dose
1	Yes	No	None	0	NA	NA	NA
2	Yes	Yes	None	0	NA	NA	NA
3	Yes	No	rhFGF18 (1x/week for 3 weeks	100	500	0.2	Day 7,14,21

4	Yes	No	1x/month for 3 months)	100	500	0.2	Day 28,56,84
5	Yes	Yes	rhFGF18 (1x/week for 3 weeks	100	500	0.2	Day 7,14,21
6	Yes	Yes	1x/month for 3 months)	100	500	0.2	Day 28,56,84

Results:

Necropsy Findings (Table 3): The ICRS gross cartilage score was 1.9+/-0.3 SE for Group 5 animals and 2.4+/-0.2 SE for Group 6 animals indicating that the monthly injection scheme was superior compared to the weekly one. In Group 6 animals the intercondylar groove was filled in 3/10 animals with finely granular to granular cartilage, the remaining 7/10 animals had the groove 50% filled up to nearly completely filled with granular to coarsely granular cartilage. In summary, the injection of rhFGF18 alone or in combination with microfracture, administered as a single weekly or monthly injection, resulted in thickening or enlargement of the femoral condyle region and a proliferation of rough or coarsely granular cartilage in the intercondylar groove lesion and stimulation of osteophytes on the medial and lateral trochlear ridges, occasional tibial plateau osteophyte formation, or abnormal cartilage growth on the patella or adjacent to the patella in the synovial fat pad.

Morphologic Pathology when no microfracture: Right femur lesion sections from animals treated monthly for three months with rhFGF18 had significantly increased defect fill percentages (48%), resulting in a significant 49% increase in the defect fill score. Other scores were non-significantly increased by 20-23%. The total width of the groove lesion was nonsignificantly increased by 36%, while the width of the lesion with no viable cartilage was significantly decreased by 94%. All sections had degeneration that ranged from minimal to severe, was generally focal, and was typically seen in conjunction with fibrocartilage. The central MFC thickness was significantly increased by 120%.

Morphologic Pathology –when microfracture: Sections of the cartilage lesion area from untreated controls with microfracture had overall moderate reconstitution of the osteochondral junction, moderately reduced matrix staining, and 50% fill of the defect. Cell morphology was mostly fibrocartilage.

Lesion area sections from animals treated weekly for three weeks with rhFGF18 had significant 44-69% increases (toward normal) in all scored parameters, as well as the defect fill percent. Summed scores were significantly increased by 53%. The total width of the groove lesion was slightly increased by 5% while the width of the lesion with no viable cartilage was decreased (non-significantly) by 59%. All sections had cartilage hypertrophy. Central MFC thickness in these sections was significantly increased by 112%.

Lesion area sections from animals treated monthly for three months with rhFGF18 had significant 61-97% increased (toward normal) in all scored parameters, as well as the defect fill percent. Summed scores were significantly increased by 76%. The total width of the groove lesion and the width of the lesion with no viable cartilage were non-significantly decreased by 19% and 69%, respectively. All

sections had cartilage hypertrophy. Central MFC thickness in these sections was significantly increased by 106%.

Conclusions:

Abnormal clinical signs were mild and consistent with those typically seen in rabbits following knee surgery and/or as a result of repetitive sample collection, either blood collected from the lateral ear veins or synovial fluid collected from the knee joint. Comparison of inter-condylar groove healing of animals in Group 1 and Group 2 showed good spontaneous filling of the groove with what grossly appears to be cartilage. There is a suggestion that microfracture may enhance cartilage regrowth in the groove since 9/10 animals in Group 2 had filling of the groove with cartilage compared to 7/10 animals in Group 1, but this difference is slight.

Likewise, there is no difference between ICRS or osteophyte scores between the two groups so the quality of cartilage healing was good, and there was little stimulation of osteophyte formation in either group. Of the remaining groups treated with rhFGF18, it appears that Group 4 (Intercondylar groove and three monthly intra-articular injections of 100 µg of rhFGF18) showed the best response with 6/9 animals having the intercondylar groove filled with cartilage that appeared nearly normal to slightly roughened or granular in gross appearance. In addition, Group 4 had the next to lowest ICRS cartilage score (2.1 +/- 0.3) of the four groups treated with rhFGF18, and this group had the lowest osteophyte score (3.8 +/- 0.8) of any of the rhFGF18 groups. In contrast, Group 6 (Intercondylar groove with microfracture and three monthly intraarticular injections of 100 µg of rhFGF18) had inter-condylar groove filling in only 3/10 animals, the ICRS score was the highest of any group (2.4 +/- 0.2) and the osteophyte score was the second highest (5.1 +/- 0.7) of any rhFGF18 treated group. Likewise, Group 5 (Intercondylar groove with microfracture and three weekly intra-articular injections of 100 µg of rhFGF18) had the highest osteophyte score of any group (5.7 +/- 0.7).

Beneficial effects were greater when treatment was given over an extended time period, and effects were more evident in rabbits with microfractures than in rabbits without microfractures.

Example 4

Method:

Porcine chondrocytes were isolated from the cartilage of a femoral head of a pig hip (pig were approximately one year old. After dissection of the joints, the cartilage was harvested and digested 45 minutes with collagenase 0.25 % (1/10 dilution of collagenase NBG4 2.5 % in HAM's F12) at room temperature. The loosened cells were discarded and the cartilage further digested overnight with collagenase 0.1 % (1/25 dilution of collagenase NBG4 2.5 % in HAM's F12) at 37°C to extract the chondrocytes. For this study, the chondrocytes were cultured in monolayer.

Primary articular porcine chondrocytes were stimulated or not with 10 ng/mL lL1α and were either treated immediately or 6 hours later with Anakinra 100 ng/mL and/or trFGF-18 100 ng/mL. Each condition was performed in 4 or 6-plicates. As a control, cells were also cultured with Anakinra alone, trFGF-18 alone or in absence of any treatment (Medium).

Pre-culture: After cell isolation porcine chondrocytes were inoculated at 20 000 cells /cm2 and cultivated for one week in complete HAM's F12. Cells were then harvested with accutase, counted and used as described below.

For cells treated directly with Anakinra: Chondrocytes were inoculated in a 24-well plate at 15 000 cells/well in 0.5 mL of complete HAM's F12. Then, 0.25 mL of trFGF-18 400 ng/mL and/or 0.25 mL of Anakinra 400 ng/mL were added to the cells. In the challenged samples, 10 µL of IL1α at 1 000 ng/mL, were also added to the cells. trFGF-18, Anakinra and IL1α were all diluted in complete HAM's F12. The final volume in the culture well was adjusted at 1 mL with complete HAM's F12. Final concentrations were 10 ng/mL IL1α, 100 ng/mL trFGF-18 and 100 ng/mL Anakinra and the total culture time was eight days. A complete medium change was performed after four days. N=4.

For cells treated with Anakinra and trFGF-18 6 hours after the IL1α challenge: Chondrocytes were inoculated in a 24-well plate at 15 000 cells/well in 1 mL of complete HAM's F12 containing or not IL1α 10 ng/mL. After 6 hours the medium was removed and replaced with 0.25 mL trFGF-18 400 ng/mL and/or 0.25 mL of Anakinra 400 ng/mL. In the challenged samples, 0.25 mL of IL1α at 40 ng/mL was also added to the cells. trFGF-18, Anakinra and IL1α were all diluted in complete HAM's F12. The final volume in the culture well was adjusted at 1 mL with complete HAM's F12. Final concentrations were 10 ng/mL IL1α, 100 ng/mL trFGF-18 and 100 ng/mL Anakinra and the total culture time was eight days. A complete medium change was performed after four days. N=6.

After eight days of culture, cell were harvested with accutase and resulting cell suspensions were analyzed for cell concentration and cell viability with a ViCell™ Cell analyzer (from Beckman Coulter). Statistic analysis consisted in a 1-way ANOVA followed by a Dunnett post hoc analysis.

Results and conclusions:

As expected rhFGF18 was found to increase porcine chondrocyte proliferation in absence of IL1α. In both experiments in comparison with the control (medium, no IL1α) a 11.25 and 7.75 fold increase in the cell number was observed in presence of rhFGF18 100 ng/mL after 8 days of culture (Figure 6). However, in presence of IL1α 10 ng/mL, the stimulation of the proliferation by rhFGF18 was only 2.38 and 2.44 fold respectively in comparison to the control (medium, IL1α, 10ng/mL) for both experiments. Anakinra 100 ng/mL, for both the direct and the delayed treatments, was shown to fully restore rhFGF18 activity. The cell density for cells cultured with rhFGF18 and without IL1α or challenged with IL1α but treated with Anakinra was found to be not statistically different. Finally, Anakinra alone had no effect on chondrocyte proliferation.

In the present study, Anakinra 100 ng/mL has been shown to fully block the inhibitory effect of IL1α on the proliferative activity of rhFGF18. This in accordance with the fact that Anakinra is a IL1 receptor antagonist, blocking the inflammatory signaling triggered by IL1. It has been presently demonstrated that anakinra restores the proliferative effect of rhFGF18 in porcine chondrocytes challenged with IL1α.

Example 5

Method:

Male Lewis rats underwent surgery to induce a medial meniscal tear in the right kneejoint. Animals were dosed i.a. with FGF-18 (10 µg/joint) on days 21, 28, and 35 and dosed orally with diclofenac (either 1 mg/kg or 3 mg/kg) or vehicle on days 21-23, 28-30, and 35-37, then terminated on day 42 or day 63. Serum was collected and evaluated for alpha 2 macroglobulin (α2MG) levels on days -3, 21, 42, and 63. α2MG is an inflammation serum biomarker. The link between α2MG and inflammation has already been shown (Kuribayashi et al., 2013).

Results

FGF-18+vehicle controls had mild to moderate swelling on day 24, which increased to severe by day 36, although no limping was observed. Knee swelling diminished slightly to marked severity beginning on day 44. Caliper measurements supported these observations, with significant differences between right and left knees at day 21 and later time points, but not at the baseline. Animals given 3 mg/kg of diclofenac had significantly reduced swelling scores on days 24-29, 31, and 36-43, compared to the vehicle controls. Knee caliper measurements were significantly reduced on day 42, but were not significantly affected at any other time point. Animals given 1 mg/kg of diclofenac had significantly reduced swelling scores on days 24-29, 31, and 36-43, compared to the vehicle controls. Knee caliper measurements were significantly reduced on day 42, but were not significantly affected at any other time point. (data not shown).

α2MG levels were higher on day -3 (pre-surgery) than at day 21 post-surgy. Levels in animals given 3 mg/kg of diclofenac were slightly, but significantly reduced compared to those of the vehicle controls at the pre-surgery time point. Levels on day 21, prior to treatment, were essentially the same for all groups. On day 42, the disease controls had markedly elevated α2MG levels (approximately four times the day 21 levels), which was a significant difference from the two diclofenac groups. On day 63, levels for all groups were similar again. (figure 7)

Conclusions:

Overall, results of this study indicate that administration of 1 or 3 mg/kg of diclofenac in rats with medial meniscal tear that were also given FGF-18 significantly reduced knee swelling, based on both clinical observations and caliper measurements. These effects were evident for approximately one week after the final dose of diclofenac. Serum levels of α2MG tracked with the vehicle controls on days -3, 21, and 63, however a sharp reduction was seen on day 42 as a result of a massive spike in the control levels.

Example 6

Method:

The goal of this study was to evaluate the effect of different intracycle dosing frequency of the same total dosage (3x 1µg) of sprifermin on cartilage volume in a rat model of OA. The anterior cruciate

ligament transection (ACLT) with resection of the medial meniscus (tMx) was performed as disclosed in example 1. Joints from male Lister Hooded Rats (200 – 260 g, Charles River) were used in this study. Animals were euthanized 18 weeks post surgery.

The changes in the joint are related to clinical assessments in OA (cartilage loss, osteophytes, subchondral sclerosis). One µg sprifermin in saline were injected three times either weekly, every 2nd, every 3rd, every 4th or every 5th week and compared to appropriate vehicle groups. Body weight, joint diameters and clinical health scores were investigated weekly.

Results

Results shown that intraarticular injections had no influence on the body weight gain: No significant drug or treatment regime effect was seen on *in-life* parameter. However, groups injected every second week with saline (n=4) had highest body weight gain in tendency (data not shown).

With injections in week 3, 4 and 5, joint diameters were significantly higher than after injections in week 3, 8 and 13 (see figure 8). No significant differences were seen between injections every 2nd, 3rd or 4th week. When injected only every fifth week AUC of joint diameters was the same than with saline injections. So, in tendency, the joint diameter AUC decreases with lower injection frequency.

The quantitavie histological analysis via stereology reviled severe OA-like changes in the affected joints. rhFGF18 prevented the more or less complete cartilage denudation. One µg/joint and injection given once every 3rd week (three injections in total) resulted in pharmacological meaningful and statistical significant difference over saline (endpoint: cartilage volume on medial tibia, see Figure 9).

Conclusions:

Lower injection frequencies than once weekly over three weeks seem to allow better recovery from joint swelling after injection. All groups treated with rhFGF18 displayed structural benefit illustrated by higher cartilage volume values compared to placebo. However, under the circumstances of a time-fixed study (same study duration for all animals) and a fixed dosis, the injection frequency once every 3rd week resulted in the most beneficial structural outcome. It can be speculated that longer pauses between injections of rhFGF18 are more beneficial because of better translation of chondrocyte proliferation into extracellular matrix production compared to the the once weekly over three weeks injection regime.

The resulted bell shaped curve is a common observation for efficacy readoutsof growth factors.

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Claims

1. Use of an FGF-18 compound for the manufacture of a medicament for the treatment of a cartilage disorder wherein the FGF-18 compound is to be administered intra-articularly at least three times per treatment cycle, said administrations being separated by 2 weeks, wherein said cartilage disorder is osteoarthritis.

2. The use according to claim 1, wherein said administrations are separated by 2 weeks.

3. The use according to any of the preceding claims, wherein the FGF-18 compound is to be administered at least 3 times or at least 4 times per treatment cycle.

4. The use according to any of the preceding claims, wherein treatment cycles are repeated after 2, 3, 4, 5 or 6 months.

5. The use according to any of the preceding claims, which comprises 1, 2, or 3 treatment cycles per year.

6. The use according to any one of the preceding claims, wherein the FGF-18 compound is to be administered at a dose of 3-300 mcg, or preferably 10-200 mcg, or more preferably 30-150 mcg, or even more preferably 30-120 mcg per single intra-articular administration.

7. The use according to any one of the preceding claims, wherein the FGF-18 compound is to be administered at a dose of about 3, 10, 20, 30, 40, 50, 60, 90, 100, 120, 150, 180, 200, 240 or 300 mcg per single intra-articular administration of the FGF-18 compound.

8. The use according to any of the preceding claims, wherein the cartilage is articular cartilage.

9. The use according to any of the preceding claims, wherein the FGF-18 compound is selected from the group consisting of:

a) a polypeptide comprising or consisting of the human FGF-18 mature form comprising residues 28-207 of SEQ ID NO:1, or

b) a polypeptide comprising or consisting of SEQ ID NO:2.

10. The use according to any of the preceding claims, wherein the FGF-18 compound is to be administered together with a anti-inflammatory drug.

11. The use according to claim 10, wherein the anti-inflammatory drug is anakinra or diclofenac.

12. The use according to claim 10 or claim 11, wherein the anti-inflammatory drug is to be administered at a dose of 0.001-500 mg, or preferably 0.1-250 mg, or more preferably 0.5-150 mg per single administration.

13. The use according to claim 12, wherein the anti-inflammatory drug is to be administered at a dose of 0.03, 0.1, 0.25, 0.3, 0.5, 1, 1.5, 2, 5, 10, 15, 20, 30, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or 300 mg per single administration

14. The use according to any of the preceding claims, wherein the FGF-18 compound is to be administered 3 times per treatment cycle, said administrations being separated by about 2 weeks.

15. The use according to any of the preceding claims, wherein the FGF-18 compound is to be administered bi-weekly for 3 consecutive times.