VILNIUS UNIVERSITY
MEDICAL FACULTY

The Final Thesis

Evidence-Based Therapy for Osteoarthritis

Louis Ferdinand Gallmann, VI year, group 2

Clinic of Rheumatology, Orthopaedics Traumatology and Reconstructive Surgery, Institute of Cinical Medicine

Supervisor Assoc. Prof. Dalia Miltinienė

The Head of Clinic Prof. Irena Butrimienė

2024

ferdinand.gallmann@mf.stud.vu.lt

Table of Contents

1. Summary

This comprehensive literature review investigates Disease Modifying Osteoarthritis Drugs aiming to modify osteoarthritis progression. Focusing on cartilage-driven endotypes, the review evaluates drugs such as Sprifermin, Lorecivivint, MIV-711, S201086/GLPG1972, and Metformin. The FORWARD study emphasises the potential of Sprifermin for lasting structural changes and highlights its possible role in transforming osteoarthritis treatment. Lorecivivint shows significant pain relief, but is insufficient in improving joint space width, so further studies are needed to contribute to a more nuanced understanding of osteoarthritis treatment. MIV-711, a Cathepsin K inhibitor, exhibits promise in attenuating femoral cartilage loss and bone area progression, offering a potential disease modifying effect. S201086/GLPG1972, an ADAMTS-5 inhibitor, faces challenges in reducing cartilage loss but maintains a well-tolerated safety profile, calling for further exploration. Metformin displays potential in diminishing knee cartilage loss and lowering replacement risks, introducing a unique perspective in the context of osteoarthritis treatment. Despite hurdles, Sprifermin and MIV-711 offer potential for structural modification and underline the need for ongoing research to refine personalized treatment guidelines and biomarker understanding in the treatment in osteoarthritis. The lack of approved Disease Modifying Osteoarthritis Drugs for osteoarthritis treatment accentuates the ongoing challenges to an all-encompassing comprehension of the pathophysiology of osteoarthritis and thereby difficulties of a personalized medicine that would enable comprehensive care for osteoarthritis.

2. Keywords

Osteoarthritis; Osteoarthritis Epidemiology; Osteoarthritis Risk factors; Osteoarthritis Diagnostics; Osteoarthritis pathophysiology; (disease modifying drugs) AND (Osteoarthritis); (Osteoarthritis) AND (Sprifermin); (Osteoarthritis) AND (Lorecivivint); (Osteoarthritis) AND (Cathepsin K inhibitor); (ADAMTS inhibitors) AND (Osteoarthritis) AND (Treatment); (Osteoarthritis) AND (Metformin)

3. Introduction

Osteoarthritis affects a large proportion of the population's musculoskeletal system in different parts of the body and in different joints. Osteoarthritis results in a reduced quality of life, increased disease burden, high economic costs and lengthy surgical procedures that ultimately lead to arthroplasty. Although it is a long-known disease, its treatment is based on symptom relief through non-steroidal anti-inflammatory drugs, physical therapy, or surgery in advanced

stages of the disease. Osteoarthritis affects not only the cartilage on the bone, as previously assumed, but the entire joint and all surrounding structures. Therefore, a change in the treatment dogma is required to slow down or even reverse the progression of the disease. Disease Modifying Drugs are a possible solution for the future to meet these requirements in the treatment of osteoarthritis. As osteoarthritis affects the entire joint, different approaches of Disease Modifying Drugs are being investigated, including cartilage-driven endotype, bone-driven endotype and inflammation-driven endotype. The former can be further subdivided into growth factors, Wnt signalling pathways, Cathepsin K inhibitors, ADAMTS-5 inhibitors and Metformin, a well-known antidiabetic drug that is an option for treating the disease progression of osteoarthritis. The potential of these drugs and drug classes is investigated in the following paper through a narrative literature review to determine whether the aforementioned options can slow down the progression of the disease or even reverse the caused damage. The efficacy of the drugs can be measured and is evaluated based on joint space width, cartilage thickness, but also clinical symptoms such as pain, functional scores, and the need for surgery in order to categorise their potential as a Disease Modifying Drug for osteoarthritis.

4. Literature Selection Strategy

The literature search was conducted from June 1, 2023 to January 10, 2024 with the above-mentioned keywords in PubMed. Only original research articles and books in English language were selected. For the extraction of data on drugs, only clinical trials and randomized control trials published after the year 2000 and written in English were considered. All animal trials were excluded, and only human trials were considered for the further selection. After screening the titles and abstracts, the full texts of the relevant articles were extracted.

5. Osteoarthritis

Osteoarthritis (OA) is the most common musculoskeletal disease resulting in reduced functionality, reduced quality of life and high socioeconomic burden. Although OA is a long known disease, its pathophysiology is still being investigated(1). Therefore, OA treatment remains challenging, as it is a more complex disease that goes beyond what was previously considered a “wear and tear” arising condition(2). Until now, the treatment prescribed for OA is mainly symptomatic, but treating the symptoms alone is not sufficient for many patients, as it is not stopping the progression of the disease.

OA is meanwhile defined as a disease of the musculoskeletal system which affects the entire joint, including the cartilage, the subchondral bone, the surrounding ligaments, joint capsule and synovial membrane. Long-term OA usually results in joint destruction and failure of small

and large joints(3). Most often OA affects the hip, knee, hand, foot, and spine. OA can be divided into primary and secondary OA. Primary or idiopathic OA is defined as the absence of any identifiable underlying cause, contrary to secondary OA, in which a correlation to an event, surgery, joint abnormalities at birth, other condition is resulting in OA(2).

5.1 Epidemiology

OA can be defined according to radiological, clinical, or combined clinical and radiological changes, which challenges the estimation of OA prevalence. Poor concordance between radiological changes and clinical symptoms is frequent and can be explained by the fact that not all affected structures include nociceptive innervation. Additionally factors like psychological aspects might contribute to pain and it is not a pure reaction to structural changes, which complicates the calculation of OA patients and only allows estimations(4).

An estimated 240 million people suffer from symptomatic OA including 10 % of men and 18 % of women at age of 60 or older(5). The Global Burden of Disease injuries and risk factor studies found that the incidence rate of symptomatic, radiographically confirmed hip OA has risen to 9.3 % and knee OA to 8.2 % since 1990, which represents a continuous increase(6).

Overall, the Framingham study revealed, in the age group of ≥ 45 years the prevalence of radiographic OA was 17 % while in the age group 63 to 94 years, the prevalence rate of knee OA was estimated to be 33 %, with a higher prevalence in women (34 %) than in men (31%). Out of these 9.5 % had symptomatic knee OA(7). Data from the Framingham cohort study show that 19.6 % of adults ≥ 50 years are affected by hip OA, 4.2% of them had symptomatic hip OA. Contrary to knee OA, the prevalence of radiographic hip OA was greater in men than in women (24.7 % vs. 13.6 %), along with a broadly similar prevalence of symptomatic hip OA (5.2 % vs. 3.0 %)(8). Different studies have shown that geographical variation in OA exist, for example in Korea knee OA prevalence was higher on average(10).

Approximately 40 % of individuals aged 45 and above will experience symptomatic hand OA by the time they reach 85 years, similar to the likelihood of developing symptomatic knee OA (45 %), but higher than the risk of hip OA (25 %)(11).

5.2 Aetiology and Risk Factors

Another reason challenging the treatment and prevention of OA is the multifactorial aetiology of the disease, which can be divided into local and systemic factors, or also referred to as person-level and joint-level factors that contribute to increased susceptibility and progression of OA.

Local risk factors are mostly related to biomechanical changes contributing to adversely forces applied to the joint, while systemic risk factors increase the susceptibility of joints to injury(4).

5.2.1 Person-Level Risk Factors

Firstly, sociodemographic aspects influence susceptibility to OA. Age appears to be one of the strongest risk factors contributing to the development of OA, the reduced capacity of the joint to compensate applied biomechanical forces might explain the higher risk. Moreover, with exception of the cervical spine, the female gender seems to have a higher risk of OA(12). Another sociodemographic aspect includes ethnicity. Studies have shown that Afro-Americans have a higher prevalence of knee and hip OA, also disease expression in Afro-Americans is more severe in tibiofemoral knee OA(13).

Obesity is a strong risk factor for the development of OA, especially for knee OA, studies have shown that weight reduction decreases the risk. BMI has been shown to be moderately associated with the development of OA of the hand(11). Similar for the metabolic syndrome, some studies did not find an association with increased OA risk, while other demonstrated higher incidence of knee pain and cartilage loss(5). The role of nutrition as risk factor and the beneficence of vitamin D, is controversial with insufficient evidence for its benefits. Adequate 25-hydroxyvitamin D levels, potentially combined with vitamin K, may positively affect cartilage, but more research is needed as well as on the impact of Mediterranean diet, soy milk, and high-fibre diets(5,11). Another risk factor for OA includes high bone mineral density which results in higher risk for radiographic knee and hip OA(14).

5.2.2 Joint-Level Risk Factors

Joint structure and malalignment contribute to the development of OA, as well as limb length inequality. The nested case control study using Johnston County Osteoarthritis Project data, revealed that moderate hip OA is linked to deformities as *cam morphology* or *protrusio acetabuli*(16). These findings apply also to knee OA. Varus knee alignment is associated with higher incidence of radiographic tibiofemoral OA and faster disease progression. Developmental joint dysplasia is also crucial for the development of OA, especially for developmental hip dysplasia(11). Another mechanism involved in the development of OA includes injuries and surgeries. Posttraumatic OA (PTOA) results in biomechanical changes of the joint and additionally overloading of the joint tissue leads to irreparable joint tissue and OA, especially after knee injuries(17). Iatrogenic causes include surgeries and its technique, e.g. meniscectomies, which result in development and progression of OA, contrary meniscus

sparing surgeries had no higher incidence of knee OA compared to conservative treatment(18). Muscle strength, mass, and quality influence the development of OA. Flexor as well as extensor weakness of the leg have higher odds for the development of knee OA and faster worsening of symptoms.

Occupation and physical activity, especially physically demanding occupations which require a lot of carrying or working kneeing on the floor, increase the risk for knee and hip OA (19). While moderate physical activity protects from OA, competitive athletes have a higher risk for developing OA. Especially in competitive runners compared to non-competitive runners, competitive weightlifters and football players the incidence of OA is increased(5). Other joint-level factors include meniscal shape or higher signal intensity of the infrapatellar fat pad on MRI were associated with the progression of knee OA(5,20).

5.3 Symptoms

OA symptoms are mostly related to pain, which can be divided into constant background aching pain and intermittent intense pain. While pain is often predictable in the early stages of OA and associated with certain exercises, it becomes less predictable as OA progresses. The 2008 study of Hawker showed the high variation of pain patterns and pain related consequences. Most often, patients suffered from sharp pain resulting in limitation of daily activities in knee OA [Table 1, in Appendices] and ache and sharp pain in hip OA [Table 2, in Appendices] (21). Typical for OA pain is an increase during the day and after specific exercises, as well as short-term morning stiffness of the affected joint. To understand OA symptoms, it is important to emphasize that there is no concordance between morphological changes and pain. Previous pain experiences, expectations regarding treatment, psychological factors, and the sociocultural environment all have the potential to influence an individual's pain experience(22). Non pain related symptoms include joint swelling, clicking, locking, grating, crepitus, cramping, reduced range of motion, and deformity. The symptoms restrict the patients ability to perform activities and ultimately result in reduced quality of life(23).

5.4 Diagnosis

In diagnosing OA, the medical history and physical examination are of fundamental importance for further diagnostic procedures. Indicative for OA is pain as the first occurring symptom, including the pain pattern and occurrence. In primary OA the disease is usually symmetrical in weightbearing joints. Physical examination may show reduced range of motion, crepitus, swelling, and joint effusion, while signs of inflammation are less common. At later stages of

OA muscle atrophy around the involved joint can be seen. OA at the hand affects the proximal interphalangeal joint (PIP), distal interphalangeal joint (DIP) and trapeziometacarpal joint. In PIP and DIP joints, osteophytic growths are referred as Heberden nodes and Bouchard nodes and can be palpated in progressed OA(24). Classical inflammatory markers like C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and uric acid levels should be in range of physiologic norms. Plain radiography is a cost effective tool for detecting OA in later stages and can visualize joint space width (JSW) narrowing or loss, subchondral bony sclerosis, osteophyte formation, and cyst formation(25). CT and MRI are only rarely used in classic OA diagnostics, but compared to plain radiography they are superior in detecting joint malalignment, visualizing changes in non-bony joint structures such as menisci, tendons, ligaments, and also joint effusion.

5.5 Pathogenesis-Molecular Mechanisms

As previously mentioned, OA was long regarded as a “wear and tear” arising condition solely caused by mechanical forces and leading to pure cartilage degradation. Meanwhile it is known that OA affects the entire joint and many different risk factors promote the development of OA and go far beyond cartilage degradation. Different molecular mechanisms might represent a possible therapeutic treatment in the future. Chondrocyte inflammatory conditions, joint aging, senolytics and epigenetics could present future therapeutic targets for OA treatment.

In the early stages of OA, the cartilage surface is unchanged. Otherwise, in the molecular composition and organization of the extracellular matrix (ECM), it is altered by the stimulation of chondrocytes collagen type II (Col2) and aggrecan synthesis in response to pathological stimulation, leading to hypertrophic differentiation and more catabolic factors that cause cartilage degradation as proteoglycans and the collagen network break down(26). As OA progresses, chondrocytes undergo apoptosis and the articular cartilage may be lost completely, resulting in joint space narrowing, friction, pain, and limited joint mobility. Other signs mentioned such as subchondral bone sclerosis, osteophyte formation, bone cyst also occur.

5.5.1 Growth Factors and Osteoarthritis

Transforming growth factor β (TGF-β) super family are of high relevance in the pathogenesis and also a possible treatment option for OA due to its ability to enhance cartilage matrix synthesis(27). Inhibition of TGF-β represents a potential mechanism of OA development, as its physiologic function is to inhibit chondrocyte hypertrophy and maturation and eventually prevent cartilage degradation.

When one of the three isoforms of TGF-β binds to the type II receptor, it activates the canonical TGF-β/Smad signalling cascade. It includes Smad2 and 3 phosphorylation, which forms with the common Smad, a heteromeric Smad complex that is associated with DNA binding protein and gene transcription(28). TGF-β's role in cartilage protection the cartilage was displayed when the signalling of TGF-β was lost, it is associated with OA progression and osteophyte formation(29) [Figure 9, in Appendices]. Similar results were observed in genetic manipulation of TGF-β. When a dominant-negative type II TGF-β receptor (dnTgfbr2) was overexpressed, the skeletal tissue showed articular chondrocyte hypertrophy with increased type X collagen expression, cartilage disorganization and progressive degradation. These findings were consistent with Smad3 knockout in mice that revealed progressive articular cartilage degradation resembling human OA(30). Further evidence between the importance of TGF-β in OA is that a single nucleotide polymorphism in the human Smad3 gene is associated with the incidence of hip OA(31). TGF-β is recognized as a key player in OA as it has a protective and catabolic impact. The homeostasis of TGF-β seems to be of high importance, as its overactivity in subchondral bone can result in primary OA and initiate disease progression and loss of TGF-β is associated with chondrocyte hypertrophy and possibly cartilage degradation(32). The switch of TGF-β pathways in age from canonical anabolic ALK5-Smad2/3 pathway to the catabolic ALK1Smad1/5/8 pathway would exacerbate cartilage destruction and TGF-β supplementation could cause harm(33).

Other growth factors involved in the pathogenesis that might represent potential treatment possibilities include fibroblast growth factor (FGF)-2 and FGF-18. FGF-2 can influence the cartilage by different mechanisms to catabolic and anti-anabolic ways. Increased amounts of FGF-2 are released by cartilage injuries and loading. It results in activation of different transduction signal pathways as the mitogen-activated protein kinase (MAPK) pathway. Thereby, it could stimulate the expression of matrix metallopeptidase (MMP)-13, a potent enzyme degrading enzyme of Col2(34). Another pathway resulting in upregulation of matrix-degrading enzyme expression (ADAMTS-5 and MMP-13) and additional down-regulation of aggrecan expression includes the FGFR1-Ras/PKCδ-Raf-MEK1/2ERK1/2 signalling pathway, which is also activated by FGF-2(35). Therefore, the inhibition of PKCδ peptide might present a potential effective treatment for OA.

FGF-18 is involved in cartilage growth, maturation, processes within mature cartilage and even enhancing regeneration and repair of cartilage(36). Repair of cartilage is associated with stimulated chondrogenesis in vitro as in vivo damage/repair model by using rhFGF-18 increased proteoglycan synthesis was observed, repair cell number and prevention of

apoptosis(37). Therefore, FGF-18 may be a good option not only to stop progression, but also to reverse the cartilage changes.

5.5.2 Wnt/β-catenin Signalling Pathway

The Wnt signalling pathway begins by binding to its receptor and co-receptor, ultimately inhibiting the degradation and instead leading to the accumulation of β-catenin in the nucleus and expression of Wnt target genes [Figure 10, in Appendices]. In the absence of Wnt ligand or inactivation, β-catenin is degraded by proteasomal action and the expression of Wnt genes is suppressed. It was shown that overexpression of active β-catenin results in loss of phenotype of chondrocytes and reduced Col2 expression(38). A mutation of sFRP3, a protein responsible for antagonizing Wnt ligands, resulted in increased levels of β-catenin, that ultimately resulted in aberrant articular chondrocyte hypertrophy and thus leading to hip and knee OA(39), which enforces the importance of Wnt in OA. Increased Wnt signalling pathway is associated with increased cartilage proteoglycan loss and also increased expression of MMP (40). It is suggested that the Wnt/β-catenin signalling pathway plays a major role in OA pathogenesis. In knee joint and disc samples from OA patients, elevated levels of Wnt signalling related genes were significantly upregulated(41). The reason why the inhibition of Wnt signalling causes increased cell apoptosis and cartilage destruction needs to be investigated in further studies in order to determine a complete picture.

5.5.3 MMP-13 and ADAMTS

MMP-13, an enzyme responsible for collagen degradation, preferentially cleaves Col2, which is abundant in articular cartilage and vertebral disk and is considered as the most potent peptidolytic enzymes among other collagenases(42) [Figure 11, in Appendices]. It also targets aggrecan, types IV and IX collagen, gelatin, osteonectin, and perlecan, proteins that contribute to the cartilage.

High MMP-13 expression in patients with articular cartilage destruction suggests that it is responsible for the pathogenesis. The relevance of MMP-13 was demonstrated by a mice model, low MMP-13 showed no phenotypic changes, while MMP-13 overexpression resulted in spontaneous cartilage damage and excessive cleavage of Col2(43). It suggests that MMP-13 can lead to cartilage destruction and gene deletion prevents articular cartilage erosion.

Clinical studies proved that ADAMTS-4 and 5 expression levels are significantly increased, furthermore knockout of ADAMTS-5 gene or double knockout of ADAMTS-4 and 5 genes showed prevention of cartilage degradation in mice model. It is assumed that normal levels of ADAMTS are necessary for physiological cartilage function(44). These findings show the importance of these catabolic enzymes and could represent a therapeutic strategy to prevent or

reduce articular cartilage degradation and the tissue inhibitors of metalloproteinases could be used to attenuate the severity of OA.

5.6 Recommended Treatment

In 2019, the American College of Rheumatology (ACR) published their latest guidelines for treatment of OA. A multi-level treatment plan of should be considered that includes educational, behavioural, psychosocial, and physical interventions, as well as topical, oral, and intraarticular medications. Depending on the patient's needs, these modalities must be evaluated for each patient individually and can be used alone or in combination. The ACR differentiates treatment into two groups, firstly physical/psychosocial/mind body approach and secondly pharmacological approach. Regarding the first group, physical exercise is strongly recommended and should be chosen according to the patient's preferences, access, and affordability. For knee and hip joint OA, weight loss is also strongly recommended if the patient is overweight or obese, study results demonstrated better results the more weight was lost. Even though the benefit of self-efficacy and self-management programs is small, the risks are minimal and are therefore strongly recommended. Furthermore, Tai Chi is strongly recommended for patients with knee and/or hip OA, hand orthoses for patients with first carpometacarpal joint OA, cane usage can be highly advised for patient groups with knee and/or hip OA, as well as tibiofemoral knee braces. Recommendations from the ACR include cognitive behavioural therapy, acupuncture, thermal interventions, balance exercises for knee and/or hip OA, yoga for knee OA, patellofemoral braces for knee OA and, and radiofrequency ablation for knee OA, paraffin for hand OA, if other joints as mentioned are affected, hand orthoses are also conditionally recommended in hand OA.

The above-mentioned modalities are often not sufficient to treat OA alone, so the use of pharmacological agents is indicated. The ACR strongly recommends the use of topical NSAIDS prior to oral NSAIDS for knee OA. Nevertheless, usual therapy for OA includes the use of oral NSAIDS, which are strongly recommended for OA, noting that the dose should be as low as possible and the duration as short as possible to minimize side effects. For knee and hip OA, intraarticular glucocorticoid injections are also strongly recommended, which should be ultrasound guided if possible, in hip OA. For hand OA, intraarticular glucocorticoid injections are conditionally advised. In addition, conditionally recommended by the ACR is acetaminophen if NSAIDS are contraindicated. Also, duloxetine is conditionally recommended, which can be used alone or in combination with NSAIDS. In cases where NSAIDS are either

ineffective or contraindicated, the use of tramadol is conditionally recommended for knee and hip OA, although its addiction potential and adverse effects must be considered(45).

6. Role of Disease Modifying Drugs in Osteoarthritis Treatment

The recommended treatment strategy consists of symptom alleviation, which often results in reduced function, quality of life and ultimately in surgical arthroplasty of hip or knee joint. The aim of Disease Modifying Osteoarthritis Drugs (DMOAD) is to modify the pathophysiology and alleviate the progression or even reverse the process of OA. New knowledge of molecular mechanisms contributing to OA enable new approaches of treatment possibilities in the future to restore the homeostasis of joint metabolism. These approaches can be divided into cartilage-driven endotype, bone-driven endotype, and inflammation-driven endotype(46).

Cartilage-driven endotype includes proteinase inhibitors like MMP-13 inhibitors and ADAMTS-5 inhibitors which should prevent ECM proteolysis(47), Sprifermin, a human recombinant FGF-18 for stimulation of articular chondrocytes(48), Wnt signalling inhibitors as Lorecivivint, to stop induction of metalloproteinases and induction of chondrogenesis(49). Senolytics therapies, another subgroup, can be subdivided into senolytics, which eliminate senescent cells, senomorphics, which change the phenotype of senescent cells (SnCs) into the phenotype of young cells, and senoinflammation, to induce immune mediated clearance of SnCs(50). Bone-driven endotype therapy include Cathepsin K inhibitors, which otherwise induce both bone resorption and cartilage damage, parathyroid hormone such as teriparatide, antiresorptive drugs including bisphosphonates, denosumab, and vitamin D(46). Inflammation-driven endotype treatment targeting inflammatory markers such as anti-IL 1, anti-IL 6, anti-TNF agents.

A different approach includes RNA therapeutics, which are divided into small interfering RNAs (siRNAs), microRNAs (miRNAs) or antisense oligonucleotides (ASOs) to modulate previously undruggable targets in joint tissues and to silence target genes. Noncoding RNAs (ncRNAs) have emerged as regulators of inflammation, chondrocyte apoptosis, and ECM degradation and may contribute as further option to delay OA progression(51).

Nevertheless, no DMOAD has been approved by the FDA or EMA because structural endpoints have not been met, the effect does not exceed the placebo effect, occurrence of adverse events and side-effects or structure versus symptoms discordance. Latter could be explained by the reason that the correlation between symptoms and structural changes are not concordant or time staggered(46). The heterogeneity and complexity of OA pathogenesis, disease presentation and

progression in different patients should direct our treatment guidelines in future towards personalized medicine. Furthermore, a better understanding of biomarkers needs to be developed to establish an early diagnosis and prognosis of OA progression as well as to distinguish between different phenotypes and endotypes of OA patients(52).

7. Upcoming Drugs Targeting Cartilage

7.1 Sprifermin (FGF-18)

Sprifermin, a recombinant FGF-18, is considered a potential anabolic DMOAD. Accumulated evidence demonstrates that Sprifermin induces chondrocyte proliferation, thereby increasing the production of extracellular matrix and hyaline-like cartilage in vitro and ultimately increasing cartilage thickness in vivo(53,54). Several studies have been conducted, including the phase II FORWARD study – a 5-year randomized clinical trial to evaluate the efficacy and safety of Sprifermin among 549 patients with symptomatic radiographic knee OA(55). Patients were randomized to receive intra-articular Sprifermin 100 µg or 30 µg every 6 or 12 months, or placebo (PBO)for total duration of 18 months. The primary analysis was performed at year 2, with follow-up at years 3, 4 and 5(55). Changes in cartilage thickness was evaluated by performing MRI on a target knee. Sprifermin was given either in cycles of three injections over three consecutive weeks every six months (at 0, 6, 12, and 18 months) or every twelve months (at 0 and 12 months, with a placebo administered at months 6 and 18). Patients aged 40 to 84, with 69 % being female, participated. Baseline characteristics like age, sex, BMI, minimum joint space width (mJSW), and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain were balanced among study arms [Figure 12, in Appendices].

Results can be divided into structural changes, declared as primary endpoint and functional changes (secondary endpoint). Primary endpoint demonstrated a dose dependent increase in total femorotibial joint (TFTJ) cartilage thickness compared to placebo at 2 year the result remained up to year 5 ($p<0.001$), but in the further statistical analysis it was shown that only the group of 100 µg q6 could preserve a statistically significant increase in total femorotibial joint cartilage by 0.05 mm on average up to year 5 ($p<0.015$) [Figure 1)(56).

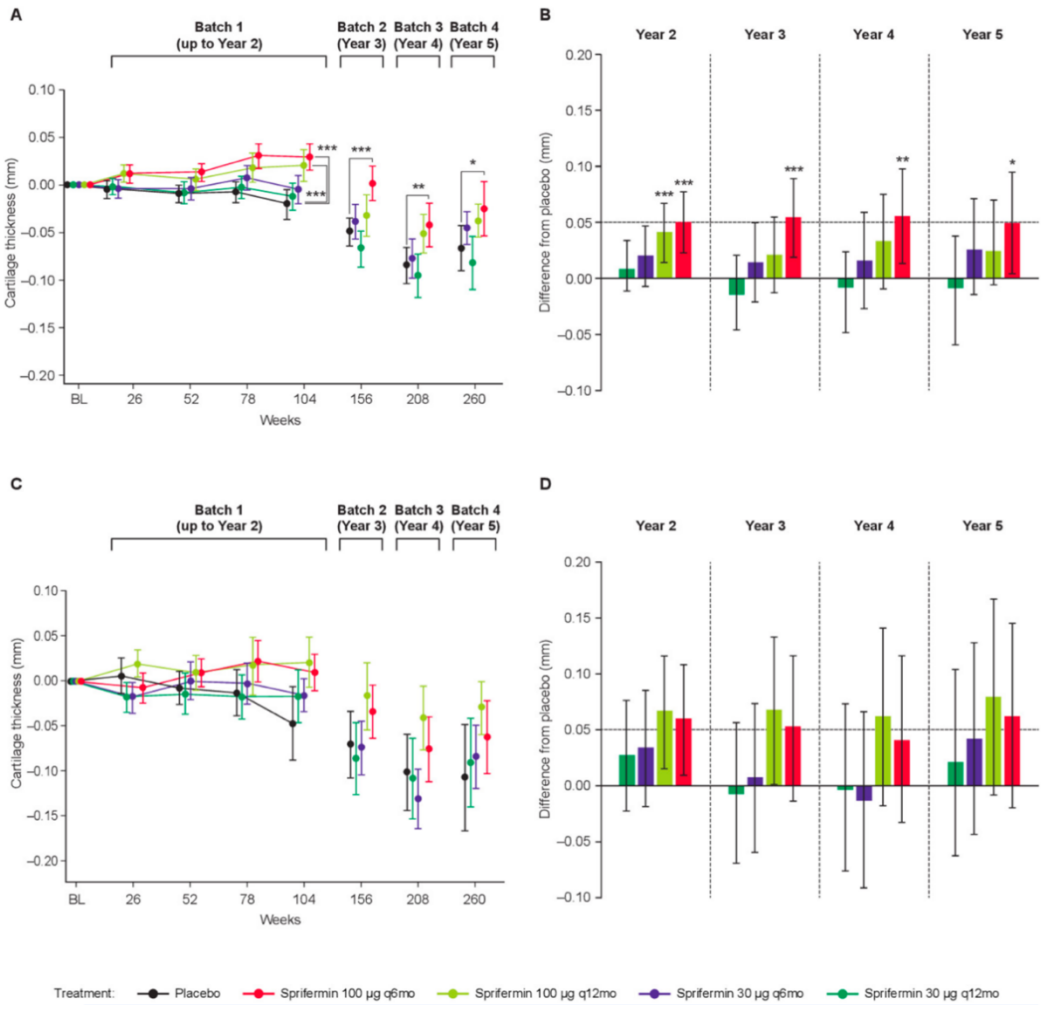

Figure 1 Change in TFTJ cartilage thickness up to year 5 by Sprifermin

(A) Absolute change from baseline in TFTJ cartilage thickness (mm) and (B) difference from placebo in TFTJ cartilage thickness (mm) for the mITT population (n=494). (C) Absolute change from baseline in TFT and (D) difference from placebo in TFTJ cartilage thickness (mm) for the SAR (n=161) (56)

Cartilage change in the medial femorotibial compartment (MFTC) for the highest dose compared to placebo was maintained at approximately 0.05 mm at each timepoint from years 2 to 5, although not statistically significant after year 3. Changes on the lateral femorotibial compartment (LFTC) was preserved from years 2 to 5 and achieved a mean increase of 0.04 mm in LFTC compared with placebo to year 5 with the highest dose. Regarding JSW Sprifermin did not cause any change from the baseline measurement of medial mJSW from year 2 through year 5. Changes on lateral mJSW was observed at each time point, but not statistically significant at year 5.

As secondary endpoint achievement, Eckstein et al.(56) showed that in the FORWARD study, every cohort improved by around 20 points from baseline in pain subscore at year 2 and up to year 5, including the placebo group, and that no differentiation in WOMAC pain was observed between different cohorts and placebo. These results were similar in WOMAC total scores, which improved by around 20 points (50 %) from baseline in all groups including placebo.

A performed post hoc analysis detected a subgroup at risk (SAR) with narrower JSW (<3.5 mm) and non-acceptable OA related pain. A dose-dependent improvement in WOMAC pain in the SAR was observed with Sprifermin, after year 3(57), clinical meaningful improvement in pain with the highest Sprifermin dose versus placebo was observed at year 3, and sustained up to year 5 in the SAR [Figure 2] (56).

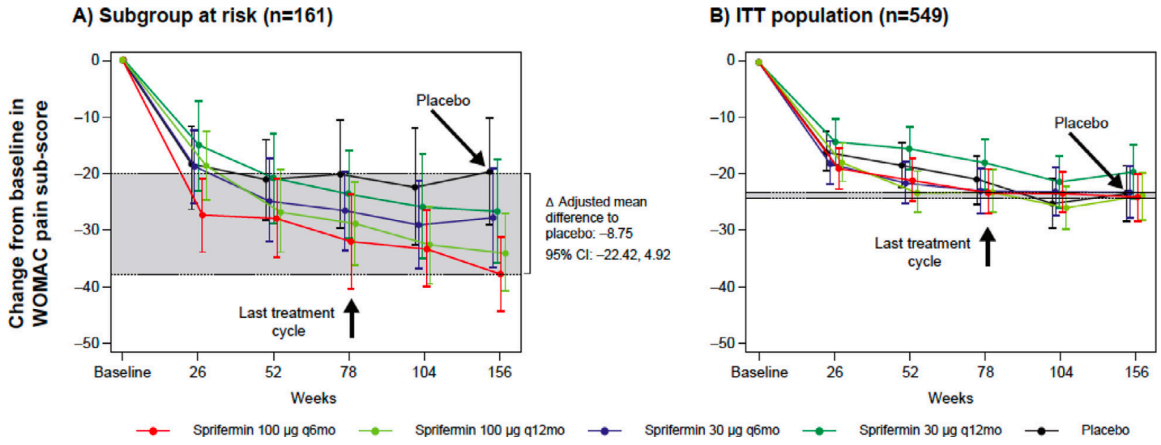

Figure 2 Observed change in WOMAC pain sub-score at year 3 by Sprifermin

CI, confidence interval; ITT, intention-to-treat; q6mo, every 6 months; q12mo, every 12 months; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index(57)

Additionally, faster cartilage loss was demonstrated in the placebo group of SAR. These results show that structural modification by Sprifermin is at least equally strong in severe and milder OA. Additional FORWARD study shows that patients with progressed OA and more pain at baseline are likely to benefit not only from structural improvements but also from clinical symptoms improvement compared to patients with only mild disease.

Adverse events (AE) were similar between different Sprifermin groups and the placebo group and were mostly mild or moderate in severity. 79 % were considered unrelated to treatment. All serious reported AE, 29-38 % in Sprifermin groups and 36 % in the placebo group, were not considered treatment related(56). Most of local related AE were classified as musculoskeletal and soft tissue disorders. Most often reported local AE was arthralgia. 9-13 % of patients receiving Sprifermin and 9 % of the placebo group experienced arthralgia. No additional safety concerns, either systemic or local, were detected.

In another study reported by Eckstein et al., the location independent effect of Sprifermin was investigated, whereby the knee joint was divided into 16 subregions in which cartilage changes were either evaluated by thickening or thinning scores(58). Results show that the overall cartilage loss/thinning in subregions was statically significant less in the group treated with Sprifermin 100 µg (p=0.03) and that the patients treated with Sprifermin gained statistically

significant more cartilage (p=0.029) in subregions of cartilage increasement compared to the placebo group after one year [Figure 3].

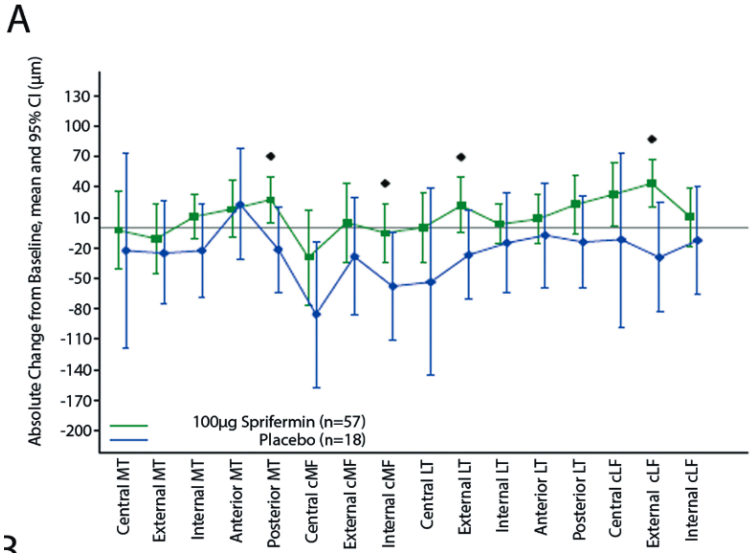

Figure 3 Change from baseline in subregional cartilage thickness at 12 months of follow up by Sprifermin

Symbols indicate individual change values that differed significantly between the 100 mg Sprifermin–treated and placebo-treated patients. MT = medial tibia; cMF = central part of the medial weight-bearing femur; LT = lateral tibia; cLF = central part of the lateral weight-bearing femur(58).

In conclusion, the findings of Sprifermin's efficacy and safety present promising outcomes for addressing cartilage-related concerns in OA. The observed alleviation of symptoms coupled with structural modifications indicates a potential opportunity for managing the progression of this condition. The FORWARD study, the longest DMOAD study, underscores the durability of Sprifermin's impact on cartilage thickness without any detectable systemic exposure or safety concerns. Importantly, the sustained cartilage gains following treatment cessation indicate robust mechanical properties similar to natural cartilage, supporting the notion of potential long-lasting structural modifications.

However, it is essential to note that although structural modifications were evident, the translation into symptomatic relief could require longer observation periods. This emphasizes the need for continued research to elucidate the precise correlation between structural changes and symptomatic improvements. Overall, these findings underscore the promising role of Sprifermin not only in potentially alleviating OA symptoms, but also in modifying cartilage structure, thereby presenting a significant advancement in addressing this challenging condition. According to clinicaltrials.org, there are currently no ongoing clinical studies regarding Sprifermin and OA.

7.2 Lorecivivint (Wnt Signalling Pathway)

Lorecivivint (LOR), a small molecule, is currently under investigation as a possible intraarticular injectable DMOAD. LOR aims to modulate the Wnt pathway by inhibiting CLK2 and DYRK1A, two intranuclear kinases, and should thereby lead to improvements in pain, function and potentially joint structure in knee OA(59).

On this subject, several studies have been conducted. The most recently published clinical phase IIB trial, a 24-weeks, multicenter, randomized, double-blind, placebo-controlled study in which subjects received injections of 2 ml LOR (0.03, 0.07, 0.15, or 0.23 mg), PBO or dryneedle sham. Main objective of the study was to determine effective doses of LOR(60). The primary efficacy endpoints were changes in reduction in pain (NRS) [0-10], WOMAC pain [0-100], WOMAC function [0-100], and radiographic mJSW outcomes. Adults aged 40 to 80 years with a diagnosis of primary idiopathic femorotibial OA in the target knee were included in the study. Participants were expected to be in general good health and with Kellgren-Lawrence (KL) grade 2 or 3 in their target knee. Throughout the entire study, patients were only allowed to continue or start NSAIDs. Treatment with opioids as well as other IA (intraarticular) injections were not permitted [Figure 13, in Appendices].

LOR demonstrated significant reduction in pain NRS at week 24 in the treatment groups receiving 0.07 mg and 0.23 mg of LOR. In the 0.23 mg treatment group, significant improvements in WOMAC pain and WOMAC function were observed at week 12, 16, 20 and 24 compared to PBO. The 0.07 mg treatment group showed significant improvements in week 12 for WOMAC pain score and week 12 and 16 for WOMAC function score [Figure 4].

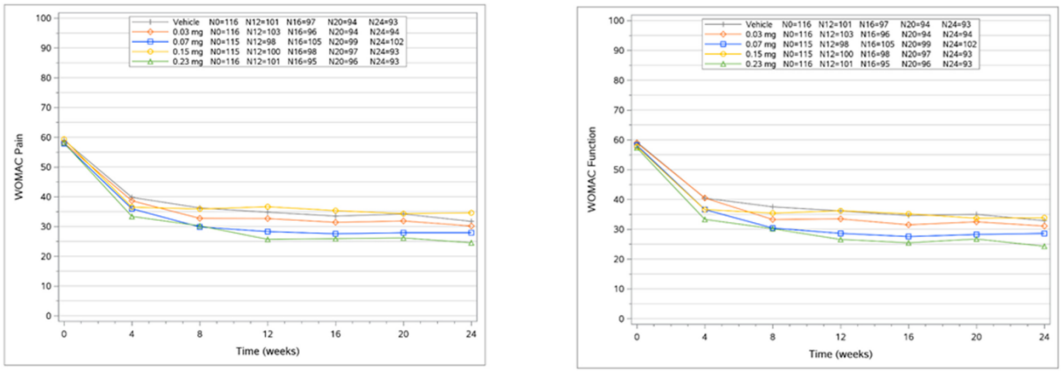

Figure 4 Effect of Lorecivivint on WOMAC pain and WOMAC function

WOMAC pain and function scores for the vehicle (PBO) group and all LOR dose (0.03, 0.07, 0.15, and 0.23 mg) groups at each timepoint. Lower scores indicate symptomatic improvements(60)

No group demonstrated statistically significant differences in mJSW at week 24 compared to PBO, although the 0.07 mg group and the 0.15 mg group demonstrated the best result, with a mean change in mJSW at week 24 of -0.11 mm from baseline. All doses appeared to be well tolerated and all reported serious AE were unrelated or unlikely to be related to therapy.

Additionally, no significant differences were seen in the active treatment group and the PBO group in terms of treatment emergent AE (TEAE)(60). The most frequent TEAE were arthralgia and upper respiratory tract infection. In summary, the LOR phase IIB study showed a good safety profile with significant improvements in function and pain and met the primary endpoints. Nevertheless, it failed to improve the mJSW. Most significant improvements were achieved in the 0.07 mg and 0.23 mg groups, therefore the lowest and most effective dose appeared to be 0.07 mg.

Further and most importantly longer studies are needed to evaluate the potential to change the joint structure and mJSW and to establish a more detailed drug safety profile.

In a post hoc analysis of the phase IIB study(61), the proportion of subjects treated with intraarticular injection with 0.07 mg LOR or placebo who achieved a clinically meaningful response was examined and demonstrated that 0.07 mg LOR treatment yielded consistent patient reported outcome (PRO) responder scores, often statistically significant over PBO and sustained over 24 weeks. Moreover, patients wo received 0.07 mg LOR showed durable, clinically meaningful improvements in pain and function compared to PBO.

A phase III study is currently underway evaluating the safety and efficacy of 0.07 mg LOR in moderate to severe symptomatic OA. The study is expected to be completed in February 2024 (62). No results have been published at this time for other phase III trials that have already been completed.

7.3 Cathepsin K Inhibitor

Cathepsin K (CatK) inhibitor is a lysosomal cysteine protease mostly available in osteoclasts, which is responsible for bone resorption, but also in chondrocytes, in which it is able to cleave Col2 and aggrecan(63). Due to its function of bone resorption, CatK can thus serve as potential therapeutic pathway for diseases affected by increased bone resorption and reduced subchondral bone density by inhibiting its function(64). MIV-711, a potent CatK inhibitor, is considered a DMOAD since it affects both bone and cartilage. Lindström et al. demonstrated its dose dependent effect on biomarkers of bone and cartilage degradation in monkeys and humans, thereby raising expectations for the treatment of diseases such as OA(65). The latest published study conducted by Conaghan et al. is a 26-week, multicenter, randomized, placebo-controlled, double-blind, 3-group, parallel phase IIA study (MIV-711-201). 244 participants were included(66). Participants aged 40 to 80 years with diagnosis of primary knee OA, a KL grade of 2 or 3 and an average pain NRS score of at least 4 were divided into 3 groups in a 1:1:1 ratio to receive MIV-711 (100 mg), MIV-711 (200 mg) or placebo once daily for 26 weeks, with

continuation of stable usual analgesic treatment allowed [Figure 14, in Appendices]. The primary outcome measure included change in pain NRS score from baseline to week 26, meanwhile the secondary outcome measure was the change from baseline to week 26 in medial femoral bone area in the target knee joint on MRI, the change in cartilage thickness and bone marrow lesion volume on MRI, the change in WOMAC score from baseline, and serum CTX-I and urine CTX-II levels. Safety and tolerability were assessed as well.

It was shown that MIV-711 was able to reduce the pain NRS score in target knee by -1.5 at 200 mg/d and -1.7 at 100 mg/d compared to baseline after 26 weeks, but was not statistically significantly different from placebo (-1.4 from baseline) and therefore the primary endpoint was not achieved [Figure 5].

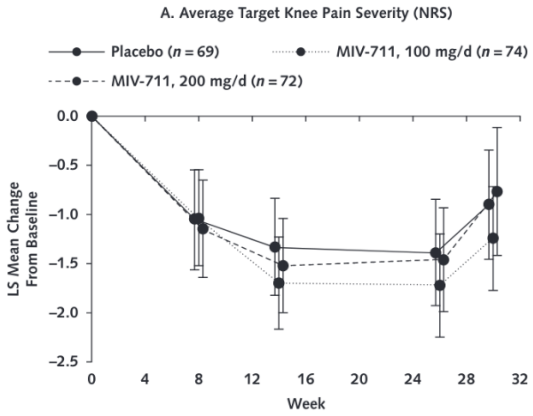

Figure 5 Mean change from baseline, by treatment, in average pain severity in the target knee by MIV-711

Estimated mean change from baseline, by treatment, in average pain severity in the target knee (NRS) (primary outcome)(66)

Assessment of bone area progression by MRI revealed that benefit was observed in groups receiving MIV-711. Compared to placebo (23.2 mm^2), both MIV-711 100 mg/d (7.9 mm^2) and 200 mg/d (8.6 mm^2) showed a statistically significantly reduced bone area progression [Figure 6].

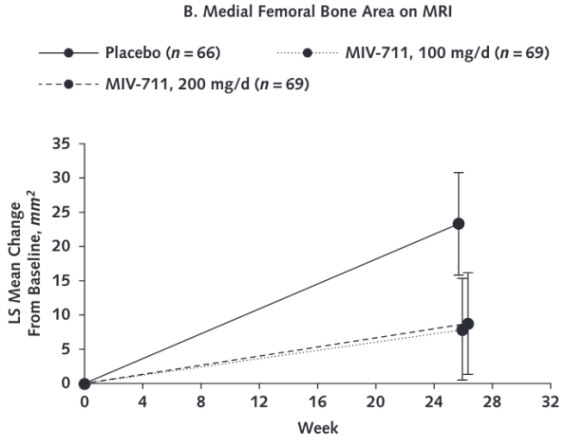

Figure 6 MIV-711 effect on on medial femoral bone area

Estimated mean change from baseline, by treatment medial femoral bone area on MRI(66)

Additionally, the attenuation of medial femoral cartilage loss was measured after 26 weeks, with only the 100 mg/d group displaying a statistically significant attenuation of femoral cartilage loss. On the contrary, tibial cartilage loss as well as changes in bone marrow lesions were not statistically significantly different [Figure 7]. Considering the ability to affect the symptoms, the study has shown that WOMAC scores for pain, function and stiffness were not statistically significantly different between the MIV-711 groups and the placebo groups.

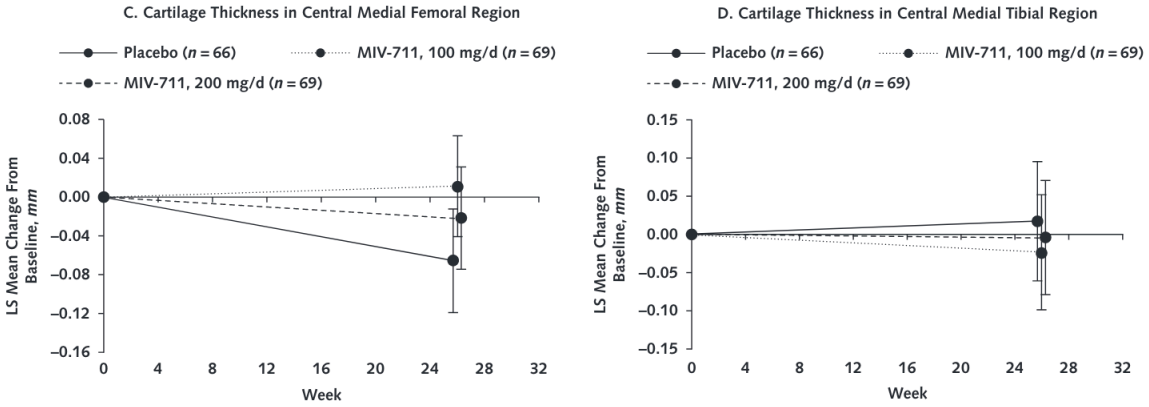

Figure 7 MIV-711 effect on cartilage thickness

Change by treatment in cartilage thickness in the central medial femoral (1) and central medial tibial (2) regions(66)

Biomarkers of bone resorption (type I collagen C-telopeptide [CTX1]) and cartilage loss [CTX2] were both statistically significantly reduced by MIV-711 100 mg/d (-27.8 % and -34.4 %) and 200 mg/d (-50.3 % and -51.6 %) and returned to normal levels at the end of treatment after 26 weeks.

Occurrence of TEAE were mostly similar in all groups, of 345 AE, most AE were mild (46.1 %) or moderate (50.7 %), only 9 severe AE occurred, and none were considered treatment related. Morphea and cardiovascular side effects were of particular interest as other studies with CatK inhibitors were discontinued due to the increased occurrence of these side effects. An increased frequency of skin disorders was observed in both treatment groups, 100 mg/d (7.3 %) and 200 mg/d (12.2 %), compared to placebo (2.5 %).

In summary, the study has not met the primary outcome by improving patients pain in OA, although it showed reduced medial femoral bone progression in both treatment groups and medial femoral cartilage loss in the 100 mg/d group. Furthermore, it demonstrated relevant improvements in biomarkers representative for bone resorption and cartilage loss, all within an acceptable tolerability safety profile. However, longer studies and larger study groups are needed to confirm these findings. There are currently no recent studies ongoing for MIV-711 as per information on clinicaltrials.gov.

7.4 ADAMTS-5 Inhibitor

Another potential therapeutic target depicts S201086/GLPG1972, a highly potent and selective ADAMTS-5 inhibitor that inhibits aggrecan cleavage 16, which is upregulated in the pathophysiology of OA(67). It was shown that S201086/GLPG1972 was able to significantly reduce ADAMTS-5 regulated aggrecan degradation in mouse and human cartilage explants(68). Following the initial human study conducted on S201086/GLPG1972, the findings indicated that it is well tolerated and demonstrated a significant reduction in aggrecanase activity of ADAMTS-5 compared to the placebo(69).

ROCCELLA comprised a 52-week randomized, double-blind, placebo-controlled, dose-ranging phase II trial, complemented by a 2-week safety follow-up period. Participants were randomly allocated in a 1:1:1:1 ratio to receive S201086/GLPG1972 at doses of 75 mg, 150 mg, 300 mg or a placebo taken orally once daily(70). The main inclusion criteria included participants aged between 40 and 75 years, a clinical diagnosis of knee OA, reported pain levels ranging from 40 to 90 mm on a 100 mm visual analogue scale (VAS), KL grade 2 or 3, and medial joint space narrowing (JSN) grade 1 or 2 [Figure 15, in Appendices].

The primary objective was to prove the efficacy of S201086/GLPG1972 in reducing cartilage loss measured by the change in central medial femorotibial compartment (cMFTC) cartilage thickness. Secondary structural endpoints encompassed the change in radiographic medial JSW. Additional secondary structural measures included cartilage thickness in the total femorotibial compartment (tFTC) and changes in subchondral bone area of the medial femoral condyle surface. Clinical secondary endpoints assessment included the WOMAC total score and scores for functions, pain, and stiffness, along with pain assessment using a 100 mm VAS. Safety endpoints were monitored for TEAE.

Primary objective could not be met, all treatment groups displayed a cMFTC cartilage loss. The greatest loss was observed in the placebo group (mean -0.12 mm) compared to the treatment group 150 mg (mean -0.10 mm), 300 mg (mean -0.09 mm) and 75 mg (mean -0.07 mm). The differences were not statistically significant ($p=0.165$ for the 75 mg group) [Table 3, in Appendices].

Similar results were observed for secondary structural endpoints. Mean radiographic JSW decreased in all groups. Lowest JSW thinning progression was observed in the 75 mg S201086/GLPG1972 treatment group (13.6 %), followed by the 300 mg group (16.6 %) and the 150 mg group (21.5 %). Compared to the placebo group (20.3 % progression), the difference to the 75 mg S201086/GLPG1972 treatment group is not statistically significant.

Other structural endpoints such as total FTC and the change from baseline in the bone area of the medial femoral condyle surface revealed no significant differences between the placebo and S201086/GLPG1972 treatment groups.

Further data showed that the clinical scores of all S201086/GLPG1972 treatment groups, including the WOMAC total score, the functional subscore, the pain subscore and the stiffness subscore, did not improve statistically significantly compared to the placebo group [Figure 8].

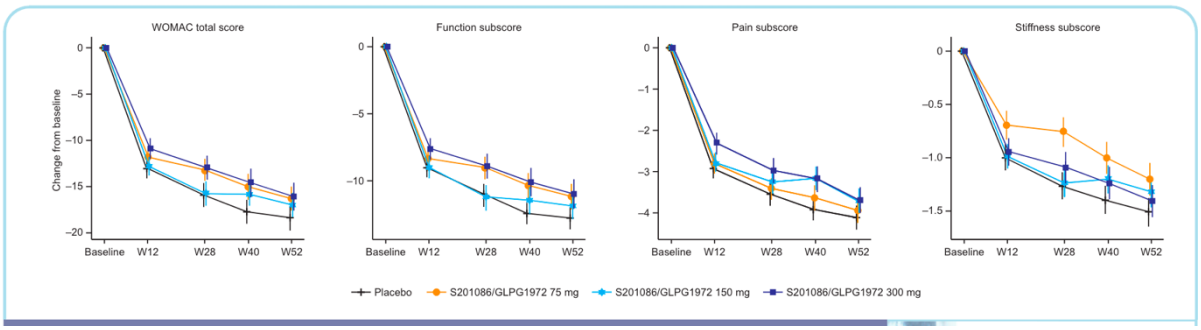

Figure 8 Effect of S201086/GLPG1972 on WOMAC total score and subscale scores

Mean change over time in WOMAC total score and subscale scores. Negative changes represent improvements in function, pain and stiffness(70)

The ROCCELLA study revealed that similar proportions of participants across treatment groups experienced serious TEAE. The most frequently reported TEAE in the placebo and S201086/GLPG1972 75, 150, and 300 mg groups included arthralgia (8.1 %, 11.5 %, 15.2 %, and 11.2 %), nasopharyngitis and falls. Notably, a numerically greater proportion of participants in the S201086/GLPG1972 300 mg group reported increased gamma-glutamyl transferase. Furthermore, no clinically relevant differences were observed between groups in mean changes for body weight, heart rate, blood pressure, and ECG parameters during the trial.

In summary, the 52-week treatment with S201086/GLPG1972 failed to demonstrate the anticipated anti-catabolic effect on cartilage loss. The inability of the study drug to reach the target tissue after oral administration remains a potential factor. Additionally, the duration of the trail may have been insufficient to determine a treatment effect. S201086/GLPG1972 did not prove efficacious in reducing cMFTC cartilage loss or improving function or pain in the target knee. Despite these limitations, the treatment was generally well-tolerated, with no identified safety concerns. According to clinicaltrials.gov, there are presently no ongoing recent studies for ADAMTS-5 inhibitors.

7.5 Metformin

Another possible disease modifying approach to target OA includes the use of Metformin, a safe and well tolerated drug for treatment of diabetes. Besides its primary effect, to lower glucose levels, it results in weight loss and reduced inflammation by modulating inflammatory

and metabolic factors(71). Results of human studies suggest Metformin might modulate inflammatory and metabolic pathways and thereby reduce OA progression. Cyclooxygenase (COX)-2 inhibitors and Metformin combined, in patients with OA and diabetes resulted in reduced rate of joint implantation over 10 year period compared to COX-2 inhibitors alone(72). A study by Wang et al. investigated the effect of Metformin on knee cartilage volume over a 4-year period and total risk of knee replacement over a 6-year period in obese individuals with knee OA(73). Participants with knee OA (KL ≥2), obese (BMI >30 kg/m^2) were included, additionally participants were divided into Metformin user and non-Metformin user groups. WOMAC pain subscale was used for knee pain assessment at baseline and yearly follow-up. Participants had to indicate at each follow-up whether they received knee replacement, if no information was available, or if they were classified as conservative/no knee replacement. Knee cartilage volume was divided into medial and lateral tibiofemoral compartments and measured by MRI. Thereby, the annual rate of cartilage volume loss over 4 years was obtained by the ratio of 4-year follow-up volume to baseline volume, expressed as a percentage. The study included 818 participants, of whom 56 (6.8 %) were Metformin users. In 540 participants, the knee cartilage volume was measured at the 4-year follow-up.

Metformin users had a statistically significant (p=0.04) lower cartilage loss in medial compartment (0.83 %) compared to non-Metformin users (1.55 %). Lateral cartilage volume loss was not statistically significantly different, 0.98 % in Metformin users vs. 1.22 % in non-Metformin users (p=0.43). The use of Metformin showed a reduction in the risk of total knee replacement over a span of 6 years, although the decrease was not statistically significant. Over 4 years, there was a negligible difference in WOMAC pain scores between Metformin users and non-users (-0.9 (SD 4.2) vs. -0.6 (SD 3.8), p=0.549), indicating no significant clinical or statistical distinction between the groups.

It is important to note that Metformin use was self-reported, with information on duration and frequency available, but data on dosage and compliance were not reported. Additionally, the study's limited power to detect a significant association between Metformin use and the risk of total knee replacement is attributed to the small number of Metformin users in this category.

Metformin's potential impact on slowing knee cartilage volume loss is ascribed to its ability to target various metabolic and inflammatory pathways. This suggests that focusing on obesity-related inflammatory and metabolic pathways could have a disease modifying effect in knee OA, with Metformin presenting as a potential disease modifying drug for obese individuals with knee OA. Clarification on this matter requires randomized controlled trials. Per information on clinicaltrials.gov, several studies are ongoing to investigate the effect of

Metformin in OA, such as the promising trial ‘Effect of Metformin on Tibiofemoral Cartilage Volume and Knee Symptoms Among Overweighted Knee Osteoarthritis patients – a Randomized Clinical Trial’ [NCT05034029], expected to be completed by the end of 2024.

8. Discussion

The landscape of DMOAD is diverse, each holding unique promises and facing individual challenges. Sprifermin, a recombinant fibroblast growth factor 18, exhibits notable anabolic effects, inducing chondrocyte proliferation and increasing cartilage thickness. The FORWARD study, spanning 5 years, establishes its structural benefits, particularly in the 100 µg q6 cohort, showcasing sustained gains up to year 5. Secondary endpoints reveal consistent pain reduction across all cohorts, suggesting potential symptom management. The safety profile remains favourable, and sustained cartilage gains post-treatment cessation hint at enduring structural modifications. However, the translation into symptomatic relief may require extended observation. Ongoing clinical trials for Sprifermin are limited, underscoring the need for continued research to unveil its full potential.

In comparison, Lorecivivint, a Wnt signalling pathway modulator, demonstrates significant pain reduction and functional improvement in a 24-week phase IIB trial. Despite falling short in improving mJSW, the 0.07 mg group showcases the most significant benefits. A phase III study is underway, focusing on safety and efficacy in moderate to severe symptomatic OA. The advantages lie in substantial pain reduction, functional improvement, and the ongoing phase III study. However, its limitations include the failure to improve mJSW, emphasizing the necessity for longer studies to assess joint structural changes.

MIV-711, a CatK inhibitor, reveals attenuation of femoral cartilage loss and reduced bone area progression in a 26-week phase IIA study. Although the primary endpoint of pain reduction is not achieved, the biomarker analysis indicates a notable reduction in bone and cartilage degradation markers, suggesting a potential to modify disease progression. Challenges include the failure to meet the primary endpoint and the necessity for longer studies and larger cohorts.

S201086/GLPG1972, a selective ADAMTS-5 inhibitor, falls short in reducing cartilage loss in the ROCCELLA study. Despite not meeting primary objectives, it demonstrates a well-tolerated safety profile. The study raises questions about the drug's ability to reach the target tissue, suggesting the need for trials of longer duration. The advantages include being well-tolerated with no safety concerns, potentially offering anti-catabolic effects. However, the disadvantages include the failure to demonstrate anti-catabolic effects on cartilage loss, an inability to reach the target tissue, and limited trial duration.

Metformin, traditionally used for diabetes, is explored for its potential in OA. Human studies indicate reduced knee cartilage loss and a lower risk of knee replacement in Metformin users. Ongoing trials aim to validate its disease modifying effects in OA. While Metformin shows promise in reducing knee cartilage loss and lowering the risk of knee replacement, the limitations include studies with small sample sizes and the necessity for randomized controlled trials for validation.

In comparing these DMOAD, Sprifermin and MIV-711 stand out for their potential in structural modification and symptom relief. CathepsinK inhibitor and ADAMTS-5 inhibitor face challenges in meeting primary endpoints. Metformin offers a unique perspective, potentially impacting OA progression through its anti-inflammatory and metabolic effects. Ongoing and future research is crucial for a comprehensive understanding of the true potential of these DMOAD and their role in transforming OA treatment.

9. Conclusion

The absence of U.S. Food and Drug Administration or European Medicine Agency approved Disease Modifying Drugs for osteoarthritis highlights the challenges in this therapeutic landscape. Structural endpoints, the placebo effect, adverse events, and the discordance between structure and symptoms pose hurdles. The heterogeneity of the disease and the multiple pathophysiological approaches to the treatment of osteoarthritis show its complexity and could be a reason why the current studies on the different treatment approaches have not been able to find a single drug to sufficiently treat osteoarthritis. Nevertheless, drugs such as Sprifermin, which showed increased cartilage regeneration, or MIV-711, which showed attenuation of femoral cartilage loss and a reduction in bone surface progression, may represent a prospect for the future treatment of osteoarthritis by slowing or even reversing the progression of the disease. The future of osteoarthritis treatment lies in personalized medicine, fuelled by a better understanding of biomarkers. RNA therapeutics, innovative trial designs, and collaborative efforts promise a more nuanced approach to addressing osteoarthritis' complexity.

In conclusion, the pursuit of effective Disease Modifying Drugs for osteoarthritis in osteoarthritis treatment is marked by diverse strategies, promising outcomes, and ongoing challenges. As research advances, the integration of these findings into personalized treatment guidelines holds the key to transforming the landscape of osteoarthritis care.

10. References

1. Pereira D, Ramos E, Branco J. Osteoarthritis. Acta Médica Port. 2015;28(1):99–106.
2. Martel-Pelletier J, Barr AJ, Cicuttini FM, Conaghan PG, Cooper C, Goldring MB, et al. Osteoarthritis. Nat Rev Dis Primer. 2016 Oct 13;2:16072.
3. Martel-Pelletier J, Wildi LM, Pelletier JP. Future therapeutics for osteoarthritis. Bone. 2012 Aug 1;51(2):297–311.
4. Litwic A, Edwards M, Dennison E, Cooper C. Epidemiology and Burden of Osteoarthritis. Br Med Bull. 2013;105:185–99.
5. Allen KD, Thoma LM, Golightly YM. Epidemiology of osteoarthritis. Osteoarthritis Cartilage. 2022 Feb;30(2):184–95.
6. Safiri S, Kolahi AA, Smith E, Hill C, Bettampadi D, Mansournia MA, et al. Global, regional and national burden of osteoarthritis 1990-2017: a systematic analysis of the Global Burden of Disease Study 2017. Ann Rheum Dis. 2020 Jun 1;79(6):819–28.
7. Felson DT, Naimark A, Anderson J, Kazis L, Castelli W, Meenan RF. The prevalence of knee osteoarthritis in the elderly. the framingham osteoarthritis study. Arthritis Rheum. 1987;30(8):914–8.
8. Kim C, Linsenmeyer KD, Vlad SC, Guermazi A, Clancy MM, Niu J, et al. Prevalence of Radiographic and Symptomatic Hip Osteoarthritis in an Urban United States Community: The Framingham Osteoarthritis Study. Arthritis Rheumatol. 2014;66(11):3013–7.
9. Haugen IK, Englund M, Aliabadi P, Niu J, Clancy M, Kvien TK, et al. Prevalence, incidence and progression of hand osteoarthritis in the general population: the Framingham Osteoarthritis Study. Ann Rheum Dis. 2011 Sep 1;70(9):1581–6.
10. Hong JW, Noh JH, Kim DJ. The prevalence of and demographic factors associated with radiographic knee osteoarthritis in Korean adults aged ≥ 50 years: The 2010–2013 Korea National Health and Nutrition Examination Survey. PLOS ONE. 2020 Mar 20;15(3):e0230613.
11. O'Neill TW, McCabe PS, McBeth J. Update on the epidemiology, risk factors and disease outcomes of osteoarthritis. Best Pract Res Clin Rheumatol. 2018 Apr 1;32(2):312–26.
12. Vina ER, Kwoh CK. Epidemiology of Osteoarthritis: Literature Update. Curr Opin Rheumatol. 2018 Mar;30(2):160–7.
13. Braga L, Renner JB, Schwartz TA, Woodard J, Helmick CG, Hochberg MC, et al. Differences in radiographic features of knee osteoarthritis in African-Americans and Caucasians: the Johnston County Osteoarthritis Project. Osteoarthritis Cartilage. 2009 Dec 1;17(12):1554–61.
14. Nevitt MC, Felson DT. High bone density and radiographic osteoarthritis: questions answered and unanswered. Osteoarthritis Cartilage. 2020 Sep 1;28(9):1151–3.
15. Hui M, Doherty M, Zhang W. Does smoking protect against osteoarthritis? Meta-analysis of observational studies. Ann Rheum Dis. 2011 Jul 1;70(7):1231–7.
16. Nelson AE, Stiller JL, Shi XA, Leyland KM, Renner JB, Schwartz TA, et al. Measures of hip morphology are related to development of worsening radiographic hip osteoarthritis over 6 to 13 year follow-up: the Johnston County Osteoarthritis Project. Osteoarthritis Cartilage. 2016 Mar 1;24(3):443–50.
17. Poulsen E, Goncalves GH, Bricca A, Roos EM, Thorlund JB, Juhl CB. Knee osteoarthritis risk is increased 4-6 fold after knee injury – a systematic review and meta-analysis. Br J Sports Med. 2019 Dec 1;53(23):1454–63.
18. Berg B, Roos EM, Englund M, Kise NJ, Tiulpin A, Saarakkala S, et al. Development of osteoarthritis in patients with degenerative meniscal tears treated with exercise therapy or surgery: a randomized controlled trial. Osteoarthritis Cartilage. 2020 Jul 1;28(7):897–906.
19. Canetti EFD, Schram B, Orr RM, Knapik J, Pope R. Risk factors for development of lower limb osteoarthritis in physically demanding occupations: A systematic review and meta-analysis. Appl Ergon. 2020 Jul 1;86:103097.
20. Lo GH, Schneider E, Driban JB, Price LL, Hunter DJ, Eaton CB, et al. Periarticular bone predicts knee osteoarthritis progression: Data from the Osteoarthritis Initiative. Semin Arthritis Rheum. 2018 Oct 1;48(2):155–61.
21. Hawker GA, Stewart L, French MR, Cibere J, Jordan JM, March L, et al. Understanding the pain experience in hip and knee osteoarthritis--an OARSI/OMERACT initiative. Osteoarthritis Cartilage. 2008 Apr;16(4):415–22.
22. Neogi T. The epidemiology and impact of pain in osteoarthritis. Osteoarthritis Cartilage. 2013 Sep;21(9):1145–53.
23. Salaffi F, Carotti M, Stancati A, Grassi W. Health-related quality of life in older adults with symptomatic hip and knee osteoarthritis: a comparison with matched healthy controls. Aging Clin Exp Res. 2005 Aug;17(4):255–63.
24. Taruc-Uy RL, Lynch SA. Diagnosis and Treatment of Osteoarthritis. Prim Care Clin Off Pract. 2013 Dec 1;40(4):821–36.
25. Hinton R, Moody RL, Davis AW, Thomas SF. Osteoarthritis: diagnosis and therapeutic considerations. Am Fam Physician. 2002 Mar 1;65(5):841–8.
26. Mort JS, Billington CJ. Articular cartilage and changes in arthritis: Matrix degradation. Arthritis Res. 2001;3(6):337–41.
27. Schmidt MB, Chen EH, Lynch SE. A review of the effects of insulin-like growth factor and platelet derived growth factor on in vivo cartilage healing and repair. Osteoarthritis Cartilage. 2006 May;14(5):403–12.
28. Miyazawa K, Shinozaki M, Hara T, Furuya T, Miyazono K. Two major Smad pathways in TGF-beta superfamily signalling. Genes Cells Devoted Mol Cell Mech. 2002 Dec;7(12):1191–204.
29. Blaney Davidson EN, Vitters EL, van der Kraan PM, van den Berg WB. Expression of transforming growth factor-beta (TGFbeta) and the TGFbeta signalling molecule SMAD-2P in spontaneous and instability-induced osteoarthritis: role in cartilage degradation, chondrogenesis and osteophyte formation. Ann Rheum Dis. 2006 Nov;65(11):1414–21.
30. Shen J, Li J, Wang B, Jin H, Wang M, Zhang Y, et al. Deletion of the transforming growth factor β receptor type II gene in articular chondrocytes leads to a progressive osteoarthritis-like phenotype in mice. Arthritis Rheum. 2013 Dec;65(12):3107–19.
31. Chia SL, Sawaji Y, Burleigh A, McLean C, Inglis J, Saklatvala J, et al. Fibroblast growth factor 2 is an intrinsic chondroprotective agent that suppresses ADAMTS-5 and delays cartilage degradation in murine osteoarthritis. Arthritis Rheum. 2009 Jul;60(7):2019–27.
32. Zhen G, Wen C, Jia X, Li Y, Crane JL, Mears SC, et al. Inhibition of TGF–β signaling in subchondral bone mesenchymal stem cells attenuates osteoarthritis. Nat Med. 2013 Jun;19(6):704–12.
33. van der Kraan PM, Goumans MJ, Blaney Davidson E, ten Dijke P. Age-dependent alteration of TGF-β signalling in osteoarthritis. Cell Tissue Res. 2012 Jan;347(1):257–65.
34. Im HJ, Muddasani P, Natarajan V, Schmid TM, Block JA, Davis F, et al. Basic Fibroblast Growth Factor Stimulates Matrix Metalloproteinase-13 via the Molecular Cross-talk between the Mitogen-activated Protein Kinases and Protein Kinase Cδ Pathways in Human Adult Articular Chondrocytes. J Biol Chem. 2007 Apr 4;282(15):11110.
35. Yan D, Chen D, Im HJ. Fibroblast Growth Factor–2 Promotes Catabolism Via FGFR1–Ras–Raf–MEK1/2–ERK1/2 Axis That Coordinates With the PKCδ Pathway in Human Articular Chondrocytes. J Cell Biochem. 2012 Sep;113(9):2856–65.
36. Moore EE, Bendele AM, Thompson DL, Littau A, Waggie KS, Reardon B, et al. Fibroblast growth factor-18 stimulates chondrogenesis and cartilage repair in a rat model of injury-induced osteoarthritis. Osteoarthritis Cartilage. 2005 Jul;13(7):623–31.
37. Barr L, Getgood A, Guehring H, Rushton N, Henson FMD. The effect of recombinant human fibroblast growth factor-18 on articular cartilage following single impact load. J Orthop Res. 2014;32(7):923–7.
38. Geetha-Loganathan P, Nimmagadda S, Scaal M. Wnt signaling in limb organogenesis. Organogenesis. 2008;4(2):109–15.
39. Valdes AM, Doherty S, Muir KR, Zhang W, Maciewicz RA, Wheeler M, et al. Genetic contribution to radiographic severity in osteoarthritis of the knee. Ann Rheum Dis. 2012 Sep;71(9):1537–40.
40. Lories RJU, Peeters J, Bakker A, Tylzanowski P, Derese I, Schrooten J, et al. Articular cartilage and biomechanical properties of the long bones in Frzb-knockout mice. Arthritis Rheum. 2007 Dec;56(12):4095–103.
41. Blom AB, Brockbank SM, van Lent PL, van Beuningen HM, Geurts J, Takahashi N, et al. Involvement of the Wnt signaling pathway in experimental and human osteoarthritis: prominent role of Wnt-induced signaling protein 1. Arthritis Rheum. 2009 Feb;60(2):501–12.
42. Walling HW, Raggatt LJ, Irvine DW, Barmina OY, Toledano JE, Goldring MB, et al. Impairment of the collagenase-3 endocytotic receptor system in cells from patients with osteoarthritis. Osteoarthritis Cartilage. 2003 Dec;11(12):854–63.
43. Neuhold LA, Killar L, Zhao W, Sung ML, Warner L, Kulik J, et al. Postnatal expression in hyaline cartilage of constitutively active human collagenase-3 (MMP-13) induces osteoarthritis in mice. J Clin Invest. 2001 Jan;107(1):35–44.
44. Xia B, Chen D, Zhang J, Hu S, Jin H, Tong P. Osteoarthritis Pathogenesis: A Review of Molecular Mechanisms. Calcif Tissue Int. 2014 Dec;95(6):495–505.
45. Kolasinski SL, Neogi T, Hochberg MC, Oatis C, Guyatt G, Block J, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee. Arthritis Rheumatol. 2020 Feb;72(2):220–33.
46. Oo WM, Little C, Duong V, Hunter DJ. The Development of Disease-Modifying Therapies for Osteoarthritis (DMOADs): The Evidence to Date. Drug Des Devel Ther. 2021 Jul 6;15:2921–45.
47. Troeberg L, Nagase H. Proteases involved in cartilage matrix degradation in osteoarthritis. Biochim Biophys Acta. 2012 Jan;1824(1):133–45.
48. Li J, Wang X, Ruan G, Zhu Z, Ding C. Sprifermin: a recombinant human fibroblast growth factor 18 for the treatment of knee osteoarthritis. Expert

Opin Investig Drugs. 2021 Sep;30(9):923–30.
49. Deshmukh V, O'Green AL, Bossard C, Seo T, Lamangan L, Ibanez M, et al. Modulation of the Wnt pathway through inhibition of CLK2 and DYRK1A by lorecivivint as a novel, potentially disease-modifying approach for knee osteoarthritis treatment. Osteoarthritis Cartilage. 2019 Sep 1;27(9):1347–60.
50. Kim EC, Kim JR. Senotherapeutics: emerging strategy for healthy aging and age-related disease. BMB Rep. 2019 Jan;52(1):47–55.
51. Cho Y, Jeong S, Kim H, Kang D, Lee J, Kang SB, et al. Disease-modifying therapeutic strategies in osteoarthritis: current status and future directions. Exp Mol Med. 2021 Nov 30;53(11):1689–96.
52. Makarczyk MJ, Gao Q, He Y, Li Z, Gold MS, Hochberg MC, et al. Current Models for Development of Disease-Modifying Osteoarthritis Drugs. Tissue Eng Part C Methods. 2021 Feb 1;27(2):124–38.
53. Gigout A, Guehring H, Froemel D, Meurer A, Ladel C, Reker D, et al. Sprifermin (rhFGF18) enables proliferation of chondrocytes producing a hyaline cartilage matrix. Osteoarthritis Cartilage. 2017 Nov 1;25(11):1858–67.
54. Moore EE, Bendele AM, Thompson DL, Littau A, Waggie KS, Reardon B, et al. Fibroblast growth factor-18 stimulates chondrogenesis and cartilage repair in a rat model of injury-induced osteoarthritis. Osteoarthritis Cartilage. 2005 Jul 1;13(7):623–31.
55. Hochberg MC, Guermazi A, Guehring H, Aydemir A, Wax S, Fleuranceau-Morel P, et al. Effect of Intra-Articular Sprifermin vs Placebo on Femorotibial Joint Cartilage Thickness in Patients With Osteoarthritis. JAMA. 2019 Oct 8;322(14):1360–70.
56. Eckstein F, Hochberg MC, Guehring H, Moreau F, Ona V, Bihlet AR, et al. Long-term structural and symptomatic effects of intra-articular sprifermin in patients with knee osteoarthritis: 5-year results from the FORWARD study. Ann Rheum Dis. 2021 Aug;80(8):1062–9.
57. Guehring H, Moreau F, Daelken B, Ladel C, Guenther O, Bihlet AR, et al. The effects of sprifermin on symptoms and structure in a subgroup at risk of progression in the FORWARD knee osteoarthritis trial. Semin Arthritis Rheum. 2021 Apr;51(2):450–6.
58. Eckstein F, Wirth W, Guermazi A, Maschek S, Aydemir A. Brief report: intraarticular sprifermin not only increases cartilage thickness, but also reduces cartilage loss: location-independent post hoc analysis using magnetic resonance imaging. Arthritis Rheumatol Hoboken NJ. 2015 Nov;67(11):2916–22.
59. Yazici Y, McAlindon TE, Gibofsky A, Lane NE, Clauw D, Jones M, et al. Lorecivivint, a Novel Intraarticular CDC-like Kinase 2 and Dual-Specificity Tyrosine Phosphorylation-Regulated Kinase 1A Inhibitor and Wnt Pathway Modulator for the Treatment of Knee Osteoarthritis: A Phase II Randomized Trial. Arthritis Rheumatol Hoboken NJ. 2020 Oct;72(10):1694–706.
60. Yazici Y, McAlindon TE, Gibofsky A, Lane NE, Lattermann C, Skrepnik N, et al. A Phase 2b randomized trial of lorecivivint, a novel intra-articular CLK2/DYRK1A inhibitor and Wnt pathway modulator for knee osteoarthritis. Osteoarthritis Cartilage. 2021 May;29(5):654–66.
61. Tambiah JRS, Kennedy S, Swearingen CJ, Simsek I, Yazici Y, Farr J, et al. Individual Participant Symptom Responses to Intra-Articular Lorecivivint in Knee Osteoarthritis: Post Hoc Analysis of a Phase 2B Trial. Rheumatol Ther. 2021 Jun;8(2):973–85.
62. Study Details | A Study Utilizing Patient-Reported Outcomes to Evaluate the Safety and Efficacy of Lorecivivint (SM04690) for the Treatment of Moderately to Severely Symptomatic Knee Osteoarthritis (STRIDES) | ClinicalTrials.gov [Internet]. [cited 2023 Dec 22]. Available from: https://clinicaltrials.gov/study/NCT05603754?cond=Osteoarthritis%20&intr=Lorecivivint&rank=3
63. Drake FH, Dodds RA, James IE, Connor JR, Debouck C, Richardson S, et al. Cathepsin K, but Not Cathepsins B, L, or S, Is Abundantly Expressed in Human Osteoclasts (∗). J Biol Chem. 1996 May 24;271(21):12511–6.
64. Karsdal MA, Bay-Jensen AC, Lories RJ, Abramson S, Spector T, Pastoureau P, et al. The coupling of bone and cartilage turnover in osteoarthritis: opportunities for bone antiresorptives and anabolics as potential treatments? Ann Rheum Dis. 2014 Feb 1;73(2):336–48.
65. Lindström E, Rizoska B, Henderson I, Terelius Y, Jerling M, Edenius C, et al. Nonclinical and clinical pharmacological characterization of the potent and selective cathepsin K inhibitor MIV-711. J Transl Med. 2018 May 9;16(1):125.
66. Conaghan PG, Bowes MA, Kingsbury SR, Brett A, Guillard G, Rizoska B, et al. Disease-Modifying Effects of a Novel Cathepsin K Inhibitor in Osteoarthritis. Ann Intern Med. 2020 Jan 21;172(2):86–95.
67. Verma P, Dalal K. ADAMTS-4 and ADAMTS-5: Key enzymes in osteoarthritis. J Cell Biochem. 2011;112(12):3507–14.
68. Clement-Lacroix P, Little CB, Smith MM, Cottereaux C, Merciris D, Meurisse S, et al. Pharmacological characterization of GLPG1972/S201086, a potent and selective small-molecule inhibitor of ADAMTS5. Osteoarthritis Cartilage. 2022 Feb 1;30(2):291–301.
69. van der Aar E, Deckx H, Dupont S, Fieuw A, Delage S, Larsson S, et al. Safety, Pharmacokinetics, and Pharmacodynamics of the ADAMTS-5 Inhibitor GLPG1972/S201086 in Healthy Volunteers and Participants With Osteoarthritis of the Knee or Hip. Clin Pharmacol Drug Dev. 2022 Jan;11(1):112–22.
70. Schnitzer T, Pueyo M, Deckx H, van der Aar E, Bernard K, Hatch S, et al. Evaluation of S201086/GLPG1972, an ADAMTS-5 inhibitor, for the treatment of knee osteoarthritis in ROCCELLA: a phase 2 randomized clinical trial. Osteoarthritis Cartilage. 2023 Jul;31(7):985–94.
71. Saisho Y. Metformin and Inflammation: Its Potential Beyond Glucose-lowering Effect. Endocr Metab Immune Disord - Drug TargetsFormerly Curr Drug Targets - Immune Endocr Metab Disord. 2015 Sep 1;15(3):196–205.
72. Lu CH, Chung CH, Lee CH, Hsieh CH, Hung YJ, Lin FH, et al. Combination COX-2 inhibitor and metformin attenuate rate of joint replacement in osteoarthritis with diabetes: A nationwide, retrospective, matched-cohort study in Taiwan. PLoS ONE. 2018 Jan 31;13(1):e0191242.
73. Wang Y, Hussain SM, Wluka AE, Lim YZ, Abram F, Pelletier JP, et al. Association between metformin use and disease progression in obese people with knee osteoarthritis: data from the Osteoarthritis Initiative-a prospective cohort study. Arthritis Res Ther. 2019 May 24;21(1):127.
74. Cherifi C, Monteagudo S, Lories R. Promising targets for therapy of osteoarthritis: a review on the Wnt and TGF-β signalling pathways. Ther Adv Musculoskelet Dis. 2021 Apr 16;13:1759720X2110069.
75. Liu J, Xiao Q, Xiao J, Niu C, Li Y, Zhang X, et al. Wnt/β-catenin signalling: function, biological mechanisms, and therapeutic opportunities. Signal Transduct Target Ther. 2022 Jan 3;7(1):1–23.
76. Vincent TL, Alliston T, Kapoor M, Loeser RF, Troeberg L, Little CB. Osteoarthritis pathophysiology – therapeutic target discovery may require a multi-faceted approach. Clin Geriatr Med. 2022 May;38(2):193–219.

11. Appendices

PGI results for knee OA subjects (n = 91)

Rank	Feature	Frequency *N* (%)	Distress (/6) mean ± SD (range)	Points (/10) mean ± SD (range)
1	Sharp pain	65 (71.4)	4.2 ± 1.4 (1–6)	2.8 ± 2.1 (0–9)
2	Limitation of activities	63 (69.2)	4.1 ± 1.3 (0–6)	2.6 ± 2.1 (0–10)
3	Ache/dull	60 (65.9)	3.6 ± 1.6 (0–6)	2.4 ± 2.1 (0–10)
4	Triggered by activity	46 (50.5)	4.2 ± 1.3 (1–6)	3.0 ± 2.1 (0–10)
5	Stiffness	24 (26.4)	4.0 ± 1.2 (2–6)	2.9 ± 2.7 (0–10)
6	Unpredictability	23 (25.3)	3.4 ± 1.6 (1–6)	1.4 ± 1.5 (0–6)
7	Constant	21 (23.1)	3.9 ± 1.5 (1–6)	2.1 ± 1.4 (0–5)
8	Unstable	20 (22.0)	4.3 ± 1.6 (1–6)	2.2 ± 1.5 (0–5)
9	Night pain/impact on sleep	16 (17.6)	3.9 ± 1.4 (1–6)	2.9 ± 1.4 (1–5)
10	Mood	16 (17.6)	3.8 ± 1.5 (1–6)	1.6 ± 1.7 (0–5)
11	Swelling	14 (15.4)	3.9 ± 1.8 (0–6)	1.6 ± 1.2 (0–4)
12	Grating	12 (13.2)	4.3 ± 1.3 (2–6)	1.8 ± 1.3 (0–4)
13	Inactivity	12 (13.2)	3.5 ± 1.2 (1–5)	2.0 ± 1.0 (0–3)
14	Burning pain	6 (6.6)	4.2 ± 2.3 (0–6)	3.7 ± 1.4 (2–6)
15	Weakness	6 (6.6)	2.5 ± 1.9 (0–5)	2.2 ± 0.8 (1–3)
16	Fear	6 (6.6)	4.0 ± 2.0 (1–6)	2.0 ± 1.7 (0–4)
17	Use of medication/devices	5 (5.5)	4.2 ± 1.3 (3–6)	1.4 ± 1.1 (0–3)
18	Numbness	4 (4.4)	3.5 ± 2.1 (1–6)	1.5 ± 1.9 (0–4)
19	Locking	4 (4.4)	4.5 ± 1.3 (3–6)	2.3 ± 1.3 (1–4)
20	Cramping/muscle spasms	3 (3.3)	4.7 ± 0.6 (4–5)	2.3 ± 2.3 (1–5)
21	Clicking/cracking	3 (3.3)	3.0 ± 0.0 (3)	2.0 ± 2.7 (0–5)
22	Radiating pain	1 (1.1)	6 (6)	1 (1)

Table 1 Frequency of pain complaints in knee osteoarthritis

Patient generated index (PGI) for knee OA subjects (n = 91)(21)

PGI results for hip OA subjects (n = 52)

Rank	Feature	Frequency *N* (%)	Distress (/6) mean ± SD (range)	Points (/10) mean ± SD (range)
1	Ache	48 (92.3)	3.3 ± 1.5 (1–6)	3.3 ± 3.0 (0–10)
2	Sharp pain	33 (63.5)	4.2 ± 1.5 (1–6)	2.8 ± 2.7 (0–10)
3	Limitation of activities	24 (46.2)	4.6 ± 1.4 (1–6)	2.7 ± 2.7 (0–10)
4	Triggered by activity	18 (34.6)	3.7 ± 1.7 (0–6)	4.2 ± 3.3 (0–10)
5	Mood	16 (30.8)	3.3 ± 1.4 (0–5)	3.1 ± 2.4 (0–10)
6	Constant pain	13 (25.0)	3.5 ± 1.8 (0–5)	3.1 ± 2.2 (0–7)
7	Night pain/impact on sleep	9 (17.3)	3.4 ± 1.7 (0–5)	2.9 ± 2.6 (0–8)
8	Triggered by inactivity	7 (13.5)	3.3 ± 1.5 (1–5)	1.4 ± 1.5 (0–4)
9	Stiffness	7 (13.5)	3.0 ± 0.6 (2–4)	1.9 ± 1.2 (1–4)
10	Burning pain	6 (11.6)	4.0 ± 1.7 (1–6)	2.8 ± 1.8 (1–5)
11	Radiating pain	6 (11.6)	3.5 ± 1.6 (1–5)	1.8 ± 1.7 (0–4)
12	Numbness	5 (9.6)	3.6 ± 0.9 (3–5)	2.6 ± 1.7 (1–5)
13	Unstable	4 (7.7)	3.3 ± 1.7 (1–5)	1.8 ± 0.5 (1–2)
14	Unpredictability	3 (5.8)	3.3 ± 2.5 (1–6)	0.7 ± 0.6 (0–1)
15	Clicking	2 (3.8)	1.5 ± 2.1 (0–3)	6.0 ± 5.7 (2–10)
16	Weakness	2 (3.8)	4.0 ± 1.4 (3–5)	2.0 ± 1.4 (1–3)
17	Cramping	1 (1.9)	5 (5)	1 (1)
18	Fear	1 (1.9)	6 (6)	0 (0)
19	Use of medication/devices	1 (1.9)	3 (3)	0 (0)
20	Locking	1 (1.9)	5 (5)	1 (1)
21	Grating pain	0 (0.0)	–	–
22	Swelling	0 (0.0)	–	–

Table 2 Frequency of pain complaints in hip osteoarthritis

Patient generated index (PGI) for hip OA subjects (n = 52)(21)

Endpoints	Placebo (n = 234)	S201086/GLPG1972 75 mg (n = 234)	S201086/GLPG1972 150 mg (n = 231)	S201086/GLPG1972 300 mg (n = 233)
Primary endpoint				
Cartilage thickness in cMFTC, mm				
Change from baseline at week 52				
Number of participants	172	162	158	151
Mean (SD)	−0.116 (0.273)	−0.068 (0.202)	−0.097 (0.268)	−0.085 (0.217)
Treatment effect at week 52				
E (SE)	–	0.045 (0.025)	0.012 (0.026)	0.023 (0.025)
95% CI	–	−0.003 to 0.093	−0.039 to 0.063	−0.026 to 0.073
P value	–	0.165	0.939	0.682
Structural secondary endpoints				
Joint space width, mm				
Change from baseline at week 52				
Number of participants	179	169	163	155
Mean (SD)	−0.174 (0.470)	−0.087 (0.397)	−0.167 (0.506)	−0.113 (0.464)
Treatment effect at week 52				
E	–	0.095	0.016	0.075
95% CI	–	−0.003 to 0.193	−0.086 to 0.118	−0.029 to 0.179
P value	–	0.141	0.981	0.349
Proportion of structural progressors*				
Number of participants	172	162	158	151
Progressor at week 52, *n* (%)	35 (20.3)	22 (13.6)	34 (21.5)	25 (16.6)
Treatment effect at week 52				
E	–	1.47	0.89	1.08
95% CI	–	0.8 to 2.6	0.5 to 1.5	0.6 to 1.8
P value	–	0.396	0.951	0.985

CI: confidence interval; cMFTC: central medial femorotibial compartment; E: treatment effect estimate; OA: osteoarthritis; SD: standard deviation; SE: standard error.
* Defined as a patient who had ≥8% cartilage loss in the cMFTC between baseline and week 52.

Table 3 Results ROCCELLA study

Summary of primary and key secondary structural endpoints in participants with knee OA of ROCCELLA study(70)

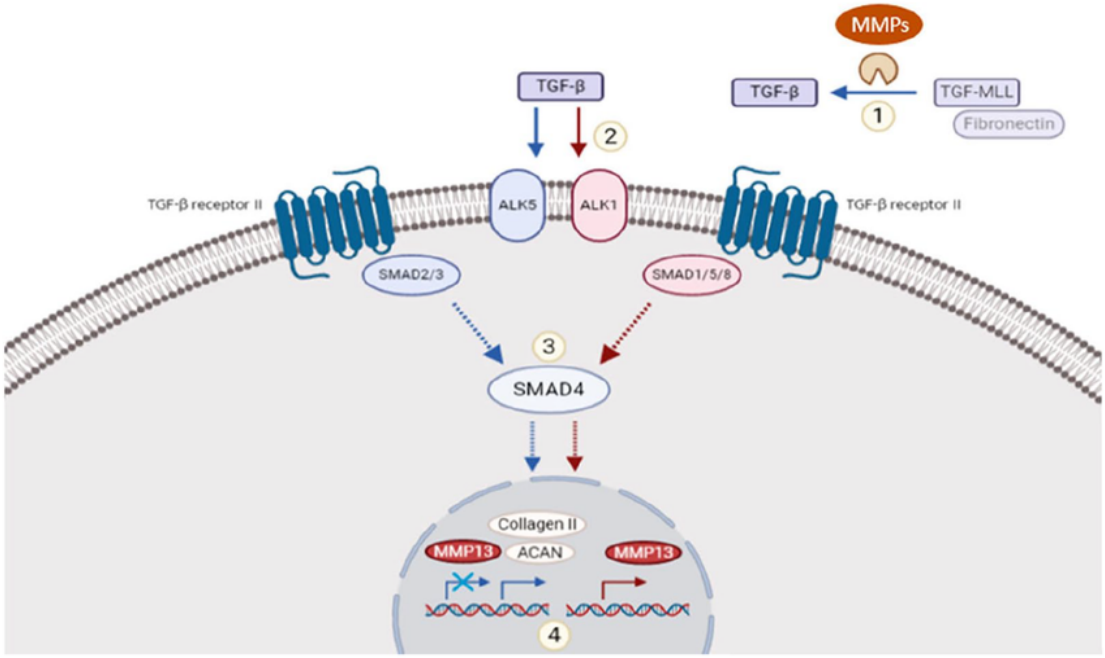

Figure 9 Transforming growth factor β in pathogenesis of osteoarthritis

TGF-β signalling in chondrocytes(74)

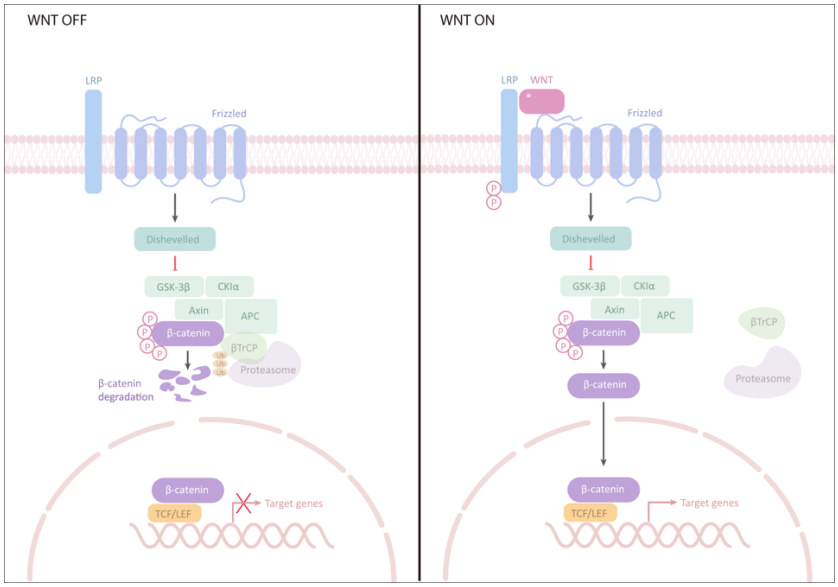

Figure 10 Wnt/β-catenin signalling in pathogenesis of osteoarthritis

Wnt/β-catenin pathway: Inactivation of Wnt signalling (Left) and activation of Wnt signalling (Right)(75)

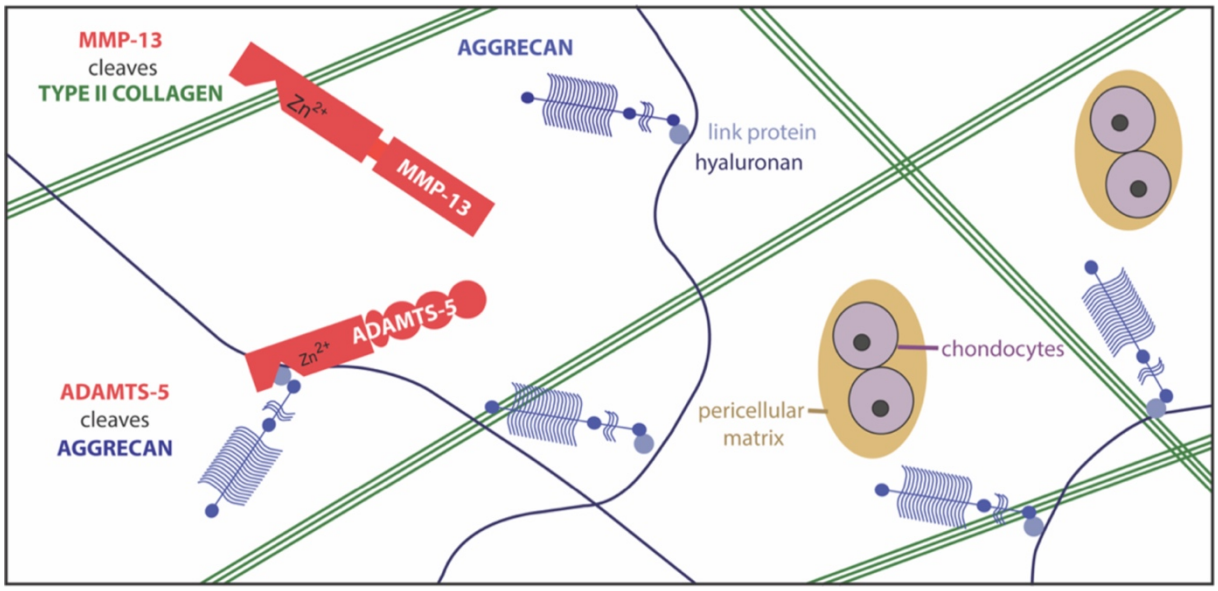

Figure 11 MMP-13 and ADAMTS-5 in pathogenesis of osteoarthritis

MMPs and ADAMTSs metalloproteases cleave type II collagen and aggrecan in the OA cartilage extracellular matrix (76)

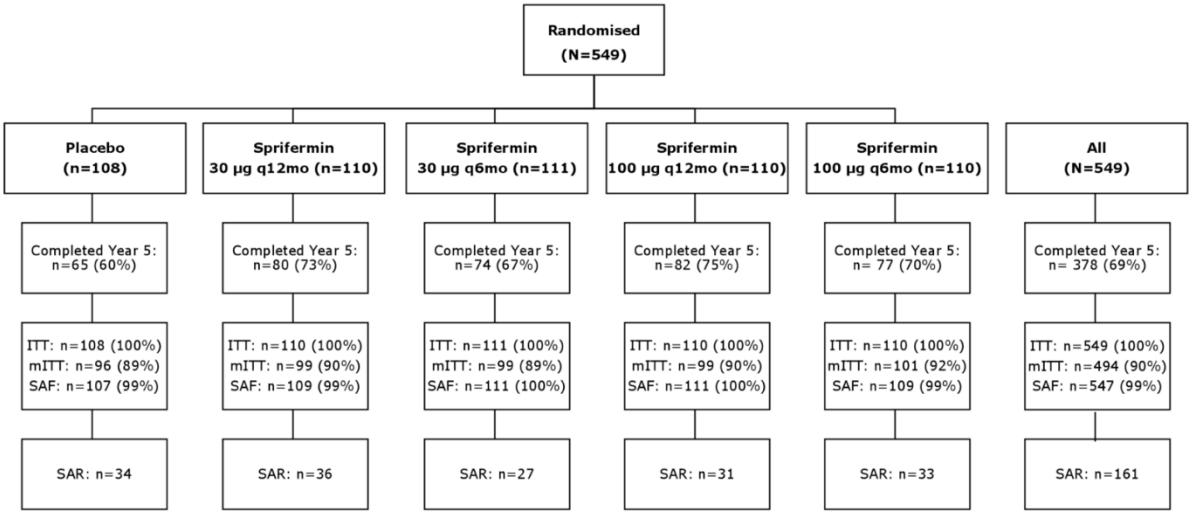

Figure 12 Patient disposition of FORWARD study

q6mo, every 6 months; q12mo, every 12 months; SAF, safety; SAR, subgroup at risk(56)

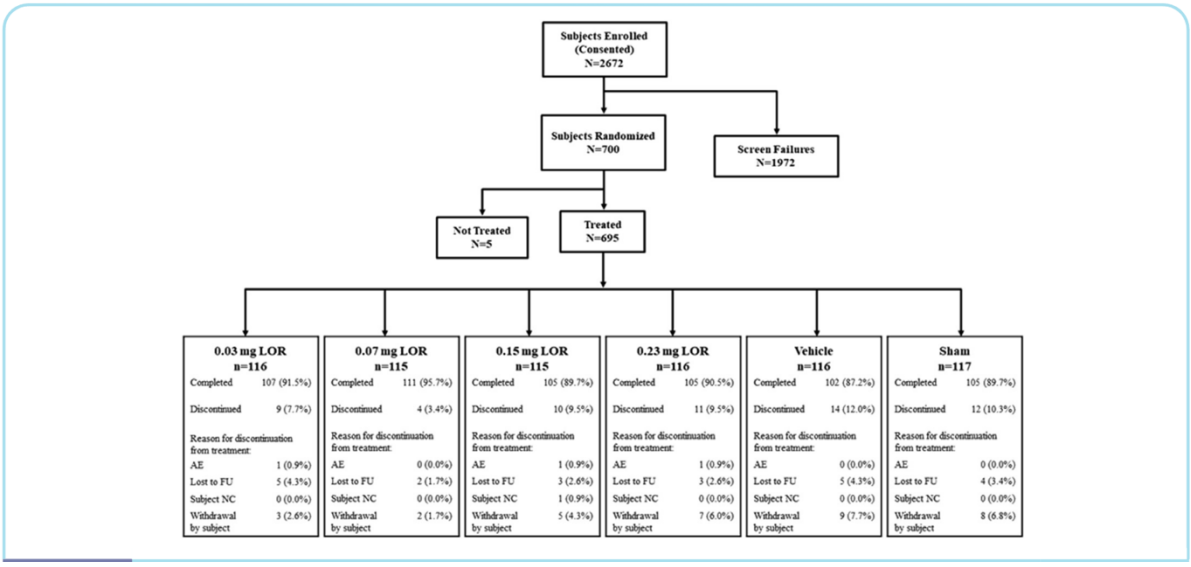

Figure 13 Lorecivivint study subject disposition and reasons for discontinuation

The number and percent of subjects are provided for all treatment groups. The numbers are based on the planned treatment. Abbreviations AE: Adverse event, FU: Follow-up, LOR: Lorecivivint, NC: Noncompliance(60)

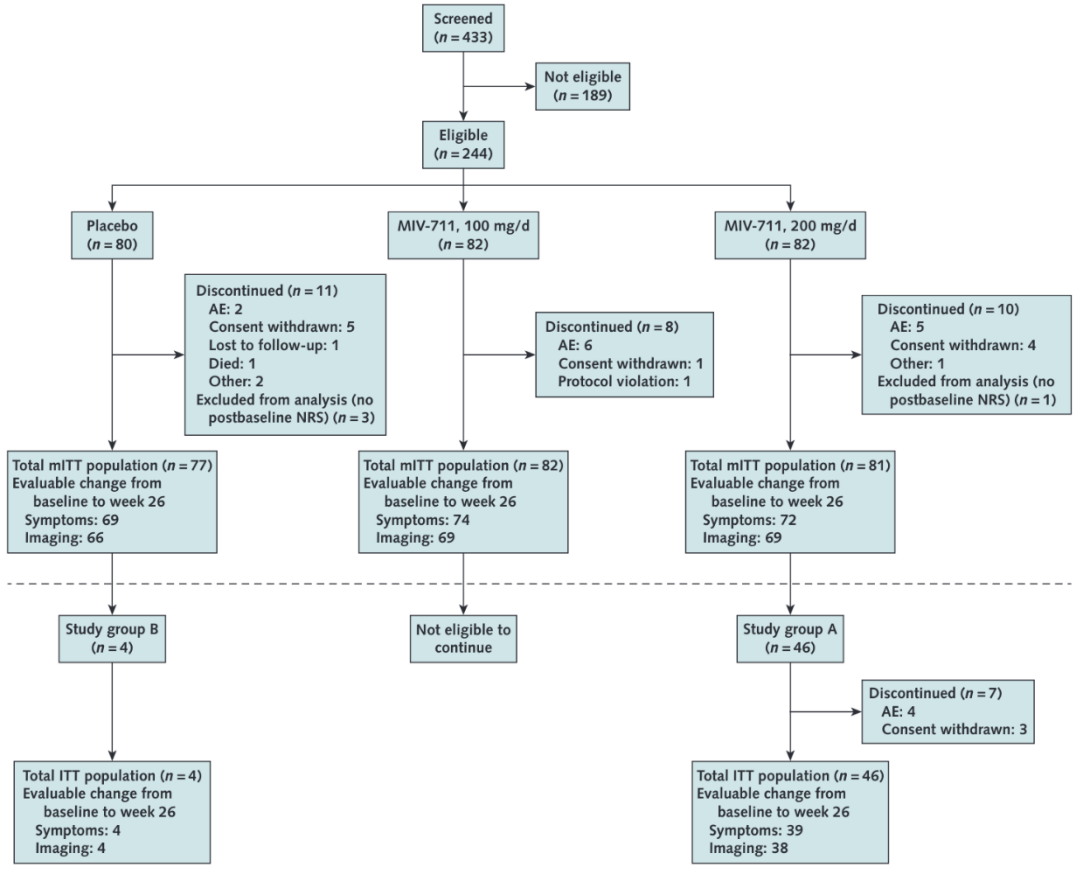

Figure 14 Study flow diagrams for the placebo-controlled study (top) and the extension substudy of MIV-711 study

AE = adverse event; ITT = intention-to-treat; mITT = modified intention-to-treat; NRS = numerical rating scale(66)

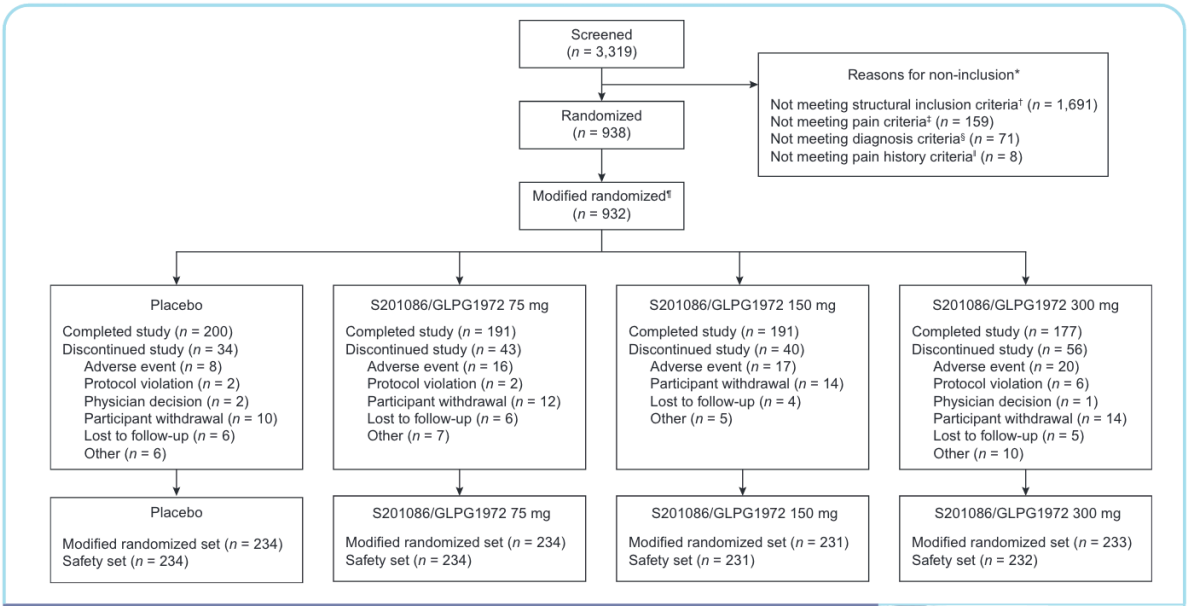

Figure 15 Participant disposition of S201086/GLPG1972 ROCCELLA study

Study flow diagram for the placebo-controlled study(70)

12. Warranty

WARRANTY

of Vilnius University Student Thesis

Name, Surname: Louis Ferdinand Gallmann
Faculty: Faculty of Medicine
Study programme: Medicine
Thesis topic: Evidence-Based Therapy for Osteoarthritis
Thesis type: Narrative Literature Review

I guarantee that my thesis is prepared in good faith and independently, there is no contribution to this work from other individuals. I have not made any illegal payments related to this work.

Quotes from other sources used in this thesis, directly or indirectly, are indicated in literature references.

I, Louis Ferdinand Gallmann, confirm (check) [X]

I declare that this thesis is submitted to the Vilnius University Study Information System.

Louis Ferdinand Gallmann	L. F. Gall	06. May, 2024
(vardas, pavardė / *name, surname*)	(parašas / *signature*)	(data / *date*)