symptom benefits may reflect that the study duration was not sufficient to see symptom reduction following structure modification. Data from the OAI cohort indicate that changes in bone shape over 24 months are associated with radiographic and concomitant pain progression over 48 months. Further evaluation of MIV-711 in longer and larger DMOAD trials is therefore warranted.

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SYNTHETIC TRANSDERMAL CANNABIDIOL FOR THE TREATMENT OF KNEE PAIN DUE TO OSTEOARTHRITIS

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Purpose: Cannabidiol (CBD) has shown promise in reducing pain and inflammation in pre-clinical models of arthritis. However, there have been no well controlled studies evaluating CBD for osteoarthritis (OA) in humans. This study evaluated safety and efficacy of ZYN002 (transdermal synthetic CBD gel) for the treatment of knee pain due to OA in adults.
Methods: A Phase 2A, randomized, double-blind, placebo-controlled, multiple-dose study assessed ZYN002 administered twice daily for 12 weeks to adults with knee pain due to OA. Patients met ACR criteria for OA of the knee and underwent a 1-week washout to stop current anti-inflammatory agents/other analgesics (except paracetamol) followed by a 7 to 10-day baseline period capturing daily worst pain ratings using a 0 to 10 numeric rating scale. Eligible patients were randomized 1:1:1 to ZYN002 250 mg daily in 2 divided doses, ZYN002 500 mg daily in 2 divided doses, or placebo. The primary efficacy endpoint was change from baseline in the weekly mean of the 24-hour average worst pain score at Week 12. A key secondary endpoint was a responder analysis, defined as average weekly improvement in worst pain score of $\geq$ 30% and decrease in WOMAC physical function sub scale of at least 20% at last observation.
Results: Three hundred and twenty patients were randomized. Mean age was 62 (41–78) years, baseline mean worst knee pain score was 6.9. ZYN002 was not statistically different from placebo on the primary endpoint; week 12 mean reduction from baseline in average worst knee pain was −2.64 for ZYN002 250 mg/day (n = 106), −2.83 for ZYN002 500 mg/day (n = 105) and −2.37 for placebo (n = 103). However, patients using ZYN002 250 mg/day (n = 93) significantly outperformed placebo (n = 88) for the responder analysis (52.7% vs 34.1%, $p = 0.016$). Post-hoc analyses revealed that men treated with ZYN002 250 mg/day (n = 43) had significantly greater reductions from baseline in average worst knee pain scores than placebo-treated men (n = 31; 2.68 vs 1.70, $p = 0.049$) and greater performance in the responder analysis (n = 45; 60% vs 26.7%, $p = 0.003$), as compared to men who received placebo (n = 45). Indeed, women on ZYN002 did not differ from placebo in changes in average worst knee pain scores or responder analysis. Patients with the least amount of variability in baseline pain scores had greater performance in the responder analysis in both the 250 mg/day (n = 34; $p = 0.055$) and 500 mg/day (n = 29; $p = 0.046$) compared to placebo (n = 37). There were 2 treatment emergent adverse events that exceeded 3% of patients on ZYN002 and were greater than placebo: application site dryness (3.8% vs 0.9%) and headache (3.3% vs 1.9%).
Conclusions: After 12 weeks of blinded treatment, while ZYN002 250 mg/day produced numerically better mean reductions from baseline in average worst knee pain scores, it was not statistically different than placebo. In contrast, the responder endpoint showed statistically significant differences between 250 mg/day and placebo. Significant gender differences were noted with the responder analysis and pain scores. Both doses of ZYN002 were well tolerated.

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ADAMTS-5 INHIBITION WITH THE POTENT AND HIGHLY SELECTIVE INHIBITOR GLPG1972 RESULTS IN STRONG DISEASE-MODIFYING OA DRUG EFFECTS IN THE RAT MENISCECTOMY MODEL

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Purpose: Aggrecan is a major structural component of articular cartilage and halting its degradation is a promising strategy towards the discovery of new disease-modifying OA drugs (DMOADs). A disintegrin and metalloproteinase with thrombospondin motifs-5 (ADAMTS-5) is a key player in pathological human cartilage aggrecanolysis. We previously reported the discovery of GLPG1972: a potent, selective and orally bioavailable ADAMTS-5 inhibitor endowed with strong chondroprotective effects in cartilage explants and high DMOAD efficacy in the destabilization of the medial meniscus (DMM) model in mice. Here we report the evaluation of GLPG1972 in a second pre-clinical model of surgery induced OA: the rat meniscectomy (MNX) model.
Methods: OA was induced by meniscectomy in the rat right hind leg by a transection of the medial collateral ligament and removal of 4 mm of ligament. Sham animals only underwent anaesthesia, skin and muscle incision followed by suture. On day 1 post surgery, rats were randomly assigned to a treatment group (n = 20 per group) according to their body weight. GLPG1972 (formulated in Tween 80/Methylcellulose 0.5% (2/98, v/v)) was administered orally over 3 weeks at dose levels of 10, 25 and 50 mg/kg b.i.d. At sacrifice, the right tibia was collected and processed for histological analysis. OA development in the tibial plateau was evaluated using the OARSI score. Structural parameters relative to the articular cartilage and subchondral bone were also measured by imaging histomorphometry. Among the five sections of each tibia generally produced, the one with the highest OARSI score was selected for the histomorphometry analysis. The following structural parameters were measured: were measured by imaging histomorphometry analysis: subchondral bone plate thickness (SCBPT) (mm), proteoglycan (PG) content (%), fibrillation index (mm) and chondrocyte density (number cells/mm^2). Blood samples were collected at steady state (day 12) at predose, 1, 3 and 6 h postdose for determination of GLPG1972 plasma concentrations using LC–MS/MS. Pharmacokinetic parameters were calculated using Phoenix® 6.4 (Certara).
Results: Three weeks post-surgery, treatment with GLPG1972 resulted in significant reduction in OARSI score at 25 and 50 mg/kg b.i.d. (-24% and -23%, respectively, compared to vehicle-treated rats). GLPG1972 also significantly reduced cartilage fibrillation from 25 mg/kg b.i.d. and prevented proteoglycan loss and subchondral bone plate thickening from 10 mg/kg b.i.d.. Plasma exposure increased slightly more than dose-proportionally over the dose range tested. At 25 mg/kg b.i.d., the average plasma concentration over 24 h was found to be in line with the value observed in other rat MNX experiments (385 ng/mL). Finally, the average condyle to plasma ratio was 0.14, demonstrating that GLPG1972 efficiently reached its target tissue.
Conclusions: GLPG1972 is a potent ADAMTS-5 inhibitor showing high selectivity against other metalloproteases and strong anti-catabolic properties both *in vitro* and *in vivo*. Efficacy in the rat MNX model provides additional convincing preclinical evidence for GLPG1972 DMOAD potential. A Phase 1 first-in-human study was successfully completed with GLPG1972, a dose-escalation Phase 1b study in OA patients is ongoing in the United States (NCT03311009) and a Phase 2 program is currently being prepared with this highly promising OA drug candidate.

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EFFICACY AND SAFETY OF INTRA-ARTICULAR SPRIFERMIN IN SYMPTOMATIC RADIOGRAPHIC KNEE OSTEOARTHRITIS: PRE-SPECIFIED ANALYSIS OF 3-YEAR DATA FROM A 5-YEAR RANDOMIZED, PLACEBO-CONTROLLED, PHASE II STUDY

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Purpose: Sprifermin, a novel recombinant human fibroblast growth factor-18, is currently being investigated as a potential disease-modifying osteoarthritis (OA) drug. Two-year results of the 5-year Phase II FORWARD study showed a statistically significant dose-dependent increase in total femorotibial joint (TFJ) cartilage thickness, as well as in the medial, lateral and central medial sub-region TFJ compartments by quantitative magnetic resonance imaging (qMRI). Here we report the results of the pre-specified 3-year analyses.
Methods: Patients (pts) aged 40–85 years with symptomatic radiographic knee OA, Kellgren-Lawrence grade (KLG) 2 or 3, and medial