question in order to further characterize its utility as an outcome measure.

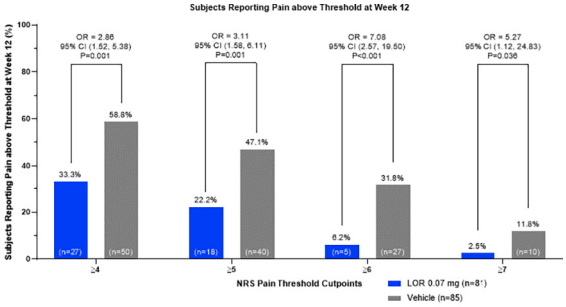

Figure 1. Subjects with Not Tolerable Pain NRS scores at Week 12. Logistic regression of lorecivivint (LOR) versus placebo (Vehicle) using the Full Analysis Set (widespread-pain negative subjects).

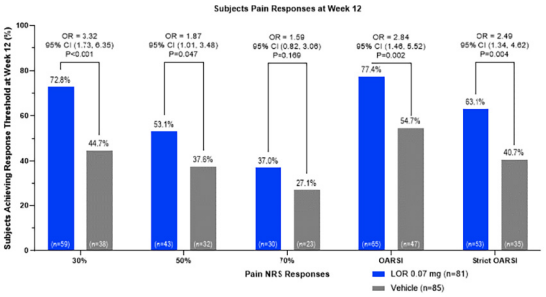

Figure 2. Subjects achieving 30%, 50%, or 70% improvement over baseline, or meeting OARSI response criteria. OARSI "strict" response: ≥50% improvement in pain or function and absolute change ≥20-point [0-100]. OARSI response: OARSI "strict" or ≥20% improvement and absolute change ≥10-point [0-100] in two of pain, function, and/or patient global assessment. Comparisons of lorecivivint (LOR) versus placebo (Vehicle) via logistic regression.

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DISTINCTIVE THERAPEUTIC EFFECTS OF NON-EUPHORIGENIC HEMP EXTRACTS IN OSTEOARTHRITIS

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Purpose: Osteoarthritis (OA) is the leading cause of disability in older adults and involves complex interactions of local and systemic factors clinically characterized as joint pain and loss of function. Current treatment offers symptoms management and joint replacement surgery, with no disease modifying agents available. Hemp products, specifically cannabinoids, are widely used by the public to control pain and inflammation in many diseases; but there is not scientific evidence demonstrating their efficacy in OA. **Aim:** Our study investigated the effects of non-euphorigenic hemp extracts, cannabidiol oil (CBD oil) and cannabigerol oil (CBG oil), on OA pain and disease progression in mice. **Methods:** Twelve-week-old male C57BL/6J mice received either sham or destabilization of the medial meniscus (DMM) surgery. DMM is a model of slowly progressing OA that replicates all the clinical aspects of the disease: inflammation, pain, and joint remodeling. DMM mice were randomized into three groups that received treatment with vehicle (V, coconut oil), CBD oil (50 mg/ml CBD content) at 20 mg/kg/day, or CBG oil (25 mg/ml CBG and 25 mg/ml CBD content) at 10 mg/kg/day of each; with N=6-8 mice per group. Treatments were administered by subcutaneous injection at the DMM knee region to simulate topically applied oils in OA patients, starting from day 3 following injury and continuing every other day for 8 weeks. We performed gait analysis, acetone test, Von Frey test, and open-field test to quantify changes in gait, pain, and locomotor activity. OA disease progression was evaluated by histology and histomorphometry, and micro-CT analysis. Molecular changes were evaluated using immunofluorescence (IF) staining. **Results:** The gait of DMM mice was impaired as early as 2 weeks following surgery and continued deteriorating until week 8, which was restored by CBD oil and CBG oil treatments starting from week 2 and throughout the disease course-until week 8. Mechanical allodynia (measured by von Frey test) developed in DMM mice, however, was not ameliorated by any of the treatments. On the other hand, both CBD oil and CBG oil ameliorated thermal allodynia, measured by acetone test. In the open field test, both oil treatments normalized changes in the locomotor activity of DMM mice. CBD oil and CBG oil treatments significantly reduced synovitis in DMM mice (Figure 1). Interestingly, only CBG oil-treated mice had reduced cartilage degeneration and chondrocyte loss, with a significant increase in the number of matrix-producing (anabolic) chondrocytes, as shown by histomorphometry (Figure 2A, B, D-F). IF staining of the catabolic enzyme Matrix Metalloproteinase 13 (MMP13) showed significantly increased expression in vehicle-treated DMM mice, with a significant reduction by CBG oil treatment only (Figure 2C, G). Micro-CT analysis showed subchondral bone remodeling in the vehicle-treated DMM mice, which was not ameliorated by either CBD or CBG oil. Finally, the expression of cannabinoid receptor 2 (CB2) in articular chondrocytes was not changed among treatment groups. In the synovium of vehicle-treated DMM mice, CB2 expression trended towards a reduction, with a trend towards an increase in CBD oil and CBG oil-treated DMM mice. **Conclusions:** Pure CBD has previously been demonstrated to have analgesic effects, diminishing hyperalgesia and mechanical/thermal allodynia with possible anti-inflammatory effects in other models. CBG oil is an emerging non-psychoactive cannabinoid with limited prior investigation. In our study, we found that both CBD oil and CBG oil ameliorate allodynia and improve gait and locomotor activity in OA mice; which represent clinical pain and function. Both oils also improved synovitis, indicating an anti-inflammatory effect. Importantly, only CBG oil had chondroprotective and chondroregenerative/anabolic effects. Prior in vitro studies showed the effectiveness of CB2 signaling in preventing the secretion of cartilage degrading enzymes and promoting the production of cartilage matrix. In our current *in vivo* study, there were no significant changes in CB2 expression among experimental groups; we are currently investigating changes in CB2 signaling versus expression in DMM mice with vehicle, CBD oil or CBG oil treatments to determine its role in DMM-induced OA. There has been incredible demand for developing disease modifying agents in OA with a recent focus on the use of cannabinoids. Our study provides scientific evidence supporting the efficacy of CBD oil and CBG oil in OA pain, and the efficacy of CBG oil as a disease modifying agent.

Figure 1