INTTEGRATED SAFETY SUMMARY OF THE NOVEL, INTRA-ARTICULAR AGENT LORECIVIVINT (SM04690), A CLK/DYRK1A INHIBITOR THAT MODULATES THE WNT PATHWAY, IN SUBJECTS WITH KNEE OSTEOARTHRITIS

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Background: Concerns over the safety of available osteoarthritis (OA) treatments have led to revision of treatment guidelines and highlight the need for new therapies. Lorcivivint (LOR; SM04690) is an intra-articular (IA), small-molecule CLK/DYRK1A inhibitor that modulates the Wnt pathway and is in development as a potential disease-modifying treatment for knee OA.\textsuperscript{1,2}

Objectives: To evaluate pooled early-phase LOR clinical data for safety, including bone health-related adverse events (AEs).

Methods: Safety data were pooled from 3 randomized controlled trials (one Phase 1, two Phase 2) evaluating 4 doses (0.03 mg, 0.07 mg, 0.15 mg, 0.23 mg) of a single IA injection of LOR in subjects with moderately to severely symptomatic knee OA. Two trials (NCT02095548; NCT03122860) evaluated subjects for 24 weeks and one trial (NCT02536833) for 52 weeks. AEs, serious AEs (SAEs), and bone health AEs were categorized by Medical Dictionary for Regulatory Activities (MedDRA) classification. Incidences of AEs and SAEs were compared between the combined LOR-treated group and a control group (subjects not treated with LOR).

Results: This analysis includes 848 LOR-treated and 360 control subjects. The incidence of AEs was similar in LOR-treated (350/848 [41.3%]) and control subjects (350/848 [41.3%]). Incidence of SAEs was 20/848 (2.4%) in LOR-treated and 8/360 (2.2%) in control subjects. All fractures (3 patellar [1 target knee, 2 non-target knee], 3 vertebral, 2 foot, 2 wrist, 2 rib, 1 fibula, 1 hand) were adjudicated and determined to be caused by trauma; all healed uneventfully within the expected time frame.

Conclusion: In exposure to date of 848 subjects, IA LOR for the treatment of knee OA appeared to be safe and well tolerated. These data support the continued evaluation of LOR as a potential treatment for knee OA.

References:


DOI: 10.1136/annrheumdis-2020-eular.6635

ASSessment of Cartilage Degradation and Protective Markers in Synovial Fluid from Osteoarthritis Patients Before and After Cycles of Intra-Articular Injections with Sprifermin

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Background: It is challenging to monitor treatment effects after intra-articular (IA) injection with tissue modifying drugs. Assessment of biomarker levels in synovial fluid may be one solution to the challenge. Sprifermin is a truncated form of fibroblast growth factor (FGF) 18 known to induce chondrocyte proliferation and type II collagen formation (1,2). Data from preclinical investigations show that cartilage formation happens in different phases after therapy with sprifermin, starting with a phase of cartilage degradation during the induction of proliferation of chondrocytes followed by a phase of cartilage formation/production of extracellular matrix.

Objectives: The aim was to investigate the effect of IA administrated sprifermin on cartilage turnover activity as compared to placebo in the injected joint by measurement of markers using longitudinal synovial fluid samples of patients participating in the FORWARD study.

Methods: Each included patient had baseline and at least one FU sample available. Synovial fluid (SF) from participants receiving injections at three consecutive weeks in six month intervals through to week (wk) 80 (fig.A) available from the phase II clinical trial evaluating the efficacy and safety of LOR. Subjects were selected for the investigations. Biochemical markers were measured in available SF samples of the placebo (containing saline IA; n=38) and the highest sprifermin dose group (100 mcg/IAx4, n=59). Samples were pretreated with ultrasound and centrifugation to decrease viscosity. Markers from the phase II clinical trial evaluating the efficacy and safety of LOR were selected for the investigations. Biochemical markers were measured using longitudinal synovial fluid samples of patients participating in the FORWARD study.

Results: Baseline mean (SD) levels of the markers in SF at BL were: PRO-C2, 214 (13.6) ng/mL, huARGS, 1117 (516) pM and FBN-C, 2556 (1959) ng/mL. PRO-C2 was initially decreased (from BL to wk 2) after injection with sprifermin; however, the level was increased at the beginning of each new injection cycle followed by a decrease after 80 weeks (Fig.B). Overall synovial PRO-C2 levels increased over time in therapy with sprifermin, while no change was observed for the placebo arm. huARGS showed a similar pattern as PRO-C2 – there was an overall increase in ARGS over time in the sprifermin group (fig.C). Interestingly ARGS continuously decreased over time in the placebo group. FBN-C is continuously increased after injection’s cycles, whereas no effect was seen in the placebo group (fig.D).

Conclusion: Confirmatory of the preclinical investigations a biphasic response on cartilage turnover after injection with sprifermin was observed. Biochemical indications of cartilage formation and chondrocyte proliferation was only modulated in the sprifermin group, and cartilage degradation (ARGS) was temporal induced and reduced by sprifermin and placebo injections, respectively.

References:

Figure 1. Adverse event summary for events occurring in at least 1% of the treated population (N=1208).

Figure 2. Joint-specific adverse event summary, subcategorized by affected joint, for events occurring in at least 1% of the treated population (N=1208).

Background: Joint pain is the most prevalent symptom for sufferers of osteoarthritis (OA). Pharmacological management of OA is restricted by limited efficacy and considerable toxicity, with growing fears about opioid use.

Objectives: To understand the current real-world prescribed drug treatment paradigm related to OA disease severity for patients in 5 EU countries; France, Germany, Italy, Spain and the UK.

Methods: Data were drawn from the Adelphi OA Disease Specific Programme (2017-18), a point-in-time study of physicians and their patients. Physicians classified their patients as currently having mild, moderate or severe disease severity, and provided details on currently prescribed OA therapy and physician satisfaction with therapy, rated from very satisfied to very dissatisfied. Patients were excluded from these analyses if they suffered from back and neck OA only, and shoulder OA that had not been diagnosed by X-ray. Comparisons among disease severity groups were made using analysis of variance and chi-squared tests.

Results: The study included 489 physicians (primary care physicians, rheumatologists, orthopaedists) reporting on 3596 of their OA patients: 24% mild (n=874), 53% moderate (n=1904), and 23% severe (n=818). Overall, 73% patients were prescribed at least one drug for their OA (65% of mild; 76% of moderate; 77% of severe patients [<0.001]). Paracetamol (34%) was the most commonly prescribed OA treatment. NSAIDs (31%) and opioids (27%) were also frequently prescribed treatments, and worsening severity was associated with an increase in opioid use (11% of mild; 26% of moderate, 47% of severe patients [<0.001]), but not NSAID (Table 1). The mean number of prescribed medications increased (0.9 for mild; 1.4 for moderate; 1.6 for severe patients [<0.001]) and physician satisfaction with treatment decreased (86% for mild; 70% for moderate; 41% for severe [<0.001]) with worsening OA disease severity.

Conclusion: Physicians reported decreasing satisfaction with treatment for their OA patients as disease severity increased, despite increasing use of opioids and numbers of classes of prescribed drugs.


DOI: 10.1136/annrheumdis-2020-eular.3855

Table 1. Prescribed treatment by physician-reported OA severity

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Mild (n=874)</th>
<th>Moderate (n=1904)</th>
<th>Severe (n=818)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paracetamol</td>
<td>186 (21.3)</td>
<td>663 (34.8)</td>
<td>313 (38.3)</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>267 (30.5)</td>
<td>605 (31.8)</td>
<td>237 (29.0)</td>
</tr>
<tr>
<td>Any opioid</td>
<td>93 (10.6)</td>
<td>501 (26.3)</td>
<td>386 (472)</td>
</tr>
<tr>
<td>Weak opioid</td>
<td>82 (9.4)</td>
<td>407 (21.4)</td>
<td>265 (31.2)</td>
</tr>
<tr>
<td>Strong opioid</td>
<td>11 (1.3)</td>
<td>99 (5.2)</td>
<td>146 (17.8)</td>
</tr>
<tr>
<td>Opioid + analgesic (combined)</td>
<td>6 (0.7)</td>
<td>15 (0.8)</td>
<td>7 (0.9)</td>
</tr>
<tr>
<td>Corticosteroid</td>
<td>31 (3.5)</td>
<td>150 (79.7)</td>
<td>92 (112)</td>
</tr>
<tr>
<td>Glycosaminoglycan</td>
<td>50 (5.7)</td>
<td>149 (78.2)</td>
<td>62 (76)</td>
</tr>
<tr>
<td>Viscosupplement</td>
<td>12 (1.4)</td>
<td>93 (4.9)</td>
<td>42 (5.1)</td>
</tr>
</tbody>
</table>

Number of currently prescribed drug classes, mean (SD) 0.9 (0.8) 1.4 (1.1) 1.6 (1.2)

Background: Both tramadol (narcotic-like drug) and nonsteroidal anti-inflammatory drugs (NSAIDs) are prescribed for pain relief among osteoarthritis (OA) patients. Evidence comparing risks of adverse events between tramadol and NSAIDs users is inconclusive.

Objectives: To examine the association of tramadol with all-cause mortality, cardiovascular disease, venous thromboembolism and hip fractures among patients with osteoarthritis. A population-based study.

Methods: Design: Sequential propensity score-matched cohort study. Sample: All patients with OA who received medical care from 2005 to 2014 in the entire province of British Columbia, Canada. Tramadol cohort: Initial prescription of tramadol (n=56325). Four comparator cohorts: the initiation of one of the following: naproxen (n=137386), diclofenac (n=17675), cyclooxygenase-2 [Cox-2] inhibitor (n=17039), or codeine (n=7813). Patients required to be prescribed neither tramadol nor its comparators during the year before the initial prescription date (i.e., index date). Outcomes: 1) all-cause mortality; first ever 2) CVD, 3) VTE, 4) HFx within the 1st year after the initiation of tramadol or its comparators. Follow-up: from index date until the event occurred, disenrollment, or the end of a 1-year follow-up period. Statistical analysis: We created baseline covariates (demographics, comorbidities, medications and health resource utilization) from the year prior to the index date. Calendar years from 2005 to 2014 were divided into 10 blocks; propensity scores were calculated using logistic regression within each block. We used 1:1 greedy matching method. We estimated hazard ratios (HRs) using Cox proportional hazard models.

Results: After propensity score matching, 112650 patients with OA were included (mean age of 68 years, 62.8% were females). During the 1-year follow-up, 296 deaths (215/1000 person-years) occurred in the tramadol cohort and 246 (173/1000 person-years) in the naproxen cohort (Table 1). All-cause mortality was higher for tramadol compared with all NSAIDs cohorts, but not with the codeine cohort (Table 1, Figure 1). Tramadol initiators have also a higher risk of CVD and VTE compared with the diclofenac and Cox-2 inhibitor initiators with HRs ranging from 1.2 to 1.7. Furthermore, tramadol was also associated with a higher risk of HFx compared with all NSAIDs cohorts (HRs ranging from 1.4 to 1.5). No significant difference was found between tramadol and codeine (Table 1).

Conclusion: OA patients initiating tramadol have an increased risk of mortality, CVD, VTE, and HFx within 1 year compared with NSAIDs, but no statistically significant difference in the risk was observed between tramadol and codeine.