OP0188

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

I. Simsek¹, C. Swearingen¹, S. Kennedy¹, J. Tambiah¹, C. Damatarca¹, Y. Yazici¹, N. Lane², M. Hochberg³. ¹Samumed, LLC, San Diego, United States of America; ²University of California, Davis, Davis, United States of America; ³University of Maryland, Baltimore, United States of America

Background: Concerns over the safety of available osteoarthritis (OA) treatments have led to revision of treatment guidelines and highlight the need for new therapies. Lorecevivint (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.^{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 (subjects who received any dose of LOR) 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 (138/360 [38.3%]). Incidence of SAEs was 20/848 (2.4%) in LOR-treated and 4/360 (1.1%) in control subjects. The most commonly reported AE in LOR-treated subjects was arthralgia (treated 7.6%, control 7.2%) and was the only AE reported at >5% in either group (Fig. 1). Target-knee arthralgia was the most common joint-specific AE (treated 6.5%, control 5.3%) (Fig. 2). No AEs in other joints exceeded an incidence of 2% in either group. In all categories, individual AEs were reported at similar rates between groups and no SAEs were deemed related to LOR by investigators.

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).

There were 16 bone health-related AEs in 9/848 (1.1%) LOR-treated and 3/360 (0.8%) control subjects. Of the bone health AEs, 2 were osteopenia/osteoporosis in 2 LOR-treated postmenopausal women and 14 were fractures in 10 subjects (7 LOR-treated, 3 control). 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:

- [1] Deshmukh V, et al. *Osteoarthritis Cartilage*. 2017.
- [2] Deshmukh V, et al. *Osteoarthritis Cartilage*. 2019.

Disclosure of Interests: Ismail Simsek Shareholder of: Samumed, LLC, Employee of: Samumed, LLC, Christopher Swearingen Shareholder of: Samumed, LLC, Employee of: Samumed, LLC, Sarah Kennedy Shareholder of: Samumed, LLC, Employee of: Samumed, LLC, Jeyanesh Tambiah Shareholder of: Samumed, LLC, Employee of: Samumed, LLC, Cristina Damatarca Shareholder of: Samumed, LLC, Employee of: Samumed, LLC, Yusuf Yazici Shareholder of: Samumed, LLC, Grant/research support from: Bristol-Myers Squibb, Celgene, and Genentech, Consultant of: Celgene and Sanofi, Employee of: Samumed, LLC, Nancy Lane Consultant of: Samumed, LLC, Marc Hochberg: None declared

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OP0189

ASSESSMENT OF CARTILAGE DEGRADATION AND PROTECTIVE MARKERS IN SYNOVIAL FLUID FROM OSTEOARTHRITIS PATIENTS BEFORE AND AFTER CYCLES OF INTRA-ARTICULAR INJECTIONS WITH SPRIFERMIN

A. C. Bay-Jensen¹, A. Manginelli², F. Moreau², Y. He¹, Y. Luo¹, J. R. Andersen³, A. R. Bihlet³, M. Karsdal¹, H. Gühring², C. Ladel². ¹Nordic Bioscience, Immunoscience, Herlev, Denmark; ²Merck KGaA, Darmstadt, Germany; ³Nordic Bioscience, Clinical development, Herlev, Denmark

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 intraarticularly delivered sprifermin [3] 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 measured were PRO-C2 (type II collagen formation), huARGS (aggrecan degradation), and FBN-C (fibronectin). Markers are technically validated for synovial fluid measurement. Data were individually normalized to baseline to investigate the median proportional change over time.

Results: Baseline mean (SD) levels of the markers in SF at BL were: PRO-C2, 21.4 (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 injection of sprifermin (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:

- [1] Gigout A, et al. "Sprifermin (rhFGF18) enables proliferation of chondrocytes producing a hyaline cartilage matrix." *Osteoarthritis Cartil*. 2017;25.

- [2] Reker D, et al. "Sprifermin (rhFGF18) modulates extracellular matrix turnover in cartilage explants ex vivo" J Transl Med. 2017;15.
- [3] Hochberg MC, et al. "Effect of Intra-Articular Sprifermin vs Placebo on Femorotibial Joint Cartilage Thickness in Patients With Osteoarthritis" JAMA. 2019; Oct 8;322(14).

Fig. Assessment of cartilage markers in synovial fluid at the 4 cycles. A) Study overview. B) type II collagen formation, PRO-C2. C) Aggrecan degradation, huARG5. D) Fibronectin degradation, FBN-C. Data are shown as median of available samples at each timepoint.

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OP0190 UNDERSTANDING CURRENT PRESCRIPTION DRUG TREATMENT PARADIGMS FOR PATIENTS WITH OSTEOARTHRITIS IN EUROPE

P. G. Conaghan¹, L. Abraham², P. Graham-Clarke³, L. Viktrup⁴, J. C. Cappelleri⁵, C. Beck², A. G. Bushmakina⁵, N. Hatchell⁶, E. Clayton⁶, J. Jackson⁶. ¹University of Leeds, Leeds, United Kingdom; ²Pfizer Ltd., Surrey, United Kingdom; ³Eli Lilly and Co, Sydney, Australia; ⁴Eli Lilly and Co., Indianapolis, United States of America; ⁵Pfizer, Groton, United States of America; ⁶Adelphi Real World, Bollington, United Kingdom

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 prescription 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.

Table 1. Prescribed treatment by physician-reported OA severity

	Mild (n=874)	Moderate (n=1904)	Severe (n=818)
Current class of medication prescribed for OA, n (%)			
Paracetamol	186 (21.3)	663 (34.8)	313 (38.3)
NSAIDs	267 (30.5)	605 (31.8)	237 (29.0)
Any opioid	93 (10.6)	501 (26.3)	386 (47.2)
Weak opioid	82 (9.4)	407 (21.4)	255 (31.2)
Strong opioid	11 (1.3)	99 (5.2)	146 (17.8)
Opioid + analgesic (combined)	6 (0.7)	15 (0.8)	7 (0.9)
Corticosteroid	31 (3.5)	150 (7.9)	92 (11.2)
Glycosaminoglycan	50 (5.7)	149 (7.8)	62 (7.6)
Viscosupplement	12 (1.4)	93 (4.9)	42 (5.1)
Number of currently prescribed drug classes, mean (SD)	0.9 (0.8)	1.4 (1.1)	1.6 (1.2)

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.

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OP0191 ASSOCIATION OF TRAMADOL WITH ALL-CAUSE MORTALITY, CARDIOVASCULAR DISEASE, VENOUS THROMBOEMBOLISM AND HIP FRACTURES AMONG PATIENTS WITH OSTEOARTHRITIS. A POPULATION-BASED STUDY

L. Li^{1,2}, N. Lu², H. Xie^{2,3}, J. Cibere^{1,2}, J. Kopec^{1,2}, J. Esdaile^{1,2}, J. A. Avina-Zubieta^{1,2}. ¹The University of British Columbia, Vancouver, Canada; ²Arthritis Research Canada, Richmond, Canada; ³Simon Fraser University, Burnaby, Canada

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 (CVD), venous thromboembolism (VTE) and hip fractures (Hfx) compared with NSAIDs and codeine in OA.

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 the following: naproxen (n=13798), diclofenac (n=17675), cyclooxygenase-2 [Cox-2] inhibitor (n= 17039), or codeine (a weak opioid) (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 (21.5/1000 person-years) occurred in the tramadol cohort and 246 (17.8/1000 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.