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POS0277

ANABOLIC EFFECT OF LNA043, A NOVEL DISEASE-MODIFYING OSTEOARTHRITIS DRUG CANDIDATE: RESULTS FROM AN IMAGING-BASED PROOF-OF-CONCEPT TRIAL IN PATIENTS WITH FOCAL ARTICULAR CARTILAGE LESIONS

S. Trattig¹, C. Scotti², D. Laurent³, V. Juras¹, S. Hacker³, B. Cole⁴, L. Pasa⁵, R. Lehovc⁶, P. Szomolanyi¹, E. Raithe⁷, F. Saxer², J. Praestgaard⁸, F. La Gamba⁹, J. L. Jiménez⁹, D. S. Ramos², R. Roubenoff², M. Schieker². ¹High Field MR Centre, Medical University of Vienna, Department of Biomedical Imaging and Image-Guided Therapy, Vienna, Austria; ²Novartis Institutes for Biomedical Research, Translational Medicine, Basel, Switzerland; ³Horizon Clinical Research, Grossmont Orthopedic Medical Group, San Diego, United States of America; ⁴Rush University Medical Center, Department of Orthopedics, Chicago, United States of America; ⁵Trauma Hospital, Trauma Department, Brno, Czech Republic; ⁶Dr. Pirek's clinic, Orthopaedic surgery, Mladá Boleslav, Czech Republic; ⁷Siemens Healthcare GmbH, SHS DI MR DL, Erlangen, Germany; ⁸Novartis Institutes for Biomedical Research, Early Development Biostatistics, East Hanover, United States of America; ⁹Novartis Institutes for Biomedical Research, Early Development Analytics, Basel, Switzerland

Background: LNA043 is a modified, recombinant version of the human angiopoietin-like 3 (ANGPTL3) protein acting directly on cartilage-resident cells to transmit its cartilage anabolic effect. A first-in-human study previously demonstrated the favourable safety profile and the modulation of several pathways involved in cartilage homeostasis and osteoarthritis (OA)¹. A previous proof-of-mechanism imaging study used high field (7 Tesla) magnetic resonance imaging (MRI) to show formation of hyaline-like tissue after a single injection of 20mg LNA043 (unpublished data).

Objectives: To evaluate non-invasively the chondro-regenerative capacity of multiple intra-articular (i.a.) injections of LNA043 in patients with articular cartilage lesions in the knee (NCT03275064).

Methods: This was a randomised, double-blind, placebo (PBO)-controlled, proof-of-concept study in patients with a partial thickness cartilage lesion. In total, 58 patients (43 [20mg LNA043]; 15 [PBO]), stratified by lesion type (condylar or patellar) were treated with 4 weekly i.a. injections. The primary endpoint was T2 relaxation time measurement as a marker of collagen fiber network, and cartilage lesion-volume was a secondary endpoint, both using 3-Tesla MRI. Assessments were performed at baseline, weeks (wks) 8, 16, 28 and 52 (the latter in 23/58 patients). While lesion-volume for the secondary endpoint was determined from manually segmented images, the cartilage volume of 21 sub-regions spanning the entire knee was also measured from 3D isotropic MR images employing an automated segmentation prototype software (MR Chondral Health 2.1 [MRCH], Siemens Healthcare)². An exploratory analysis evaluated the treatment effect for the additive volume of the 3 subregions in the weight-bearing area of the medial femur.

Results: No change in T2 relaxation time was detected between treatment and PBO groups. Manual segmentation showed continuous filling of the cartilage lesions up to wk 28 in LNA043-treated patients with femoral lesions ($p=0.08$, vs PBO) while no effect was detected for patients with patellar lesions. Given the limitations of measuring small, irregularly shaped lesions with manual image-analysis, the MRCH approach was used (Figure 1). In the medial femoral weight-bearing region, refilling was detected over time ($\Delta=123\text{mm}^3$ at wk 28, $N=37$, $p=0.05$). No overgrowth was detected in the lateral femoral condyles without cartilage damage. The overall safety profile was favourable; only mild/moderate local reactions were reported, including a higher incidence of joint swelling (9.3% vs 0%) and arthralgia (11.6% vs 6.7%) for LNA043 vs PBO resolving spontaneously or with paracetamol/NSAIDs. No anti-drug antibodies were detected.

Conclusion: Treatment with 4 weekly i.a. injections of 20mg LNA043 resulted in regeneration of damaged cartilage in patients with femoral articular cartilage lesions. Automated measurement of cartilage volume in the femoral index region was able to detect a relevant treatment effect and was found to be more sensitive than the manual segmentation method. No sign of cartilage overgrowth was observed in healthy femoral regions. A Phase 2b study in patients with mild to moderate knee OA is in preparation.

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Figure 1. Example of successful lesion filling from 3D reconstruction of cartilage MRI in an LNA043-treated patient with damage in the medial femur. Note the complex nature of the lesion which turns out to be deep in its center but shallower in the periphery. No scan is available for this patient at Week 52.

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POS0278

A MULTICENTER, OBSERVATIONAL, EXTENSION STUDY EVALUATING THE SAFETY, TOLERABILITY, AND EFFICACY OF A SINGLE LORECIVIVINT INJECTION IN KNEE OA SUBJECTS

I. Simsek¹, C. Swearingen², H. Ghandehari², S. Kennedy³, J. Tambiah³, Y. Yazici⁴, N. Skrepnik⁵. ¹Samumed, LLC, Clinical Development, San Diego, United States of America; ²Samumed, LLC, Biostatistics, San Diego, United States of America; ³Samumed, LLC, Medical Affairs, San Diego, United States of America; ⁴Samumed, LLC, Chief Medical Officer, San Diego, United States of America; ⁵Tucson Orthopaedic Institute, Research, Tucson, United States of America

Background: Lorecivint (LOR), a novel intra-articular (IA) CLK2/DYRK1A inhibitor that modulates the Wnt pathway, is in development as a knee osteoarthritis (OA) treatment.

Objectives: Subjects from two consecutive Phase 2 trials were followed up in a 5-year, pooled, observational study that evaluated the safety and exploratory efficacy of a single LOR injection that was previously administered into the target knee joint of subjects with moderate to severe knee OA. The study was terminated in its third year, as relevant long-term safety information became limited in the absence of repeated LOR administration. The primary objective evaluated the incidence of serious adverse events (SAEs). Safety data for all doses and a post hoc efficacy analysis for the pivotal dose (0.07 mg LOR) are reported.

Methods: This was a Phase 3, multicenter, observational, extension study of completer subjects (OA-05; NCT02951026) from two Phase 2 trials of LOR: a 12-month Phase 2a trial (OA-02; NCT02536833)¹ and a 6-month Phase 2b trial (OA-04; NCT03122860)². Subjects received a single LOR or control (placebo or vehicle) injection at their parent-study baseline visit (OA-02 or OA-04 Visit 0 in this analysis). Pooled data from clinic visits at 6, 12, 24, and 36 months contributed to the extension-study (OA-05) analysis. SAEs, knee-related adverse events (AEs), and AEs of newly diagnosed conditions requiring treatment were collected as safety outcomes. Efficacy was assessed by target knee WOMAC Pain and Function subscores and radiographic medial joint space width (mJSW). A post hoc analysis was performed for 0.07 mg LOR versus control to assess responses in a subject subgroup (unilateral symptoms, no widespread pain, 18-month post-injection radiograph at study termination). Baseline-adjusted ANCOVA was performed using data from both the current and parent studies at 0, 3, 6, 12, and 18 months.

Results: Of 703 subjects, 119 (17%) subjects discontinued prior to study termination. Subjects had a mean age of 60.7 years and mean BMI of 29.1 kg/m², and 61% were female. The majority of subjects had KL 3 (61.2%) OA. The safety analysis set included 495 LOR-treated subjects and 208 control subjects.

There were 169 AEs reported by 110 [15.6%] subjects. Four AEs were considered to be related to study drug and were reported by 3 (0.6%) subjects across LOR groups; no subjects withdrew from the study due to a treatment-related AE. The most common AEs were osteoarthritis (28 [4.0%] subjects) and arthralgia (25 [3.6%] subjects); incidence was similar between LOR and control groups. During the study, 68 SAEs were reported by 38 (5.4%) subjects, and no SAEs were considered to be related to treatment by investigator. One death occurred in the control group. Post hoc efficacy analyses demonstrated that subjects in the 0.07 mg LOR group (n=59) showed greater improvements from baseline in both WOMAC Pain and Function at 6 and 12 months versus subjects in the control group (n=70) (Figure 1; Day 0):

6 months:Pain: -8.16, 95% CI [-15.60, -0.71], $P=0.032$

Function: -9.47, 95% CI [-17.09, -1.84], $P=0.015$

12 months:Pain: -8.51, 95% CI [-15.17, -1.85], $P=0.013$

Function: -9.62, 95% CI [-16.83, -2.42], $P=0.009$

No mJSW progression was observed in any group over 18 months.

Limitations to this analysis include 1) subjects from LOR and control groups were "completers," therefore, more likely to be responders, and 2) subjects could have been on any medication or treatment in the extension study.

Conclusion: From these data, LOR appeared to be safe and well tolerated. A post hoc-analyzed subset of completer subjects treated with a single 0.07 mg LOR injection reported durable symptom improvements in WOMAC Pain and Function for up to at least 12 months versus control subjects.

*Pooled data from the OA-02, OA-04, and extension study; includes all available data from 3, 6, 12, and 18 months after injection. * $P<0.05$, ** $P<0.01$

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POS0279

WEARABLE TRANSCUTANEOUS ELECTRICAL NERVE STIMULATION DEMONSTRATED BETTER EFFICACY AND SAFETY THAN WEAK OPIOIDS IN THE TREATMENT OF MODERATE TO SEVERE, CHRONIC NOCICEPTIVE PAIN IN KNEE OSTEOARTHRITIS. A RANDOMIZED, CONTROLLED, NON-INFERIORITY TRIAL

E. Maheu¹, S. Soriot-Thomas², E. Noel³, E. Lespessailles⁴, B. Cortet⁵ on behalf of arthroTENS. ¹Hospital Saint-Antoine Ap-Hp, Rheumatology, Paris, France; ²Chu D'amiens-Picardie Site Sud, Clinical Research Center, Amiens, France; ³Santy Orthopedic Center, Rheumatology, Lyon, France; ⁴Hospital Center Régional D'orléans Hospital La Source, Rheumatology, Orléans, France; ⁵Chu lille, Rheumatology, Lille, France

Background: In knee osteoarthritis (KOA) recommendations, the first pharmacological analgesic line is paracetamol. However, its low efficacy, frequently leads to the use of weak opioids (WO) despite their poor tolerance, especially in elderly patients. **Objectives:** The primary objective was to compare analgesic efficacy and safety of a new wearable transcutaneous electrical nerve stimulation (W-TENS) to those of WO in the treatment of moderate to severe, nociceptive, chronic pain in KOA patients.

Methods: ArthroTENS study was a phase 3, non-inferiority, multicentric, prospective, randomized, single-blinded for primary efficacy outcome, controlled, in 2-parallel groups, clinical study comparing W-TENS versus WO on two periods: a 3-month controlled period and an additional, optional, non-controlled, 3-month follow-up for patients in W-TENS group.

Eligible participants were KOA patients, ≥ 55 years old, at Kellgren-Lawrence radiographic grade ≥ 2 , with moderate to severe nociceptive chronic (≥ 3 months) mean 8-day pain ≥ 4 on a 11-point numerical rating scale, and in treatment failure with non-opioid analgesics, including NSAIDs. Patients with neuropathic pain were excluded.

Co-primary endpoints were, for efficacy, mean pain intensity (PI), assessed at M3 and, for safety, the number of adverse events (AE) during the 3-month follow-up period.

In W-TENS group, an advanced, mobile app enabled, wearable TENS was used. High (100 Hz) and low (2 Hz) frequency stimulations were delivered via electrodes with standardized positioning (Figure 1).

Figure 1. Electrode's positioning

In WO group, investigators chose, for each patient, the best suitable WO and its daily dose, and could switch to another WO, and/or adapt its daily dose if necessary.

A non-inferiority analysis was performed on the primary efficacy endpoint using a pre-defined non-inferiority margin (0.825 point) on PI, below the minimal clinically significant improvement.

Results: Demographic and baseline characteristics were balanced across both groups.

110 patients (55/group) were randomized and 48/55 (87.3%) and 44/55 (80.0%) patients completed the 3-month follow-up in W-TENS and WO groups, respectively. WO's prescriptions were balanced between codeine, opium-powder, tramadol and WO-paracetamol combinations.

Non-inferiority of W-TENS was demonstrated in the PP and ITT populations (Table 1). Since the 95% confidence interval (CI) of the between-treatments difference was below 0 in the ITT population, a planned superiority analysis was performed showing that W-TENS was significantly superior to WO at M3 ($p=0.0124$) on PI. Additionally, the number of AEs was significantly lower ($p<0.001$) in W-TENS (n=7) group than in WO (n=36) group. In WO group, AEs were systemic AEs usually reported with WO while AEs in W-TENS group were local, related to the technique used, such as local cutaneous reaction (erythema).

Table 1. Non-inferiority analyses on pain intensity at M3. ITT and PP populations. Least squares means for each study group and study group difference estimate and corresponding 95% CI

Group Population	Within-group change		Between-group difference	
	W-TENS	WO	W-TENS - WO	
ITT Population (n)	55	55		
Non inferiority				
Mean (SD)	3.83 (0.28)	4.74 (0.28)	-0.92 (0.40)	Non inferiority†
95% CI	[3.27, 4.40]	[4.18, 5.30]	[-1.71, -0.12]	demonstrated
PP Population (n)	52	47		
Mean (SD)	3.87 (0.30)	4.66 (0.32)	-0.79 (0.44)	Non inferiority†
95% CI	[3.28, 4.46]	[4.03, 5.28]	[-1.65, 0.08]	demonstrated

† Noninferiority was demonstrated when 95% CI < 0.825