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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. Trattnig1, C. Scotti2, D. Laurent2, V. Juras3, S. Hacker2, B. Cole2, L. Pasa2, R. Lehovec4, P. Szomolanyi1, E. Raithel4, F. Saxer2, J. Praestgaard2, F. La Gamba4, J. L. Jimenez4, D. S. Ramos6, 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; 3Hornzonal Clinical Research, Grossmont Orthopaedic 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. Pirk'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 protein 3 (ANGPTL3) that is secreted via cartilage matrix vesicles. A previous proof-of-mechanism imaging study using high field (7 Tesla) magnetic resonance imaging (MRI) to show formation of hyaline-like tissue after a single injection of 20 mg LNA043 (unpublished data).

Objectives: To evaluate the efficacy and safety of LNA043 in a Phase 2a clinical study in patients with articular cartilage lesions.

Methods: This was a randomised, double-blind, placebo (PBO)-controlled, proof-of-concept study in patients with a partialthickness cartilage lesion. In total, 58 patients (42 [20 mg LNA043]; 15 [PBO]) were treated with LNA043 or PBO, respectively, for 24 weeks. The primary endpoint was the change in the weight-bearing region, measured as the difference between the baseline and the 12-month visit. The safety analysis set included 49 LNA043-treated subjects and 20 control subjects. Assessments were performed at baseline, week 24, and 52 weeks after injection. Leukocyte counts were performed using data from both the current and parent studies at 0, 3, 6, 12, and 18 months.

Results: No change in the treatment area was detected during treatment and PBO groups. Manual segmentation showed continuous filling of the lesion with at least 28 LNA043-treated patients with focal lesions (p = 0.08, vs PBO) while no effect was detected for patients with peripheral 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, the lesion volume was detected over time (∆=123 mm³) at week 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 20 mg LNA043 resulted in regeneration of damaged cartilage in patients with focal articular cartilage lesions. Automated measurement of cartilage volume in the focal 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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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. Ghandehari3, S. Kennedy4, J. Tambiah5, Y. Yazici6, N. Skrepnik2, Samumed, LLC, Clinical Development, San Diego, United States of America; 3Samumed, LLC, Biostatistics, San Diego, United States of America; 4Samumed, LLC, Medical Affairs, San Diego, United States of America; 5Samumed, LLC, Chief Medical Officer, San Diego, United States of America; 6Tucson Orthopaedic Institute, Research, Tucson, United States of America

Background: Lorecivivint (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 completor subjects (OA-05; NCT02951026) from two Phase 2 trials of LOR: a 12-month Phase 2a trial (OA-02; NCT02536833) and a 6-month Phase 2b trial (OA-04; NCT03122860). 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 206 control subjects.

Figure 1. Example of successful lesion filling from 3D reconstruction of cartilage MRI in an LNA043-treated patient with damage in the tibial plateau. No new cartilage formation was found 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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