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POS0277

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


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Background: LNA043 is a modified, recombinant version of the human angiopoi- etin-like 3 (ANGPTL3) protein acting directly on cartilage-resident cells to trans- mit its cartilage anabolic effect. A first-in-human study previously demonstrated the limitations of measuring small, irregularly shaped lesions with manual assessment effect for the additive volume of the 3 subregions in the weight-bearing area. 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magnetic resonance imaging (MRI) to show formation of hyaline-like tissue after a single injection of 20 mg LNA043 (unpublished data).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 carti-ilage 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 [20 mg LNA043]; 15 [PBO]), stratified by lesion type (con- dylar 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). 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 fem- oral weight-bearing region, refilling was detected over time (Δ=123 mm²) at wk 28, N= 37, p= 0.05. No overgrowth was detected in the lateral femoral con- dyles 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 8.7%) 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 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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[1] Scotti et al. ACR Convergence 2020; Abstract #1483


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POS0278

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

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Background: Lorcivint (LOR), a novel intra-articular (IA) CLK2/DYRK1A inhibitor that modulates the Wnt pathway, is in development as a knee osteoar- thritis (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 termi- nated 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) 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 contrib- uted to the extension-study (OA-05). 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 (mJWW). 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 termi- nation. 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.
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 Kelgren-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).

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

<table>
<thead>
<tr>
<th>Group Population</th>
<th>Within-group change</th>
<th>Between-group difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>W-TENS</td>
<td>WO</td>
<td>W-TENS - WO</td>
</tr>
<tr>
<td>ITT Population (n)</td>
<td>55</td>
<td>55</td>
</tr>
<tr>
<td>Non inferiority Mean (SD)</td>
<td>3.83 (0.28)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>95% CI</td>
<td>[3.27, 4.40]</td>
<td>[4.18, 5.30]</td>
</tr>
<tr>
<td>PP Population (n)</td>
<td>52</td>
<td>47</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>3.87 (0.30)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>95% CI</td>
<td>[3.28, 4.46]</td>
<td>[4.00, 5.32]</td>
</tr>
</tbody>
</table>

‡ Noninferiority was demonstrated when 95% CI < 0.825