FRI0538

STRUCTURAL EFFECTS OF INTRA-ARTICULAR SPRIFERMIN IN SYMPTOMATIC RADIOGRAPHIC KNEE OSTEOARTHRITIS: A POST-HOC ANALYSIS OF CARTILAGE AND NON-CARTILAGINOUS TISSUE ALTERATIONS OF THE 2-YEAR DATA FROM A 5-YEAR RANDOMISED, PLACEBO-CONTROLLED, PHASE II STUDY

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Background: Sprifermin, a recombinant human fibroblast growth factor 18, is currently being investigated as a potential disease-modifying osteoarthritis (OA) drug. Recently, a dose-dependent increase in femorotibial cartilage thickness, as well as medial and lateral compartment cartilage, over two years was reported¹.

Objectives: The aim of this post-hoc analysis is to evaluate potential effects of sprifermin on additional structure endpoints, based on semi-quantitative MRI assessment over 24 months.

Methods: Patients aged 40–85 years with symptomatic radiographic knee OA, KLG 2 or 3, and medial mJSW ≥ 2.5 mm in the target knee were randomised (1:1:1:1:1) to receive double-blinded placebo or sprifermin (30 µg or 100 µg), administered as 3 weekly intra-articular injections in cycles every 6 or 12 months. 1.5T or 3T MRIs were acquired at baseline, 6, 12, 18 and 24 month follow-up visits using a standard protocol (ClinicalTrials.gov identifier: NCT01033994).

MRIs were read using the Whole-Organ Magnetic Resonance Imaging Score (WORMS) system (time points of baseline, 12 and 24 months) by three trained musculoskeletal radiologists. Analyses of all sprifermin and placebo arms included multiple MRI-defined osteoarthritis features and multi-dimensional assessments: (a) delta-subregional approach (the difference in the *number of subregions* with worsening as compared to improvement) and (b) delta-sum approach (absolute *scores of all subregions*). Analyses were performed on a whole knee level and separately for medial, lateral, and patellofemoral compartments. To test for potential dose-response effects, Jonckheere-Terpstra (asymptotic) test was used. P-values were not adjusted for multiple testing.

Results: 549 patients were included. Dose-dependent treatment effect on cartilage morphology (i.e., less cartilage damage) was observed for the entire knee from baseline to 24 months using both delta sum and delta subregion approaches (table 1). For bone marrow lesions (BMLs), a dose-dependent treatment effect (improvement of BMLs) was observed from baseline to 24 months for the patellofemoral joint using both delta sum and delta subregion approaches but not the other compartments (table 2). No significant effects were seen for baseline to 24 month changes in Hoffa-synovitis, effusion-synovitis, menisci, or osteophytes.

Abstract FRI0538 – Table 1. Cartilage morphology change from baseline to 24 months, ITT analysis set

Compartment	Analysis approach	Placebo (N=108) Mean (95% CI)	Sprifermin - 30 mcg x 2 (N=110) Mean (95% CI)	Sprifermin - 30 mcg x 4 (N=111) Mean (95% CI)	Sprifermin - 100 mcg x 2 (N=110) Mean (95% CI)	Sprifermin - 100 mcg x 4 (N=110) Mean (95% CI)	P-value ¹
Entire Knee	Delta Sum	1.61 (0.89, 2.34)	1.78 (1.25, 2.32)	1.20 (0.66, 1.74)	1.31 (0.82, 1.79)	0.98 (0.57, 1.38)	0.0284
Entire Knee	Delta Subregion	0.79 (0.49, 1.09)	0.90 (0.65, 1.15)	0.60 (0.37, 0.83)	0.59 (0.39, 0.79)	0.55 (0.35, 0.76)	0.0282
LFTJ	Delta Sum	0.29 (0.08, 0.50)	0.57 (0.25, 0.89)	0.45 (0.10, 0.81)	0.33 (0.12, 0.54)	0.22 (0.06, 0.38)	0.1026
LFTJ	Delta Subregion	0.19 (0.08, 0.29)	0.29 (0.15, 0.43)	0.24 (0.10, 0.38)	0.12 (0.01, 0.22)	0.13 (0.04, 0.22)	0.0777
MFTJ	Delta Sum	0.86 (0.32, 1.41)	0.77 (0.38, 1.16)	0.52 (0.26, 0.79)	0.81 (0.41, 1.21)	0.48 (0.23, 0.72)	0.2274
MFTJ	Delta Subregion	0.40 (0.20, 0.59)	0.38 (0.21, 0.55)	0.25 (0.13, 0.38)	0.39 (0.23, 0.56)	0.22 (0.11, 0.34)	0.2207
PFJ	Delta Sum	0.46 (0.21, 0.70)	0.43 (0.20, 0.67)	0.22 (0.00, 0.44)	0.15 (0.02, 0.28)	0.27 (0.04, 0.51)	0.0873
PFJ	Delta Subregion	0.21 (0.09, 0.33)	0.23 (0.10, 0.36)	0.10 (0.01, 0.20)	0.08 (-0.01, 0.16)	0.20 (0.08, 0.32)	0.1796

Abstract FRI0538 – Table 2. Bone marrow lesion change from baseline to 24 months, ITT analysis set

Compartment	Analysis approach	Placebo (N=108) Mean (95% CI)	Sprifermin - 30 mcg x 2 (N=110) Mean (95% CI)	Sprifermin - 30 mcg x 4 (N=111) Mean (95% CI)	Sprifermin - 100 mcg x 2 (N=110) Mean (95% CI)	Sprifermin - 100 mcg x 4 (N=110) Mean (95% CI)	P-value ¹
Entire Knee	Delta Sum	0.09 (-0.36, 0.53)	0.39 (0.01, 0.78)	0.00 (-0.39, 0.39)	0.10 (-0.34, 0.54)	-0.03 (-0.40, 0.33)	0.1087
Entire Knee	Delta Subregion	0.06 (-0.25, 0.37)	0.21 (-0.07, 0.48)	-0.05 (-0.34, 0.25)	0.07 (-0.26, 0.39)	-0.13 (-0.41, 0.15)	0.1085
LFTJ	Delta Sum	0.13 (0.00, 0.27)	0.28 (0.08, 0.49)	-0.01 (-0.23, 0.21)	0.20 (0.04, 0.37)	0.17 (-0.04, 0.39)	0.2784
LFTJ	Delta Subregion	0.13 (0.02, 0.25)	0.16 (0.04, 0.28)	-0.03 (-0.17, 0.11)	0.13 (0.03, 0.23)	0.07 (-0.05, 0.19)	0.2585
MFTJ	Delta Sum	0.05 (-0.28, 0.38)	0.14 (-0.10, 0.38)	0.12 (-0.15, 0.38)	0.13 (-0.17, 0.43)	0.06 (-0.12, 0.24)	0.1617
MFTJ	Delta Subregion	-0.02 (-0.23, 0.18)	0.13 (-0.06, 0.31)	0.08 (-0.12, 0.28)	0.15 (-0.05, 0.35)	0.08 (-0.07, 0.23)	0.1341
PFJ	Delta Sum	-0.10 (-0.30, 0.10)	-0.06 (-0.26, 0.13)	-0.13 (-0.34, 0.08)	-0.24 (-0.45, -0.03)	-0.26 (-0.50, -0.02)	0.0171
PFJ	Delta Subregion	-0.05 (-0.22, 0.12)	-0.11 (-0.28, 0.07)	-0.11 (-0.30, 0.07)	-0.22 (-0.40, -0.04)	-0.28 (-0.50, -0.09)	0.0185

¹p-values using Jonckheere-Terpstra (asymptotic) test

Conclusions: This post-hoc analysis indicates that sprifermin has a positive effect on cartilage morphology, in addition to the previously reported effect on cartilage thickness. Sprifermin was also associated with BML improvement in the patello-femoral joint. There were no significant effects associated with sprifermin on other joint tissues assessed, and no safety concerns raised.

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A SAFETY, TOLERABILITY, PHARMACOKINETICS (PK) AND PHARMACODYNAMICS (PD) STUDY WITH INCREASING ORAL DOSES OF GLPG1972 ADMINISTERED DAILY FOR 29 DAYS SHOWS A STRONG BIOMARKER EFFECT IN PATIENTS WITH KNEE AND/OR HIP OA

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Background: Osteoarthritis (OA) is characterised by structural changes of the joint, of which degradation of articular cartilage is one of the major signs¹. The main proteoglycan component of the extracellular matrix of articular cartilage is aggrecan. GLPG1972 as a potent and selective inhibitor of ADAMTS-5, a key aggrecan-cleaving enzyme involved in cartilage degradation, is being developed as a potential disease-modifying OA drug (DMOAD). Aggrecan cleavage by ADAMTS-5 results in release of N-terminal ARGS neo-epitope fragments of which serum levels significantly decreased in healthy subjects treated with GLPG1972 during 14 days in a previous study².

Objectives: To assess safety, tolerability, PK and PD (serum ARGS-aggrecan levels) during and following administration of GLPG1972 in patients with knee and/or hip OA.

Methods: This was a single centre, randomised, double-blind, placebo-controlled, age and gender stratified, ascending dose Phase Ib study, with three semi-sequential cohorts of 10 patients each, randomised to active drug or placebo in a 4:1 ratio. Doses tested were once daily 100, 200 and 300 mg. Treatment duration was 29 days. Patients had follow-up visits 14 and 21 days after last dosing for additional PD assessments. Methods for PD have been described previously³.

Results: Thirty patients were included. Of these, 24 patients (M/F rate 8/16, 14 aged 50–64 and 10 aged 65–75) received active medication.

All adverse events (AE) were mild and transient. No serious AEs were reported during the study; one female patient in the 300 mg group was discontinued after 15 days of treatment due to drug-related elevated transaminase values which returned to normal 9 days later while her bilirubin levels remained normal. There were no overall trends in lab abnormalities over time or significant changes in vital signs, ECG and Holter parameters.

Steady state in plasma exposure was reached after 3 days of dosing. Exposure increased dose-proportionally. Mean serum ARGS levels (SEM) decreased steadily over time in all patients receiving GLPG1972: –40% (2.9), –46% (4.5) and –53% (2.8) at day 15 compared to baseline in the 100, 200 and 300 mg group respectively. These levels remained stable until last dose on day 29, then consistently returned to pre-dose levels for all groups 14 and 21 days after last dose. Placebo group levels remained unchanged.

Conclusions: When administered daily for 29 days in patients with knee and/or hip OA, GLPG1972 at oral doses of 100, 200 and 300 mg q.d. was generally well tolerated and safe. Serum ARGS levels, as a marker for target engagement and potential proxy of cartilage degradation, showed a dose-dependent decrease over time up to 53% below baseline in the 300 mg group. These PK-PD findings are consistent with what we observed in a previous study in healthy subjects² and reinforce the rationale for developing GLPG1972 as a DMOAD.

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