ABSTRACT NUMBER: 1356

Increasing Oral Doses of GLPG1972 Administered Daily for 29 Days Show a Strong Target Engagement in Patients with Knee and/or Hip OA

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SESSION INFORMATION

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Session Type: ACR Poster Session B

Session Title: Osteoarthritis – Clinical Poster II

Session Time: 9:00AM-11:00AM

Background/Purpose:

Osteoarthritis (OA) is characterized by structural changes of the joint, of which degradation of articular cartilage is one of the major signs[1]. 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 neoepitope fragments of which serum levels significantly decreased in healthy subjects treated with GLPG1972 during 14 days in a previous study[2].

The objective was to assess safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD, i.e. serum ARGS-aggrecan levels) during and following administration of GLPG1972 in patients with knee and/or hip OA.

Methods: this was a single center, randomized, double-blind, placebo-controlled, age and gender stratified, ascending dose Phase Ib study, with three semi-sequential cohorts of 10 patients each, randomized to GLPG1972 or placebo in a 4:1 ratio. Doses tested were once daily 100, 200 or 300 mg given orally. 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 previously[3].

Results:

thirty patients were included. Of these, 24 patients (M/F rate 8/16, 14 aged 50-64 and 10 aged 65-75) received GLPG1972. 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 after treatment discontinuation 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 3-5 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.

Conclusion:

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 decrease over time up to 53% below baseline in the 300 mg group. These findings are consistent with what we observed in a previous study in healthy subjects[2] and reinforce the rationale for developing GLPG1972 as a DMOAD.

References:

1. Hunter, D. J., et al. *Curr. Opin. Rheumatol.* 2009, 21, 110–117
2. van der Aar E, et al. *Arthritis Rheumatol.* 2017; 69 (suppl 10)
3. Larsson et al. *Osteoarthritis Cartilage* 2014, 22(2):242-9

Disclosure: H. Deckx, Galapagos N.V., 1, 3; **S. Hatch**, Galapagos NV, 3, 5; **M. Robberechts**, Galapagos NV, 3; **S. Dupont**, Galapagos NV, 3; **J. Desrivot**, Galapagos NV, 3; **H. Coleman**, None; **S. Larsson**, None; **A. Struglics**, None; **E. van der Aar**, Galapagos N.V., 1, 3; **A. Fieuw**, Gelapagos NV, 3.
