The Objectives (fig 1).

- No change in serum ARGS levels over time in placebo patients
- Steady state after 3-5 days, no significant accumulation of GLPG1972 (Rt = 1-4)
- Decrease-proportional increase in plasma exposure

Key Message
- Increasing oral doses of GLPG1972 administered daily for 29 days showed a strong target engagement in patients
- GLPG1972 was generally safe and well tolerated

Methods
- Three semi-sequential cohorts of 10 patients each, randomized to GLPG1972 or placebo in a 4:1 ratio.
- GLPG1972 100, 200 or 300 mg or matching placebo oral tablets taken in fed state q.d. up to day 29
- GLPG1972 intensive PK profiles determined on day 1 and day 15, additional pre-dose levels between day 3 and day 29 (PK sampling scheme see fig. 1)
- PD: serum ARGs levels determined pre-dose at several time points between day 1 and day 29, follow-up at days 43 and 50 (fig. 2), methods for ARGS analysis have been described previously.

Results – Safety
- Thirty patients aged 50-75 included. Of these, 24 patients (M/F ratio 8/16) received GLPG1972.
- All adverse events (AE) were mild and transient. No serious AEs, no overall trends in lab abnormalities over time or significant changes in vital signs, 12-lead ECG and Holter parameters were reported during the study.
- One female patient (300 mg group) was discontinued after 15 days of treatment due to a drug-related, reversible ALT increase > 3x ULN (bilirubin remained normal).

Design - Objectives
- A randomized, double-blind, placebo-controlled, ascending dose Phase Ib study to assess safety, PK and PD (serum ARGS-aggrecan levels) in hip and/or knee OA patients treated with GLPG1972 given once daily (q.d.) for 29 days

Figure 1: GLPG1972 plasma profile from Day 1 up to Day 29

Figure 2: Mean (SEM) % reduction over time in Serum ARGS Levels

Results – Pharmacokinetics (PK)
- Rapid absorption (tmax = 4h) and elimination half life of approximately 10 h
- Steady state after 3-5 days, no significant accumulation of GLPG1972 (Rt = 1-4)
- Dose-proportional increases in plasma exposure

Results – Pharmacodynamics (PD)
- Serum ARGS levels decreased significantly in all patients in each GLPG1972 dose group until day 15 (up to 53% in 300 mg q.d. group)
- Decreases remained stable until last dose on day 29, then ARGS levels returned to baseline 14 days after treatment discontinuation (dotted lines)
- No change in serum ARGS levels over time in placebo patients

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

References
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