A SAFETY, TOLERABILITY, PHARMACOKINETICS AND PHARMACODYNAMICS 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 (NCT03311009)

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Key Message

- **Increasing oral doses of GLPG1972 administered daily for 29 days showed a strong target engagement in patients with knee and/or hip OA**
- **GLPG1972 was generally safe and well tolerated**

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**

Introduction

- 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**.
- **ADAMTS-5, A D**isintegrin **A**nd **M**etalloproteïnase with **T**hrombo**S**pondin-motif-**5,** is a **key aggrecan-cleaving enzyme** involved in cartilage degradation.
- Aggrecan cleavage by ADAMTS-5 results in release of N-terminal **ARGS-aggrecan** neo-epitope fragments.
- **GLPG1972** is a **potent and selective** inhibitor of **ADAMTS-5**, being developed as a potential **disease-modifying OA drug (DMOAD).**
- ARGS-aggrecan serum levels significantly decreased in healthy subjects treated with GLPG1972 during 14 days in a previous study[2].

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[3].

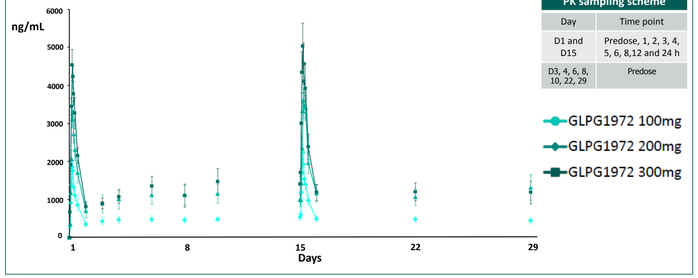
Results – Safety

- Thirty patients aged 50-75 included. Of these, 24 patients (M/F rate 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).

Results – Pharmacokinetics (PK)

- Rapid absorption (t_{max} = 4h) and elimination half life of approximately 10 h
- Steady state after 3-5 days, no significant accumulation of GLPG1972 (R_{ac} = 1.4)
- Dose-proportional increase in plasma exposure

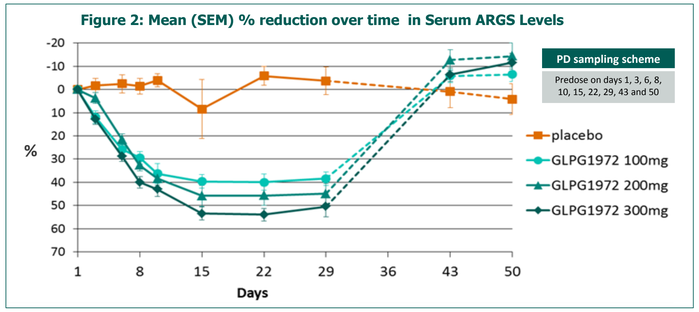
Figure 1: GLPG1972 plasma profile from Day 1 up to Day 29



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

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



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[2] and reinforce the rationale for developing GLPG1972 as a DMOAD.**

References

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