ADAMTS-5 inhibitor GLPG1972, a potential new treatment in osteoarthritis, shows favorable safety, pharmacokinetics and pharmacodynamics in healthy subjects

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Introduction

ADAMTS-5
- a disintegrin and metalloproteinase with thrombospondin motifs-5 (ADAMTS-5) is a key aggrecanase in humans1,2. Increased aggrecanase activity is a well-known trigger factor for osteoarthritis (OA), initiating loss of cartilage aggrecan that precedes more severe cartilage degradation3. Inhibition of ADAMTS-5 is a relevant approach for the development of disease-modifying OA drugs.

GLPG1972
- potent and selective inhibitor of ADAMTS-54.
- strong chondroprotective effects in mouse and human cartilage explants5.
- effective in two preclinical rodent models for OA: mouse destabilization of the medial meniscus (DDM) model6.
- rat meniscectomy (MNX) model7.
- most advanced ADAMTS-5 inhibitor evaluated in man8.

Methods

- Randomized, double-blind, placebo-controlled, single center, dose ranging study (NCT02612246).
- Healthy male subjects (18-50 years)
- In each dose group, 6 subjects received GLPG1972 and 2 received placebo.
- Single ascending dose part (SAD)
  - 7 dose levels: 60 to 2100 mg, oral solution, fasting conditions.
- Multiple ascending dose part (MAD)
  - 3 doses: 300, 600 and 1050 mg q.d., oral solution, fed conditions.
  - 14 days dosing.
  - Safety parameters: adverse events, ECG, Holter monitoring, vital signs, laboratory biochemistry/hematology and urinalysis.
- Pharmacokinetics: GLPG1972 plasma and urine concentrations determined by LC-MS/MS and analyzed by non-compartmental analysis using Phoenix WinNonlin.
- Pharmacodynamics: aggrecan ARGS neoepitope levels in plasma were determined by an enzyme-linked immunosorbent assay.

Results – Pharmacokinetics

- Rapid absorption and elimination half life of approximately 10 h.
- Dose-proportional increase in exposure between 60 and 2100 mg.
- From dose of 150 mg onwards, plasma concentrations are above the Caverage (Cav) required to observe efficacy in the rat MNX model (385 ng/mL) during approximately 24h.

Results – Pharmacodynamics

- No reduction in plasma ARGS was observed after a single dose.
- GLPG1972 reduced plasma ARGS levels progressively over time, with no significant difference between the 3 tested doses.
- Maximal reduction was about 60% at day 14, with no plateau being reached suggesting it may take longer to obtain the maximum effect.

Results – Safety

- Administration of single (up to 2100 mg) and multiple (up to 1050 mg q.d. for 14 days) ascending oral doses of GLPG1972 in healthy male subjects was well tolerated.
- No deaths, other serious adverse event, or treatment-emergent adverse events (TEAEs) leading to study drug discontinuation were reported. All reported TEAEs were rated mild in intensity, were not dose-related and were resolved at the end of the study.
- No clinically relevant abnormalities in clinical laboratory safety tests, 12-lead ECGs, vital signs, Holter monitoring or physical examination were reported.

Conclusions

- Single ascending oral doses of GLPG1972 up to 2100 mg and multiple ascending doses up to 1050 mg q.d. administered for 14 days were generally safe and well tolerated in healthy male subjects.
- A favorable pharmacokinetic and pharmacodynamic profile was observed, clearly demonstrating the ability to reduce aggrecan ARGS neoepitope levels in plasma via inhibition of ADAMTS-5.
- A global phase 2 study is planned to start in the course of 2018.

Disclosures

LSL received consultancy fees from Galapagos, GSK, and Johnson and Johnson. EvdA, DA, PV and SD are/were employees of Galapagos and receive(d) warrants (i.e. rights to subscribe to new shares at a predetermined price) from the company.

Acknowledgments

We thank the medical doctors involved in the study, Istvan Udvaros, Lien Gheyle and Josue Mpouou Kungom, and the clinical study centre (SGS LS, Clinical Pharmacology Unit Antwerp, Belgium) for their valuable support.

Results – Pharmacokinetics

- Steady state reached after 2 dosing days, with minimal accumulation.
- Dose-proportional increase in exposure over the dose range tested.
- Urinary excretion of unchanged GLPG1972 at steady state is less than 11% of the administered dose.

Results – Pharmacodynamics

- Plasma GLPG1972 [ng/mL]
  - Cavg in MNX model
  - Cav in MNX model

Results – Safety

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