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Favorable human safety, pharmacokinetics and pharmacodynamics of the ADAMTS-5 inhibitor GLPG1972, a potential new treatment in osteoarthritis

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Objectives

To evaluate the safety, tolerability pharmacokinetics (PK) and pharmacodynamics (PD) of GLPG1972 in healthy male subjects

Introduction

ADAMTS-5

- a disintegrin and metalloproteinase with thrombospondin motifs-5 (ADAMTS-5) is a key aggrecanase in humans[1,2]
- increased aggrecanase activity is a well-known trigger factor for osteoarthritis (OA), initiating loss of cartilage aggrecan that precedes more severe cartilage degradation[3]
- inhibition of ADAMTS-5 is a relevant approach for the development of disease-modifying OA drugs

GLPG1972

- potent and selective inhibitor of ADAMTS-5
- strong chondroprotective effects in mouse and human cartilage explants
- effective in two preclinical rodent models for OA:
  - mouse destabilization of the medial meniscus (DMM) model
  - rat meniscectomy (MNX) model
- most advanced ADAMTS-5 inhibitor evaluated in man

1. Fosang and Little, Nat Clin Pract Rheumatol 4(8), 420, 2008
2. Tortorella and Malfait, Curr Pharm Biotechnol 9(1), 16, 2008
3. Heinegard and Saxne, Nat Rev Rheumatol 7(1), 50, 2011

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, fasted 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 were 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[4]

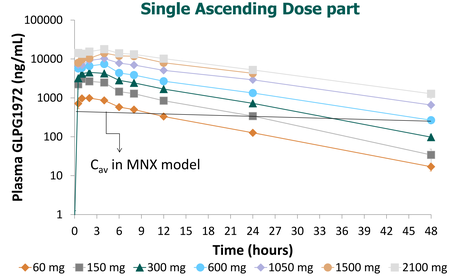
4. Larsson et al, Osteoarthritis Cartilage 22, 242, 2014

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

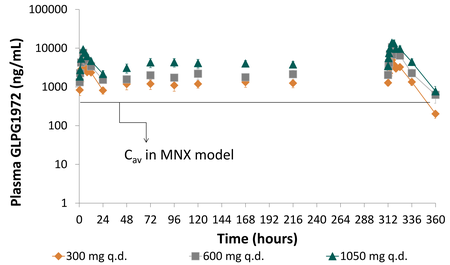
Results – Pharmacokinetics

Single Ascending Dose part



- 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 $C_{average}$ (C_{av}) required to observe efficacy in the rat MNX model (385 ng/mL) during approximately 24h

Multiple Ascending Dose part



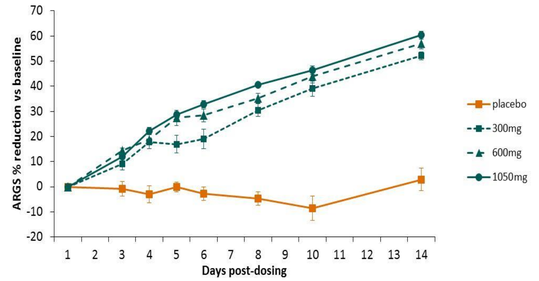
- Steady state reached after 2 dosing days, with minimal accumulation
- Dose-proportional increase in exposure over the dose range tested
- Urinary excretion of unchanged GLPG1972 at steady state is less than 11% of the administered dose

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 pharmacokinetics and pharmacodynamics profile was observed, clearly demonstrating the ability to reduce aggrecan ARGS neoepitope levels in plasma via inhibition of ADAMTS-5
- An oral dose-escalation Phase 1b study in OA patients with 4 weeks of GLPG1972 administration is ongoing in the United States (NCT03311009)

Results – Pharmacodynamics

Multiple Ascending Dose part



- No reduction in plasma ARGS 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

Disclosures

LSL received consultancy fees from Galapagos, GSK, and Johnson and Johnson. **EvdA, DA, FV** 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.

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