European Crohn's and Colitis Organisation

P612

# Human safety, pharmacokinetics and pharmacodynamics of the GPR84 antagonist GLPG1205, a potential new approach to treat IBD

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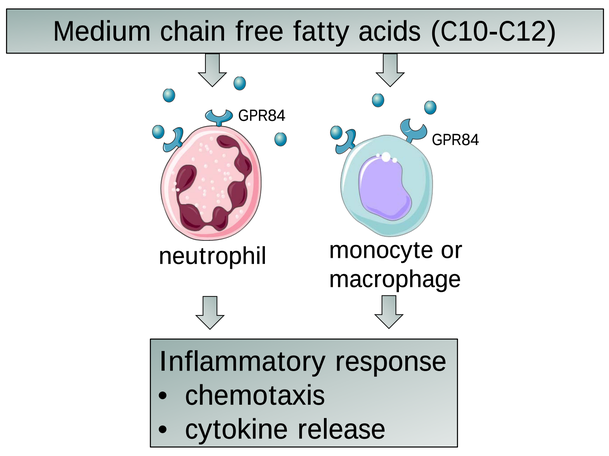
## Introduction

### GPR84, a free fatty acid receptor[1,2,3]




### GLPG1205[4]

- potent and selective antagonist of GPR84
- inhibits neutrophil and macrophage migration
- effective in DSS mouse IBD model:
  - decreases the disease activity index
  - reduces colonic neutrophil influx & MPO content
  - reduces histological colon lesion score
- the first GPR84 antagonist to be evaluated in man

1. *Hudson et al, Adv Pharmacol, 62, 175, 2011*
2. *Yonezawa, Curr Med Chem, 20, 3855, 2013*
3. *Suzuki, J Biol Chem, 288, 10684, 2013*
4. *Dupont et al, UEGW 2014, oral presentation #OP183; Dupont et al, ECCO 2015, poster P031*

## Objectives

- evaluate the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of GLPG1205 in healthy male subjects
- identify a dose for subsequent Proof of Concept studies in inflammatory bowel disease

## Methods

- Randomized, double-blind, placebo-controlled, dose ranging study
- Healthy male subjects (18-50 years)
- Single ascending dose (SAD)
  - 7 doses: 10 to 800 mg, oral suspension
- Multiple ascending dose (MAD)
  - 3 doses: 50 to 200 mg daily, oral suspension
  - 14 days dosing
- SAD & MAD: 6 subjects receiving GLPG1205 and 2 receiving placebo per dose
- Food effect & bioavailability: cross-over design
  - 1 dose: 100 mg, single dose, capsule
  - 12 subjects receiving GLPG1205
- Safety parameters
  - adverse events, ECG, vital signs, lab biochemistry & hematology and urinalysis
- Pharmacokinetics: samples were analyzed by LC-MS/MS
- Pharmacodynamics: target engagement was assessed by a competitive radiometric displacement assay in whole blood.

## Conclusions

GLPG1205, a potent and selective inhibitor of GPR84, is safe and well tolerated in healthy subjects up to 100 mg daily. It shows a favorable PK/PD profile, clearly demonstrating the ability of the compound to engage GPR84, a target which is implicated in several neutrophil- and macrophage-driven inflammatory conditions. At 100 mg once-daily, a sustained and extensive full 24-hour inhibition of GPR84 ligand binding was obtained. This dose regimen was therefore selected to explore GLPG1205's therapeutic potential in a currently ongoing Proof of Concept study in patients with ulcerative colitis

## Acknowledgements

The contribution of M. Deweer, L. Griffe, E. Staes, J. Desrivot, F. Labéguère, I. Parent, C. Sacomanni is greatly appreciated.
This work was partially supported by grant IWT-120550 from the Flemish Government.

## Safety

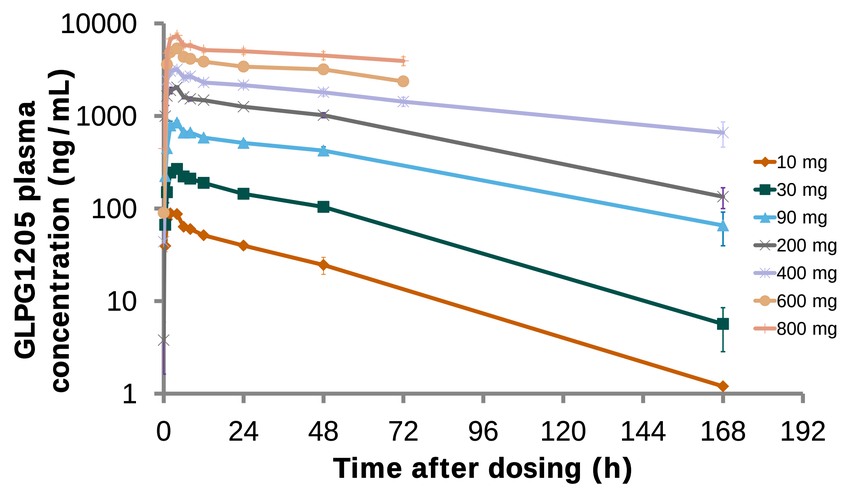
Treatment-emergent adverse events after multiple dosing considered at least possibly related to study drug occurring in ≥ 2 subjects at a given dose:

| TEAE incidence n (%) Preferred term | Placebo | GLPG1205 | | |
|---|---|---|---|---|
| | Pooled n=6 | 50 mg, q.d. n=6 | 100 mg, q.d. n=6 | 200 mg, q.d. n=6 |
| Dehydration | 0 | 0 | 0 | 2 (33.3) |
| Headache | 0 | 0 | 0 | 4 (66.7) |
| Oropharyngeal pain | 0 | 0 | 0 | 2 (33.3) |
| Vomiting | 0 | 0 | 0 | 2 (33.3) |
| Fatigue | 0 | 0 | 0 | 2 (33.3) |

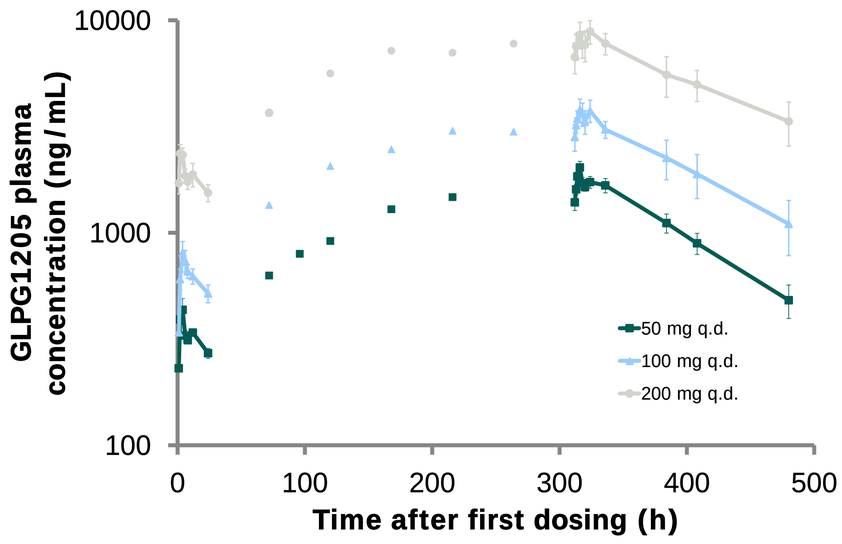
Single doses up to 800 mg and multiple doses up to 100 mg q.d. for 14 days were safe and well tolerated.
No vital sign or ECG abnormalities were reported during the study.
The only noteworthy laboratory abnormalities were signs compatible with dehydration in subjects experiencing moderate to severe headache at 200 mg.

## Pharmacokinetics

### Single ascending doses (oral suspension)




### Multiple ascending doses (oral suspension)

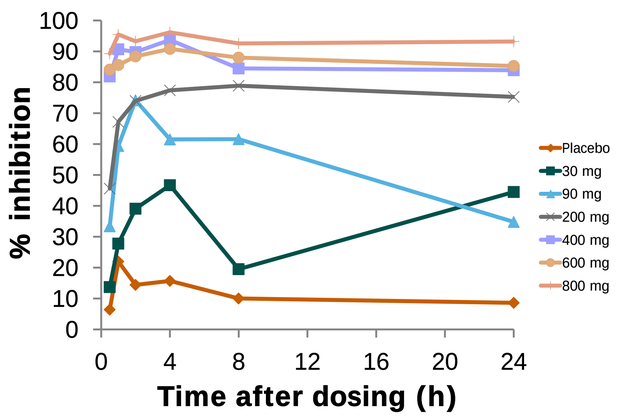



- Rapid absorption ($t_{max}$: 2-4 h) and long terminal elimination half-life (~100 h)
- Steady state reached within 10 days, with an accumulation ratio of 5.4
- Dose-proportional PK, up to 100 mg once daily
- Capsule formulation shows similar exposure as oral suspension
- No food effect

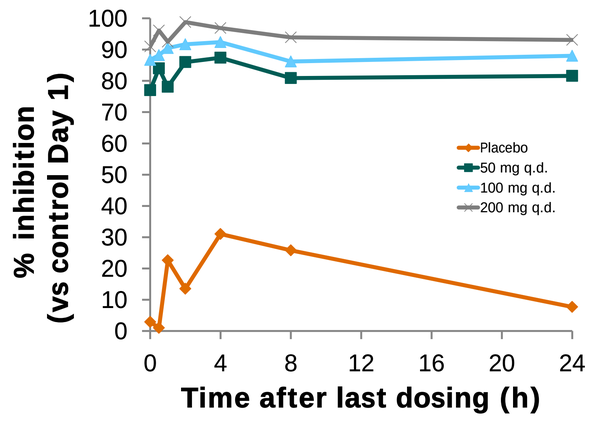
## Pharmacodynamics

*Inhibition of ligand binding to GPR84*

### Single ascending doses




### Multiple ascending doses (day 14)

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