CONCISE REPORT

Oral administration of GLPG0259, an inhibitor of MAPKAPK5, a new target for the treatment of rheumatoid arthritis: a phase II, randomised, double-blind, placebo-controlled, multicentre trial

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ABSTRACT

Background Mitogen-activated protein (MAP) kinases are key regulators of cytokine production, and are therefore potential targets for treatment of rheumatoid arthritis (RA).
Objective This two-part phase II study investigated the efficacy and safety of a once-daily 50 mg GLPG0259 (an inhibitor of MAP kinase-activated protein kinase 5) dose vs placebo (part A). An interim analysis after part A would determine whether the dose-finding part (part B) would be performed.
Methods In part A, eligible methotrexate (MTX)-refractory patients with RA were randomised to receive either a once-daily 50 mg dose of GLPG0259 or placebo, in addition to a stable dose of MTX, for 12 weeks. The primary efficacy end point was the percentage of patients achieving an American College of Rheumatology 20% improvement (ACR20) response after 12 weeks.
Results The interim analysis showed no difference between the percentage of subjects achieving the primary efficacy variable of ACR20 or the secondary efficacy variables (ACR50, ACR70 and Disease Activity Score 28) at week 12 in the GLPG0259-treated (n=19) and placebo-treated (n=11) groups. Owing to lack of efficacy, the study was terminated, and part B was not initiated.
Conclusions This innovative study design quickly provided conclusive results on the lack of efficacy of GLPG0259 in patients with RA.

INTRODUCTION

A key component of rheumatoid arthritis (RA) is inflammation of the synovial membrane, accompanied by overexpression of several proinflammatory cytokines.[1–3]

Mitogen-activated protein (MAP) kinases (eg, p38 group) are key regulators of proinflammatory cytokine and metalloproteinase production. MAP kinase-activated protein kinase 5 (MAPKAPK5) has recently been identified in synovial fibroblasts of patients with RA as a potential new target for treatment.[4] MAPKAPK5 is involved in a transduction pathway that leads to the secretion of catabolic enzymes such as matrix metalloproteinase 1, which can cause damage to bone and cartilage.

GLPG0259 is a first-in-class, small-molecule ATP-competitive inhibitor of MAPKAPK5. In cellular assays, GLPG0259 reduced the release of several mediators of inflammation and bone degradation better than or comparable to inhibitors of p38, janus activated kinase (JAK) and spleen tyrosine kinase (SYK). GLPG0259 did not block phosphorylation of c-jun NH(2)-terminal protein kinase (JNK), ERK and p38 MAP kinases, indicating inhibition of a kinase downstream in cytokine-response pathways. In addition, oral administration of GLPG0259 reduced inflammation and bone destruction in the mouse collagen-induced arthritis model.[5]

In phase I studies in healthy male subjects, the maximum tolerated dose was established at 50 mg/day—a safe and well-tolerated dose when co-administered with a single dose of 7.5 mg methotrexate (MTX).[6] The pharmacokinetic profile in phase I studies supported a once-daily oral dosing regimen.

The innovative trial design used here allows a complete phase II programme to be carried out in a single study.

METHODS
Patients
Between November 2010 and March 2011, patients with active RA and an inadequate response to MTX were treated for 12 weeks. See online supplementary text for detailed inclusion and exclusion criteria.

Trial design
This was a phase II, randomised, double-blind, placebo-controlled, multicentre trial (NCT01211249). Part A (proof-of-concept) was designed to establish efficacy and safety of a once-daily dose of 50 mg GLPG0259 compared with placebo, in addition to a stable dose of MTX, over 12 weeks. It included 30 patients. A subsequent interim analysis of the results from part A would determine whether part B (dose finding) would be initiated. Part B was designed to increase the maximum number of patients to 200, spread over four dose groups (high, middle, low, placebo). This trial design limits the number of patients exposed to high dose and placebo by including in part B data from patients receiving these doses in part A. More details on the study design are
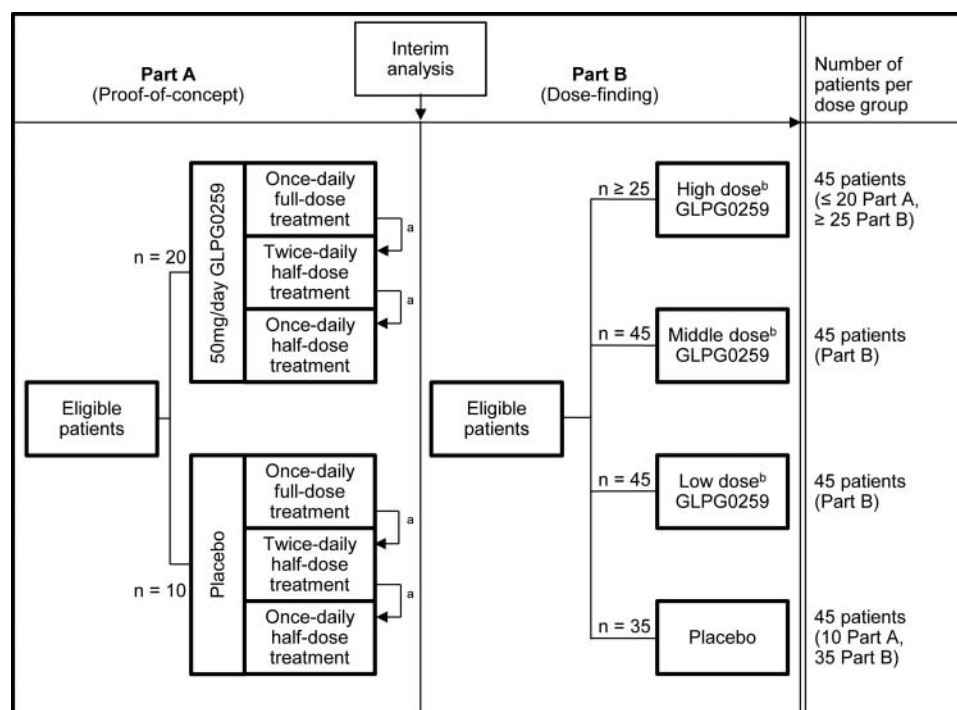
Figure 1 Design of the exploratory, randomised, double-blind, placebo-controlled, multicentre phase II trial. Duration and assessment schedule were the same for part A and part B.
[a]If the 50 mg/day dose was not tolerated by the patient, the investigator could decide to either split (twice-daily half-dose treatment) or reduce (once-daily half-dose treatment) the daily dose.
[b]The highest dose selected depends on the tolerability of the drug. If the highest dose selected for Part B was 50 mg/day, the 'High', 'Middle' and 'Low' dose groups received 50 mg, 25 mg and 12.5 mg of GLPG0259 respectively per day. If the highest dose selected for Part B was 25 mg/day, the 'High', 'Middle' and 'Low' dose groups received 25 mg, 12.5 mg and 6 mg of GLPG0259, respectively, per day.

presented in figure 1 and the online supplementary text. The study was conducted in accordance with the Declaration of Helsinki and was consistent with the International Conference on Harmonisation of Good Clinical Practice.

Efficacy

The primary efficacy variable was American College of Rheumatology 20% improvement (ACR20) response at week 12. The secondary efficacy variables were: ACR20 response in each treatment group at weeks 1, 2, 4 and 8; time to ACR20 response, ACR50/ACR70 response, and change from baseline in Disease Activity Score 28 (DAS28) using C-reactive protein (CRP) at weeks 1, 2, 4, 8 and 12.

Safety

Safety data were summarised for the safety population (all randomised patients who received one or more doses of GLPG0259). Reported adverse events were coded using the *Medical Dictionary for Regulatory Activities* 13.1 or higher (see online supplementary text).

Pharmacokinetics

The pharmacokinetic analysis was descriptive, using plasma concentrations of GLPG0259.

Statistical analysis

For the interim efficacy analysis, a selection of efficacy variables were summarised for the intention-to-treat (ITT) population (all randomised patients receiving ≥1 dose of GLPG0259 and

provided data for ≥1 post-baseline efficacy assessment). The ACR responses and DAS28 were derived using SAS V.9.1.3 or later.

RESULTS

Baseline demographics

Of the 69 patients screened, 31 met the inclusion criteria and were randomised (2 : 1) to receive 50 mg/day GLPG0259 (n=20) or placebo (n=11). One patient (GLPG0259 group) discontinued the treatment because of low back pain which occurred before treatment.

No clinically or biologically meaningful demographic or baseline differences were found between the groups (table 1).

No patient had been treated with biological agents before enrolment.

Thirty patients (19 in the GLPG0259 group; 11 in the placebo group) received ≥1 dose of treatment and were included in the safety population. All patients had ≥1 post-baseline efficacy assessment and were included in the ITT population. Thus, safety and ITT populations were identical.

Of these 30 patients, 27 (87.1%) completed the study: 17 (85.0%) in the GLPG0259 group and 10 (90.9%) in the placebo group; two withdrew consent (1 per group) and one discontinued for private reasons (GLPG0259 group). Four (20.0%) patients in the GLPG0259 group required their dose to be split (twice 25 mg/day); no patient required a dose reduction.

Primary efficacy variable

Five patients (26.3%) in the GLPG0259 group and three patients (27.3%) in the placebo group achieved an ACR20 response at week 12 (table 2). The ACR20 response rate in the

Table 1 Baseline characteristics and disease status (safety/ITT population)

	GLPG0259 (n=19)	Placebo (n=11)
Baseline characteristics		
Age (years)	50 (27, 69)	52 (30, 64)
Sex (male/female)	5/14	4/7
Race (Caucasian)	19	11
Height (cm)	169 (159, 180)	169 (158, 194)
Weight (kg)	74 (47, 98)	75 (49, 95)
BMI (kg/m^2)	25.9 (16.9, 38.3)	26.6 (17.8, 35.8)
Disease status at screening		
RF positive	73.7%	90.9%
Anti-CCP positive	78.9%	81.8%
RF and anti-CCP positive	73.7%	81.8%
Serum CRP (mg/l)	52 (18, 122)	41 (16, 107)
Disease status at baseline		
Serum CRP (mg/l)	37 (2, 129)	34 (5, 97)
SJC66	12 (6, 19)	15 (5, 33)
TJC68	20 (7, 35)	23 (0, 35)
DAS28 (CRP)	5.83 (4.98, 7.27)	6.12 (5.17, 7.20)
Use of oral steroids	57.9%	63.6%
Current dose of MTX (mg/week)	10.66 (7.5–20)	11.36 (7.5–20)

Age expressed as median (range); height, weight, BMI, serum CRP, SJC66, TJC68, DAS28 (CRP) and current dose of MTX expressed as mean (range).
BMI, body mass index; CCP, cyclic citrullinated peptide; CRP, C-reactive protein; DAS, Disease Activity Score; ITT, intention-to-treat; MTX, methotrexate; RF, rheumatoid factor; SJC, swollen joint count; TJC, tender joint count.

placebo group was as expected and at a similar level as used in the sample size calculation.

Secondary efficacy variables

No patient achieved an ACR20 response at week 1. At weeks 2 and 4, the response rate in the placebo group was 27.3%; at week 8, it increased to 45.5%, and stabilised back to 27.3% by the end of the treatment period. The response rate in the GLPG0259 group increased from 10.5% at weeks 2 and 4 to 21.1% at week 8 and 26.3% by the end of the treatment period (table 2).

The median time to ACR20 response among ACR20 responders was 41.0 days (GLPG0259 group) and 20.5 days (placebo group).

One (5.3%) patient in the GLPG0259 group and two (18.2%) in the placebo group achieved an ACR50 response at week 8. No other patients achieved an ACR50 response at any other time point. No patient achieved an ACR70 response at any time.

In the GLPG0259 group, the mean decrease from baseline DAS28 (CRP) did not exceed 0.6 across the visits, while in the placebo group it was just over 1.1 at both weeks 8 and 12.

Mean changes from baseline CRP showed a consistently larger decrease in the GLPG0259 group over the 12-week treatment period compared with the placebo group (table 2).

Safety

GLPG0259 at 50 mg/day over 12 weeks was considered safe and well-tolerated, with observed treatment-emergent adverse events (TEAEs) consistent with the expected safety profile (see online supplementary text and online supplementary table S1). No serious TEAEs or TEAEs leading to study discontinuation were reported.

Pharmacokinetics

Plasma GLPG0259 concentrations were well within the range observed in healthy volunteers at the same dose level (see online supplementary text and online supplementary figure S1).

DISCUSSION

The interim analysis of the primary efficacy variable (ACR20) showed that 50 mg GLPG0259 orally administered once daily is not superior to placebo. The innovative phase II study design allowed early independent analysis and evaluation of proof-of-concept data, eventually resulting in discontinuation of the study. All secondary efficacy variables showed results consistent with those of the primary efficacy end point. This study also confirmed the results of previous phase I studies[6] indicating that GLPG0259 is well tolerated at a once-daily 50 mg dose.

The lack of efficacy may be explained by the following. (1) The impact of MAPKAPK5 inhibition on the pathogenesis of RA has not yet been demonstrated in patients. (2) Although plasma exposures in patients were similar to exposures to active dosages in animal models, data indicating that the enzyme pathway is significantly inhibited at current plasma concentrations in the target tissues of patients are lacking. However, reduced CRP levels suggest some effectiveness of the administered dose. Higher dosages were not tested because of safety considerations. (3) This particular inflammation pathway is a complex pathway, and multiple modalities are involved in activation and inhibition. Blocking one involved kinase may lead to compensatory effects in the others. The number of failed studies with p38 MAPK inhibitors lends some weight to this.

There is a need for oral drugs that are effective in treating RA. Several drugs in development have targeted recently identified pathways[7 8]; however, not all have shown efficacy.[9] Trial designs such as ours will help shorten the development process.

Table 2 ACR20 response rates and CRP levels during the 12-week study period

	ACR20 responders, n (%)		CRP (mg/l)	
	GLPG0259 50 mg/day (n=19)	Placebo (n=11)	GLPG0259 50 mg/day (n=19)	Placebo (n=11)
Baseline			36.5±8.1	34.0±9.1
Week 1	0 [NA]	0 [NA]	37.9±6.8	39.1±10.2
Week 2	2 (10.5) [1.3 to 33.1]	3 (27.3) [6.0 to 61.0]	23.5±3.3	37.2±11.3
Week 4	2 (10.5) [1.3 to 33.1]	3 (27.3) [6.0 to 61.0]	25.4±4.7	50.1±15.5
Week 8	4 (21.1) [6.1 to 45.6]	5 (45.5) [16.7 to 76.6]	29.1±4.3	40.8±11.2
Week 12	5 (26.3) [9.1 to 51.2]	3 (27.3) [6.0 to 61.0]	27.0±4.5	42.5±12.4

Square brackets contain 95% CIs. CRP values presented as mean±SEM.
Last observation carried forward was applied to each component variable of the ACR20 response calculation. Percentages were calculated based on the number of patients in the intention-to-treat population in each treatment group.
ACR20, American College of Rheumatology 20% improvement in disease activity; CRP, C-reactive protein; NA, not applicable.

Clinical and epidemiological research

Our innovative trial design makes a complete phase II programme possible in a single study. The interim analysis provided results very quickly. Hence, the study could be terminated more quickly, thus limiting the number of subjects exposed to a drug in early development or to placebo. In general, small numbers of patients can be used in well-defined disease areas, where historical placebo response data can validate any effects observed. If the experimental medication does not show a predefined substantial increment in effect, as benchmarked by active drugs in the market, a clear cut answer can be obtained. To ensure that a novel compound is not unduly discontinued, advice from an external expert panel that has reviewed all available data is essential.

In summary, this phase II study of oral GLPG0259 was the first to investigate the efficacy of small-molecule inhibition of MAPKAPK5, a new target for the treatment of RA. Further investigations on drugs aimed at potential targets for the treatment of RA are warranted.

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