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

René Westhovens, Filip De Keyser, Dmytro Rekalov, Evgeny L Nasonov, Johan Beetens, Annegret Van der Aa, Piet Wigerinck, Florence Namour, Frédéric Vanhoutte, Patrick Durez

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 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.

GLPG0259 is a first-in-class, small-molecule ATP-competitive inhibitor of MAPKAP5. 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.

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). 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

INTRODUCTION

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

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. 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.
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 V9.1.3 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 (26.5%) 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 2  ACR20 response rates and CRP levels during the 12-week study period

<table>
<thead>
<tr>
<th>ACR20 responders, n (%)</th>
<th>CRP (mg/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GLPG0259 50 mg/day (n=19)</td>
</tr>
<tr>
<td></td>
<td>GLPG0259 50 mg/day (n=19)</td>
</tr>
<tr>
<td>Baseline</td>
<td>36.5±8.1</td>
</tr>
<tr>
<td>Week 1</td>
<td>37.9±6.8</td>
</tr>
<tr>
<td>Week 2</td>
<td>23.5±3.3</td>
</tr>
<tr>
<td>Week 4</td>
<td>25.4±4.7</td>
</tr>
<tr>
<td>Week 8</td>
<td>29.1±4.4</td>
</tr>
<tr>
<td>Week 12</td>
<td>27.0±4.5</td>
</tr>
</tbody>
</table>

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.

Acknowledgements This study was supported by Galápagos. PharmaNet/i3 was responsible for the operational management of the clinical trial. The authors would like to acknowledge the following investigators who were involved in the recruitment of patients for study NCT01211249: Professor L I Dvoretsky, Professor M F Ballyuzek, Dr I S Sardaryan, Dr V S Nemirovsky, Dr B I Palamar, Professor V V Povoroznyuk, Dr L G Kononenko and Professor M A Stanslavchuk. The authors would also like to thank Professor I McInnes, Professor R F van Vollenhoven and Professor P C Taylor who were involved in the interim analysis of the data, CRO’s Dr A La Noce and Dr O Boyarskaya from PharmaNet/i3, and Dr K Oreskovic, Dr M De Weer and Dr I Van der Taelen from Galápagos.

Contributors All authors were involved in drafting the article and revising it critically for important intellectual content. All authors approved the final version for publication. FV, JB, FN, AldA, PW, RW, FDK and PD were responsible for study conception and design. RW, PD, DR and ELN acquired the data. JB, AldA, PW, FN, FV and RW analysed and interpreted the data.

Funding Writing support was provided by Archimed Medical Communication ag, Zofingen, Switzerland.

Competing interests JB, AldA, PW, FN and FV are employees of Galápagos. RW, FDK, DR, ELN and PD received a research grant from Galápagos.

Ethics approval The clinical study protocol, informed consent document(s), and any other appropriate study-related documents were reviewed and approved by the independent ethics committees and/or competent authorities.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES
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

René Westhovens, Filip De Keyser, Dmytro Rekalov, et al.

Ann Rheum Dis published online November 17, 2012
doi: 10.1136/annrheumdis-2012-202221

Updated information and services can be found at:
http://ard.bmj.com/content/early/2012/11/16/annrheumdis-2012-202221.full.html

These include:

Data Supplement
"Supplementary Data"
http://ard.bmj.com/content/suppl/2012/11/17/annrheumdis-2012-202221.DC1.html

References
This article cites 8 articles, 1 of which can be accessed free at:
http://ard.bmj.com/content/early/2012/11/16/annrheumdis-2012-202221.full.html#ref-list-1

Published online November 17, 2012 in advance of the print journal.

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Advance online articles have been peer reviewed, accepted for publication, edited and typeset, but have not yet appeared in the paper journal. Advance online articles are citable and establish publication priority; they are indexed by PubMed from initial publication. Citations to Advance online articles must include the digital object identifier (DOIs) and date of initial publication.

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/
Articles on similar topics can be found in the following collections

- **Connective tissue disease** (2851 articles)
- **Degenerative joint disease** (3106 articles)
- **Immunology (including allergy)** (3352 articles)
- **Musculoskeletal syndromes** (3342 articles)
- **Rheumatoid arthritis** (2146 articles)

---

**Notes**

Advance online articles have been peer reviewed, accepted for publication, edited and typeset, but have not yet appeared in the paper journal. Advance online articles are citable and establish publication priority; they are indexed by PubMed from initial publication. Citations to Advance online articles must include the digital object identifier (DOIs) and date of initial publication.

To request permissions go to:  
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:  
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:  
http://group.bmj.com/subscribe/