2 SYNOPSIS

Name of Sponsor/Company: Galápagos NV	**Individual Study Table Referring to Part <XXX> of the Dossier**	**(For National Authority Use only)**
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Title of Study: Randomized, Double-Blind, Placebo-Controlled, Multicenter, Exploratory Phase II Study to Compare Three Dose Regimens of GLPG0259 vs Placebo, in Combination with Methotrexate, Administered for 12 Weeks to Subjects with Active Rheumatoid Arthritis and an Inadequate Response to Methotrexate

Investigator(s) and Study Centers: A total of 31 Investigators at 31 sites received IEC/CA approval to participate in this study. Of these, 13 sites were initiated and at least one subject was enrolled at 11 sites.

Publication(s): None

Study Period: 02 Nov 2010 to 21 Mar 2011 | **Clinical Phase:** II

Objective(s):

Primary: To preliminarily evaluate the efficacy of GLPG0259 compared with placebo in terms of the proportion of subjects achieving The American College of Rheumatology (ACR) criteria for 20% improvement in disease activity (ACR20) at Week 12 (Visit [V] 7).

Secondary: To evaluate the efficacy of GLPG0259 compared with placebo in terms of ACR response criteria, time to response, and disease status (Disease Activity Score 28 [DAS28]); to evaluate the safety and tolerability of GLPG0259 in comparison with placebo in terms of adverse events (AEs), laboratory test abnormalities, vital signs, and electrocardiograms (ECGs); and to characterize the population pharmacokinetics (PK) of GLPG0259 and determine the impact of covariates on PK parameter estimates of GLPG0259.

Methodology: This Phase II study was an exploratory, randomized, double-blind, placebo-controlled, multicenter study in a maximum of 200 randomized subjects with active rheumatoid arthritis (RA) who had an inadequate response to methotrexate.

The study was to consist of Part A and Part B. In Part A of the study, 30 eligible subjects were randomized in a 2:1 allocation ratio to a once-daily dose of 50 mg of GLPG0259 or placebo in addition to their stable dose of methotrexate (19 subjects received GLPG0259 and 11 subjects received placebo).

Number of Subjects: A maximum of 200 subjects were planned (30 subjects in Part A and at least 150 subjects in Part B).

Diagnosis and Key Criteria for Inclusion: Subjects who were to 18 to 70 years of age on the day of signing informed consent and who had fulfilled the 1987 revised ACR criteria for the classification of RA, but were not wheelchair or bed bound (functional class IV); who had active RA as shown by five or more swollen joints (from the 66-joint count), five or more tender joints (from 68-joint count), and a serum C-reactive protein (CRP) ≥1.5 mg/dL; who had received methotrexate for six months or longer and at a stable dose of 7.5 to 25 mg/week for ≥12 weeks prior to screening and was willing to continue on this regimen for the duration of the study.

Test Product, Dose, and Mode of Administration: The investigational product consisted of two 25 mg capsules of GLPG0259 for oral administration in Part A. 1090 0024 Expiry date: 09-Feb-2011; 1090 0031 Expiry date: 18-Apr-2011.

Duration of Treatment: 12 Weeks

Reference Therapy, Dose, and Mode of Administration: Matching placebo capsules for oral administration. Lot numbers 10H003 (Expiry date: 03 Aug 2011) and 10J004 (Expiry date: 04 Oct 2011).

Criteria for Evaluation:

Efficacy: The primary efficacy endpoint was the number and percentage of subjects in each GLPG0259 dose group and in the placebo group achieving ACR20 response (ACR20 response rate) at Week 12.

Secondary efficacy endpoints included number and percentage of subjects achieving ACR20 response rate at Weeks 1, 2, 4, and 8, ACR50 and ACR70 response rates at Weeks 1, 2, 4, 8, and 12, ACR-N response at Weeks 1, 2, 4, 8, and 12, time to ACR20 response; change from baseline in DAS28(CRP) at Weeks 1, 2, 4, 8, and 12, and change from baseline and percentage change from baseline in the core components of ACR response and DAS28 at Weeks 1, 2, 4, 8, and 12.

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Safety: AEs, vital signs, 12-lead ECG, physical examination findings, changes in menstrual cycle, concomitant medications, and clinical laboratory assessments.

Pharmacokinetics: PK concentrations in subjects who received GLPG0259 50 mg/day.

Statistical Methods:

Efficacy: Summaries of data at the end of Part A were generated at an interim stage of the study after 31 subjects had been randomized (30 subjects were treated and 27 subjects completed the study).

Data summaries were presented by treatment group. In the summaries and listings presented at the end of Part A, the treatment groups were labelled as GLPG 50 mg/day and Placebo.

Continuous variables were summarized using summary statistics (number of subjects [n], mean, standard deviation [SD], median, minimum [Min], and maximum [Max]). Unless otherwise specified, the mean and median for a continuous variable were presented to one more decimal place than the original (raw) values and the SD were presented to two more decimal places than the original values. The Min and Max were presented to the same number of decimal places as the original values.

Categorical variables were summarized using frequency counts and percentages. Unless otherwise stated, percentage calculations were based on the number of subjects with non-missing data in each of the treatment groups. Percentages were presented to one decimal place. In cases where the percentage calculated was >0% and <0.1%, '<0.1%' was presented against the count. A percentage was not presented against zero counts in the tables. A "Missing" category was only presented on the categorical summaries if one or more subjects had missing data for a categorical variable.

No formal hypothesis testing was performed in the analysis at the end of Part A.

The ACR responses and DAS28(CRP) were derived programmatically in SAS; only the component disease activity measures were recorded by the Investigator on the eCRF.

It was estimated that at least 180 randomized subjects in Part A and Part B would be required to provide a total sample size of 140 subjects (35 subjects in each treatment group) who completed the 12-week study treatment. This assumed a placebo response rate of 25% for the ACR20 response criteria. Thirty-five evaluable subjects in each treatment group would provide 70% power to detect a treatment difference of 25% between the GLPG0259 group and the placebo group at the one-sided 5% significance level.

Safety Analysis: The safety data were summarized for the safety population. Adverse events, vital signs, 12-lead ECG, physical examination findings, changes in menstrual cycle, concomitant medications, and clinical laboratory assessments results were summarized in a descriptive manner. No formal statistical comparisons of safety data were performed.

Pharmacokinetic Analysis: As the study was stopped at the end of Part A, the population PK analysis planned in the protocol was not performed and PK analysis was restricted to descriptive analysis using GLPG0259 concentrations from all subjects who received GLPG0259 50 mg/day.

SUMMARY – CONCLUSIONS:

The study was terminated at the end of Part A due to lack of efficacy and all planned analyses for Part B (including pharmacodynamics) were not performed. The population PK analysis planned was not performed, and the following additional changes in the statistical methods for Part A from those stated in the protocol are as follows:

- Changes in menstrual cycle were summarized for female subjects at each visit;
- A graphical summary and listing of the GLPG0259 plasma concentration data were presented.

Results show that the two treatment groups were consistent and homogenous with respect to the demographics and baseline disease characteristics, including RA history and treatment received at baseline. Both treatment groups presented a high level of disease activity as shown by high DAS28(CRP) values at baseline and during the treatment period.

Efficacy Results:

- The study failed to show any positive effect of GLPG0259 at a once-daily dose of 50 mg on symptoms and signs of

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RA. This result was consistent for both primary and secondary endpoints.

- Five (26.3%) subjects in the GLPG 50 mg/day group and 3 (27.3%) subjects in the placebo group achieved the primary efficacy variable, ACR20 response at Week 12.
- One (5.3%) subject in the GLPG 50 mg/day group and 2 (18.2%) subjects in the placebo group achieved ACR50 response at the Week 8 visit. No other subject achieved an ACR50 response at any other visit.
- No subject in either treatment group achieved an ACR70 response at any visit.
- A small mean decrease from baseline in DAS28(CRP) was observed in both treatment groups, with a greater mean decrease observed in the placebo group, although DAS28(CRP) remained elevated in both treatment groups at Week 12 at the end of treatment.
- Mean changes from baseline in CRP were consistently more decreased in the GLPG 50 mg/day group over the 12-week treatment period.
- PK analyses indicated that the GLPG0259 concentrations were within the C_{max} and C_{trough} concentration range observed previously in healthy subjects at the same doses.

Safety Results:

- GLPG0259 50 mg/day was generally well tolerated and there did not appear to be any safety concerns.
- No subject required a dose reduction, and only 4 (21.1%) subjects in the GLPG 50 mg/day group required a dose split (25 mg twice daily), indicating that the 50 mg dose level was well tolerated.
- There were no deaths, serious TEAEs, or TEAEs leading to study discontinuation reported.
- TEAEs were experienced by 12 subjects: 8 subjects (42.1%) in the GLPG 50 mg/day group and 4 subjects (36.4%) in the placebo group. All of the reported TEAEs were mild in intensity, with the exception of one moderate event.
- Treatment-related TEAEs were reported for 8 (42.1%) subjects in the GLPG 50 mg/day group and 1 (9.1%) subject in the placebo group. All of the reported treatment-related TEAEs were mild in intensity.
- The most frequently reported treatment-related TEAEs were gastrointestinal events, with 7 (36.8%) subjects in the GLPG 50mg/day and 1 (9.1%) subject in the placebo group reporting a treatment-related TEAE in the gastrointestinal disorders SOC.
- The most frequently occurring treatment-related TEAEs in the GLPG 50 mg/day group were nausea, reported in 4 (21.1%) subjects and dry mouth, reported in 2 (10.5%) subjects; dry mouth was also reported by 1 (9.1%) subject in the placebo group. All cases of dry mouth were reported by one Investigator at a single site.
- There were isolated instances of laboratory values shifting from normal to abnormal over time. These instances do not appear to be more prevalent in subjects in the GLPG 50 mg/day group than in subjects in the placebo group.
- No clinically significant observation or pattern of changes that could be attributed to study drug was observed with respect to vital signs, physical examination findings, or 12-Lead ECG results.

CONCLUSIONS: In this Phase II, exploratory study of GLPG0259 in subjects with active RA, no clinically relevant difference was observed with GLPG0259 compared to placebo, and GLPG0259 did not induce any signs of clinical improvement of RA over a 12 week treatment period. GLPG0259 concentrations in patients were within the range of those observed previously in healthy subjects at the same doses. GLPG0259 50 mg/day was well tolerated and showed a favorable safety profile.

Date of the Report: 20 September 2011