2 SYNOPSIS

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Title of Study: Randomized, Double-blind, Placebo-controlled, Multicenter, Phase II Study to Compare 4 Dose Regimens of GLPG0634 Versus Placebo, in Combination With Methotrexate, Administered for 4 Weeks in the Treatment of Subjects With Active Rheumatoid Arthritis who have an Inadequate Response to Methotrexate Alone.

Investigators and Study Centers:

A total of 19 Investigators at 19 sites in 4 countries (Moldova, Ukraine, Russia, and Hungary) received Independent Ethics Committees' (IECs) approval to participate in this study; 17 sites randomized at least 1 subject.

Publication: None

Study Period: 14 May 2012 to 06 September 2012 **Clinical Phase:** II

Objectives:

Primary Objective: The primary objective of this study was to evaluate the efficacy of GLPG0634 compared to placebo in terms of the proportion of subjects achieving the American College of Rheumatology criteria for 20% improvement in disease activity (ACR20) response at Week 4.

Secondary Objectives:

- To evaluate the efficacy of GLPG0634 compared to placebo in terms of ACR response criteria at every visit (ACR20, American College of Rheumatology criteria for 50% improvement in disease activity [ACR50], American College of Rheumatology criteria for 70% improvement in disease activity [ACR70]), time to ACR20 response, and Disease Activity Score 28 calculated using C-reactive protein (DAS28[CRP])
- To evaluate the safety and tolerability of GLPG0634 in comparison with placebo in terms of adverse events (AEs), laboratory test abnormalities, vital signs, and Electrocardiogram (ECG).
- To characterize the pharmacokinetics (PK) and pharmacodynamics (PD) of GLPG0634 and its metabolite (G254445) in targeted population.
- To explore the potential interaction of GLPG0634 on Methotrexate (MTX) PK.

Methodology: This was an exploratory, Phase II, multicenter, double-blind, placebo-controlled add-on study to compare 4 doses (30 mg, 75 mg, 150 mg, and 300 mg) of GLPG0634 with placebo, when administered once daily for 4 weeks. The study enrolled subjects with active rheumatoid arthritis (RA), who had an inadequate response to MTX alone. Ninety subjects were to be randomized to receive 1 of the 4 doses of GLPG0634 or placebo, in addition to their stable oral dose of MTX.

The screening period spanned a maximum of 21 days, occurring 2 to 22 days before the first study drug administration (i.e, Day 1). Post screening, the subjects visited the clinical center on Day -1, Week 1, Week 2, Week 3, and Week 4. Assessments for efficacy (not at Week 3), PK (not at Day -1 and Week 3), PD (not at Week 3), and safety were obtained. A follow-up visit was planned 7 to 10 days after the last dose.

For PK, 1 blood sample for analysis of GLPG0634 and its metabolite (G254445) in plasma was collected from all subjects at the time of visit at Week 1, Week 2, Week 4, and at the early discontinuation visit (EDV) (if applicable).

Subjects were invited to participate in an optional PK sub-study, which was to assess the steady state PK of GLPG0634 and its metabolite (G254445), as well as MTX and its metabolite (7-OH-MTX). These subjects took their medications (GPG0634 and MTX) on site during the visits for the PK sub-study in order to track the exact time of drug intake and blood sampling for PK evaluations. This PK sub-study was applied only if the MTX intake did not require any deviations from the usual MTX schedule of the subject.

For PD, modulation of proteins in plasma linked to Janus Kinase/Signal Transducer and Activator of Transcription (JAK-STAT) signaling pathways, and/or disease-related markers will be evaluated at a later date based on the samples

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collected during the study.

Number of Subjects: A total of 90 subjects were to be randomized to 1 of 4 dose regimens of GLPG0634 or placebo, on top of their stable dose of MTX. Thus, each of the 4 different doses of GLPG0634 and placebo groups was to have 18 subjects.

Approximately 20 subjects were planned for the PK sub-study, to allow for a minimum of 4 subjects per treatment group.

Diagnosis and Key Criteria for Inclusion: Subjects who were 18 to 70 years of age on the day of signing informed consent, and who had fulfilled the 1987 revised American Rheumatism Association (ARA) criteria for the classification of RA, who had active RA as shown by 5 or more swollen joints (from a 66 joint count), 5 or more tender joints (from a 68 joint count), and a serum CRP ≥1 mg/dL; who had received MTX for > 12 weeks and at a stable oral dose of 7.5 to 25 mg/week for at least 4 weeks prior to screening and were willing to continue on this regimen for the duration of the study.

Test Product, Dose, Mode of Administration, Batch No.s: The investigational product was [redacted] 10 mg, 25 mg, 50 mg, and 100 mg of GLPG0634 [redacted] for oral administration. Daily doses administered were 30 mg (as 3 capsules of 10 mg), 75 mg (as 3 capsules of 25 mg), 150 mg (as 3 capsules of 50 mg), or 300 mg (as 3 capsules of 100 mg). Lot number 1290 0006 (Expiry date: 31-Jan-2013).

Duration of Treatment: 4 weeks

Reference Therapy, Dose, Mode of Administration, Batch No(s): Matching placebo capsules [redacted] for oral administration. Daily dose administered was 3 placebo capsules. Lot number 1290 0006 (Expiry date: 31 Jan 2013).

Criteria for Evaluation:

Efficacy: The primary efficacy endpoint was the number and percentage of subjects in each GLPG0634 dose group and placebo group achieving an ACR 20 response (ACR20 response rate) at Week 4.

The secondary efficacy endpoints were:

- ACR20 response rate at Weeks 1 and 2;
- ACR-N at Weeks 1, 2, and 4;
- Time to ACR20 response;
- Number and percentage of subjects achieving an ACR50 response (ACR50 response rate) at Weeks 1, 2, and 4;
- Number and percentage of subjects achieving an ACR70 response (ACR70 response rate) at Weeks 1, 2, and 4;
- Change and percentage change from baseline in DAS28(CRP) at Weeks 1, 2, and 4;
- Change and percentage change from baseline in the core components of the ACR response and DAS28(CRP) at Weeks 1, 2, and 4.

Safety: The safety endpoints included:

- Incidence and severity of AEs;
- Clinical laboratory tests (hematology, serum biochemistry, coagulation, urinalysis and other tests [testosterone, luteinizing hormone, follicle stimulating hormone (FSH), prolactin, inhibin B in male subjects only]);
- Vital signs (supine heart rate, systolic blood pressure [SBP], diastolic blood pressure [DBP], and body temperature);
- 12-lead ECG;
- Physical examinations.

Pharmacokinetics: The PK endpoints included:

- For all subjects, plasma concentrations of GLPG0634/ G254445 and MTX/7-OH-MTX at Weeks 1, 2 and 4, and EDV (if applicable);
- For the subset of subjects participating in the PK sub-study, individual plasma concentrations of

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GLPG0634/G254445 and MTX/7-OH-MTX. PK parameters for GLPG0634 and G254445 as well as for MTX and 7-OH-MTX in plasma from individual concentration-time profiles.

Pharmacodynamics: The PD endpoints will include:

- Quantification of proteins (cytokines, chemokines, and others) in plasma in all subjects at Day -1, Weeks 1, 2, and 4, and EDV (if applicable).
- Modulation of plasmatic proteins linked to JAK - signal transducer and activator of transcription (STAT) signaling pathways, and/or disease.

Statistical Methods:

All data collected in this study were presented in summary tables, figures, and subject data listings. The ACR and DAS28 endpoints were derived programmatically; only the component disease activity measures were recorded by the Investigator. If any of the component disease activity data were missing for a subject at a visit, the Last Observation Carried Forward (LOCF) approach was applied prior to the calculation of the endpoints. All between-group comparisons (overall, pairwise, and total GLPG0634 dose groups versus placebo) were exploratory in nature.

Sample Size Determination: No formal sample size calculation was performed for this exploratory dose ranging study in RA subjects. A total of 90 subjects (18 subjects in each GLPG0634 dose-group and placebo group) were deemed sufficient for the purpose of this exploratory Phase II study.

Efficacy Analysis: The efficacy summaries and analyses were performed for the intent-to-treat (ITT) population (ie, all randomized subjects who received at least 1 dose of study treatment and had at least 1 post-dose baseline efficacy assessment).

The number and percentage of ACR20, ACR50, and ACR70 responders at Weeks 1, 2, and 4 were presented together with an exact 95% confidence interval (CI). Comparisons between groups were performed using the Cochran-Mantel-Haenszel (CMH) test, and these were stratified by country.

ACR-N was analyzed at Weeks 1, 2, and 4 using analysis of variance (ANOVA) models. The models included terms for treatment and country as main effects.

Time to ACR20 response was calculated as the time in days between randomization/first dose of study treatment and the achievement of ACR20 and was summarized descriptively. The Kaplan-Meier method was used to estimate the median, 25^{th}, and 75^{th} percentiles and between-group comparisons were performed using the log-rank test. Kaplan-Meier plots by treatment group were also generated.

DAS28(CRP), calculated using serum CRP levels, was summarized at baseline and Weeks 1, 2 and 4 using descriptive statistics. Change and percentage change from baseline in DAS28 were also summarized. The change from baseline in DAS28(CRP) at each visit was analyzed using analysis of covariance (ANCOVA) models. The models included terms for treatment and country as main effects and baseline DAS28(CRP) as a covariate.

The percentage change from baseline in each disease activity measure used in the calculations of ACR response and DAS28 at Weeks 1, 2, and 4 was calculated. Actual values, changes from baseline, and percentage changes from baseline at each visit for each of the component disease activity measures were summarized by treatment group using descriptive statistics.

Post database lock the following additional analyses were performed: (1) Sensitivity analysis of ACR20, ACR50 and ACR70 response rates excluding subjects in the ITT population who had an SJC66<5 or a TJC66<5 or a CRP value <10 mg/L at the baseline visit. (2) A categorical summary of DAS28(CRP) remission rates by visit (based on DAS28[CRP] at each visit). (3) A categorical summary of the change from baseline in DAS28(CRP) by visit. (4) A summary of EULAR response rates by visit.

Safety Analysis: The safety data were summarized for the safety population (ie, all randomized subjects who received at least 1 dose of study treatment). Adverse events, physical examinations, vital signs, 12-lead ECG, and laboratory assessments results were summarized descriptively.

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Pharmacokinetic Analysis:

PK sub-study: The following PK parameters were assessed:

GLPG0634 and G254445

C_{max}: the maximum observed plasma concentration

t_{max}: the time of occurrence of C_{max}

AUC_{0-24h}: the area under the plasma concentration versus time curve for a dosing interval (24h), calculated by the linear trapezoidal rule

C_{avg}: Average plasma concentration calculated as $AUC_{0-24h/24h}$

C_{24h}: Plasma concentration observed 24 hours post dose

R: metabolite over parent ratio calculated as AUC_{0-24h} G254445 / AUC_{0-24h} GLPG0634

Dose normalized parameters (C^{max}/dose, C_{24h}/dose, C_{avg}/dose, and AUC_{0-24h}/dose) were also calculated.

MTX and 7-OH-MTX

C_{max}: the maximum observed plasma concentration

t_{max}: the time of occurrence of C_{max}

AUC_{0-z}: the area under the plasma concentration versus time curve up to the last quantifiable concentration, calculated by the linear trapezoidal rule

AUC_{0-inf}: area under the curve from time 0 to infinity (MTX only)

$t_{1/2}$: apparent terminal half-life (MTX only)

Dose normalized paramaeters (C_{max}/dose, C_z/dose, and AUC_{0-z}/dose) were also calculated.

PK parameters for each analyte were listed by dose. Descriptive statistics were calculated by dose for each of the PK parameters. Treatment (dose) comparisons with respect to GLPG0634/G254445 and MTX/7-OH-MTX PK parameters were graphically presented using individual data points and arithmetic mean (+/- SEM) values vs. dose.

Dose comparisons were assessed on ln-transformed GLPG0634/G254445 PK parameters (C_{max}/dose, C_{24h}/dose, C_{avg}/dose, and AUC_{0-24h}/dose) by means of an ANOVA with dose as a fixed effect. Point estimates (least square geometric means) and associated 95% CIs were presented together with the p-value for the dose effect. Pairwise treatment comparisons were performed for the 4 dose levels, point estimates from which were expressed as a least square geometric and associated 90% CIs expressed for the differences between the dose levels. The overall dose effect for t_{max} and R was assessed using the equivalent non-parametric Kruskall-Wallis test. Median differences for each pairwise comparison were presented together with the 90% CI (calculated by the method of Moses).

Potential drug-drug interaction between GLPG0634 and MTX was assessed using ln-transformed MTX and 7-OH-MTX parameters (C_{max}, AUC_{0-z}) by means of a mixed effect ANOVA including treatment (MTX alone or MTX + GLPG0634), GLPG0634 dose group (excluding placebo once daily group) and the interaction between GLPG0634 dose group and the treatment as fixed effects, and subject nested with the GLPG0634 dose group as a random effect. Point estimates (geometric least square means) and associated 95% CIs were calculated for each level of the interaction term. The GLPG0634 + MTX versus MTX alone treatment effect was assessed for each GLPG0634 dose level separately. Estimates of the treatment differences on the ln-scale and their associated 90% CIs were exponentiated and presented in terms of treatment ratios (as a percentage) and 90% CIs for the treatment ratios. The potential interaction effect on t_{max} was assessed using the non-parametric Wilcoxon test (Signed-Rank test) for each GLPG0634 dose level, separately, and for the GLPG0634 dose levels together, the p-values from which were presented.

Pharmacodynamics Analysis: At a later stage, for all subjects, JAK-STAT and disease-related quantitative changes in plasma proteins will be analyzed descriptively. The results will be presented as concentrations of each protein and/or fold decrease or fold increase according to the effects observed on protein levels. Exploratory between-group comparisons will be performed where feasible, through graphical analyses and/or tabulations.

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Pharmacokinetic/Pharmacodynamic Correlations: At a later stage once the PD data are available, PK/PD correlations will be explored between GLPG0634 and/or G254445 plasma concentrations and PD parameters graphically and/or descriptively, but only if the latter were to be significantly altered by treatment.

SUMMARY – CONCLUSIONS:

RESULTS:

Disposition and Demographics:

Of the 214 subjects screened in this study, 91 subjects were randomized and received study treatment at 19 sites in 4 countries (Moldova, Ukraine, Russia, and Hungary). Major reasons for the high screen failure rate of subjects were low level of CRP and a positive QuantiFERON TB Gold test. There were 17 subjects in the placebo group and 74 subjects in the overall total GLPG0634 dose group (17, 22, 15, and 20 subjects in 30 mg/day, 75 mg/day, 150 mg/day, and 300 mg/day of GLPG0634 groups, respectively). Imbalance in the randomization amongst the GLPG0634 groups was due to the fact that 2 subjects each discontinued in the GLPG0634 150 mg/day (withdrawal of consent) and GLPG0634 300 mg/day (withdrawal of consent and general or specific changes in the subject's condition and treatment) groups. All 4 subjects randomized to GLPG0634 discontinued before the first dosing of the study drug. Only 1 subject in the placebo group prematurely discontinued (Investigator judgment / Sponsor request - the subject was randomized but HIV test results were not confirmed as negative).

Overall, 90 (94.7%) subjects completed the study, 16 (94.1%) subjects in the placebo group and 74 (94.9%) subjects in the total GLPG0634 group and 5 (5.3%) randomized subjects discontinued the study.

The safety and ITT populations consisted of same number of subjects in each treatment group (17 subjects in the placebo group and 74 subjects in the total GLPG0634 group). The PK population consisted of 74 subjects in the total GLPG0634 group.

There were more females (71/91, 78.0%) compared to males (20/91, 22.0%) with small variations among groups. All subjects were Caucasian. The mean age of subjects was 50.5 years (range: 24 to 70 years). The subjects in the placebo group were comparatively younger than those in the GLPG0634 dose groups (mean ages were 45.4 years for the placebo group, and 53.9, 49.9, 52.2, 51.5 years for the GLPG0634 30 mg/day, GLPG0634 75 mg/day, GLPG0634 150 mg/day, and GLPG0634 300 mg/day groups, respectively). The mean BMI of subjects across the groups was 27.1 kg/m^2, and ranged from 16.4 kg/m^2 to 52.7 kg/m^2. The slightly higher BMI observed in the placebo group (29.1 kg/m^2) compared to the total GLPG0634 dose groups (26.6 kg/m^2) was mainly due to the outlier in the placebo group with a BMI of 52.7 kg/m^2.

Overall, all treatment groups were comparable for baseline disease severity, although the GLPG0634 150 mg/day group showed slightly more severe disease at baseline with consistently higher values in DAS28(CRP) and each of the individual disease activity components (SJC66, TJC68, HAQ-DI, and CRP) compared to the other treatment groups. The mean and median values of DAS28(CRP) were both above 5.1 in all treatment groups.

Some disparities among groups were observed. Both the placebo group and the GLPG0634 300 mg/day dose group exhibited a higher RF and anti-CCP positivity compared to the other GLPG0634 dose groups. Mean serum CRP was slightly higher at screening and baseline, and the time since RA diagnosis was shortest for the placebo group compared to GLPG0634 groups.

The median time since diagnosis of RA was the lowest in the placebo group (2.3 years) compared to the GLPG0634 dose groups (5.4 years, 6.7 years, 6.5 years, and 4.3 years for 30 mg/day, 75 mg/day, 150 mg/day, and 300 mg/day dose groups, respectively). This difference in the time since diagnosis of RA between placebo and GLPG0634 dose groups corresponded with the difference in the subjects' ages (placebo group being younger than the GLPG0634 groups).

The use of oral steroids at baseline was lower for the placebo group and GLPG0634 300 mg/day group compared to the other GLPG0634 dose groups.

At baseline, comparable MTX doses were administered across all the treatment groups (10.7 mg/week in the placebo group and 11.1 mg/week to 12.8 mg/week in the GLPG0634 dose groups). The median MTX dose was 10.0 mg/week across all the 5 treatment groups.

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The mean overall compliance to the study treatment in the placebo and GLPG0634 group subjects was 100% and 99.97%, respectively. All subjects' overall compliance to the study treatment was between 96% to 104%.

Efficacy:

Primary Efficacy Parameter:

At Week 4 (primary efficacy endpoint) of treatment, a dose-related ACR20 response rate was observed across the GLPG0634 treatment groups, with the exception of the GLPG0634 150 mg/day dose group. The majority of subjects receiving 300 mg/day of GLPG0634 reached an ACR20 response. Although the ACR20 response rate attained by this group was 65%, i.e. 24% higher than observed for placebo (41.2%), the difference was not statistically significant. Among the other GLPG0634 treatment groups, the 75 mg/day dose group exhibited an ACR20 response rate of 54.5%, while the ACR20 response rates in the GLPG0634 30 mg/day and the 150 mg/day groups were both lower than placebo (35.3% and 40.0%, respectively).

An additional sensitivity analysis of ACR20 response rate excluding subjects with SJC66 < 5 or TJC68 < 5 or CRP <10 mg/L at baseline from the ITT population resulted in the overall ACR20 response rates at Week 4 to be similar for the placebo and GLPG0634 dose groups (ranging from 35.7% to 41.7%), except for GLPG0634 300 mg/day, which showed a higher response rate (76.9%).

Secondary Efficacy Parameters:

In all treatment groups, the ACR20 response rate tended to increase progressively from Week 1 to Week 4, although in the GLPG0634 300 mg/day dose group the peak response was already reached at Week 2 and this was maintained at Week 4. Consistent with this finding, the time to achievement of an ACR20 response in subjects who had an ACR20 response was shorter in the GLPG0634 300 mg/day dose group (mean time of 13.8 days) compared to all other treatment groups (between mean time of 18.7 days and 20.9 days).

The results from the summary and analysis of ACR50 response rate confirmed the finding of a dose-related increase in the rate of response, with the exception of the GLPG0634 150 mg/day group. The ACR50 response rates in all GLPG0634 dose groups except the GLPG0634 150 mg/day group were higher than the placebo group (5.9%), with the GLPG0634 300 mg/day group achieving an ACR50 response rate of 45.0% at Week 4.

The ACR70 response rate observed in this trial is negligible due to the short treatment duration.

The ACR-N responses confirmed what was observed with the ACR20 and ACR50 response rates, i.e., the response to treatment was dose-related across the GLPG0634 dose groups, with the exception of the GLPG0634 150 mg/day group, and ACR-N increased over time from Week 1 to Week 4.

The DAS28(CRP) results showed a significant and consistent reduction from baseline in all GLPG0634 treatment groups. The decrease was dose-related, ranging at Week 4 from -1.1 to -2.3 units for the 30 mg/day and the 300 mg/day dose groups, respectively, and increased over time from Week 1 to Week 4. The DAS28(CRP) reduction of the placebo group was slightly greater than that of the GLPG0634 30 mg/day group.

At Week 4, the severity of disease, as assessed by DAS28(CRP) absolute values, tended to decrease with increasing dose of GLPG0634 (except for the GLPG0634 150 mg/day group). The percentage of subjects with severe disease was higher in the GLPG0634 30 mg/day group (41.2%) as compared to the GLPG0634 75mg/day (27.3%) and GLPG0634 30 mg/day (15.0%) groups.

At Week 4, remission of the disease (DAS28[CRP] <2.6) was seen in all groups except the GLPG0634 150 mg/day group. The GLPG0634 300 mg/day group had the best remission rate (25.0%), followed by GLPG0634 75 mg/day (13.6%) and GLPG0634 30 mg/day (11.8%) groups.

In all treatment groups, the incidence of cumulative good/moderate EULAR responses increased over time. At Week 4, the cumulative good/moderate EULAR response rates of the GLPG0634 groups, except the GLPG0634 30 mg/day dose group, were higher than the placebo group. The cumulative good/moderate EULAR response rates were highest in the GLPG0634 300 mg/day group (80.0%), followed by GLPG0634 75 mg/day (68.2%) and GLPG0634 150 mg/day (66.7%) groups. In particular, a high rate of good EULAR response was observed in the GLPG0634 300 mg/day group (45%). The cumulative good/moderate EULAR response in the GLPG0634 30 mg/day and placebo groups were similar (58.8%).

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Change from baseline in the core components of the ACR response and DAS28(CRP) endpoints showed the following characteristics:

- SJC and TJC showed a progressive reduction in the number of swollen and tender joints over time, with greater reductions observed in the GLPG0634 75 mg/day to the GLPG0634 300 mg/day dose groups for SJC and in all GLPG0634 treatment groups for TJC compared with placebo at Week 4.
- The physician's global assessment score tended to decrease over time in all groups, with reductions greater than placebo in the GLPG0634 dose groups from 75 mg/day to 300 mg/day at Week 4, while reductions greater than placebo were observed only in the 75 mg/day and the 300 mg/day dose groups for the subject's global assessment score.
- Subject pain assessment scores showed a significant decrease over time with statistically significant pairwise p-value for GLPG0634 300 mg/day group compared with placebo and overall p-values for the 5 treatment groups at Weeks 1, 2, and 4. The mean decrease of the score in the GLPG0634 300 mg/day group at Week 4 was at the level of the minimal clinical important difference.
- HAQ-DI scores tended to decrease over time in all GLPG0634 treatment groups, while the reduction observed in the placebo group remained relatively stable from Week 1 to Week 4. At Week 4, a greater reduction was observed for the GLPG0634 300 mg/day group that was statistically significant compared with placebo group. In the GLPG0634 300 mg/day group, 16/20 subjects showed a decrease ≥ 0.22, which is considered a MCID, followed by the GLPG0634 75 mg/day group (14/22 subjects with a decrease ≥ 0.22). The mean decrease in the HAQ-DI score for GLPG0634 150 mg/day group was similar to the placebo group.
- Serum CRP levels progressively and consistently decreased from baseline in all GLPG0634 dose groups, with the change being statistically significant for the 300 mg/day group compared with placebo at Weeks 1, 2, and 4, and for the 75 mg/day and 150 mg/day dose groups compared with placebo at Week 4. The mean serum CRP level of the placebo group followed an opposite trend, with an initial reduction followed by a progressive return toward baseline values. Consistent with the above findings, shifts of serum CRP from high at baseline to normal at Week 4 were observed only in the GLPG0634 groups and were dose-related. At Week 4, the mean serum CRP level of the GLPG0634 300 mg/day group was within the normal range.

Although overall the different treatment groups were comparable at baseline in terms of demographic and disease characteristics, some disparities were observed among groups that may have affected the response of subjects to treatment. In particular:

- Subjects receiving placebo had a younger mean age and a shorter mean disease duration compared with all other groups.
- Subjects receiving placebo or 300 mg/day GLPG0634 exhibited a higher positivity rate to RF and anti-CCP antibodies compared with the other groups, while subjects receiving the 150 mg/day dose exhibited a low positivity rate.
- Subjects of the 150 mg/day GLPG0634 group tended to show some signs of active disease more pronounced than other groups at baseline, namely more elevated median values of SJC and TJC and more elevated median value of HAQ-DI.
- Current use of oral steroids was less frequent in the placebo and in the 300 mg/day dose groups.

Pharmacokinetics:

GLPG0634 and G254445 PK were investigated in a subset of subjects who received 30 mg to 300 mg daily dose of GLPG0634 for 4 weeks. The number of subjects per dose level was small and ranged between 2 (75 mg/day) to 5 (150 mg/day). The exposure to GLPG0634 within the 30 mg/day to 300 mg/day dose range was variable. Three subjects with high GLPG0634 levels compared to the other subjects at the same dose were responsible for this high variability observed on the parent exposure ($AUC_{0\text{-}24h}$). In addition, the exposure to the metabolite (G254445) relative to the parent in these subjects was in the lower end (R= 4.5, 4.8 and 6.2) of the range of values for the other subjects, suggesting a saturation/inhibition of the enzyme involved in metabolite formation. The concomitant medications prescribed to these

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3 subjects were also given to other subjects from the PK sub-study without impact on GLPG0634 exposure. Results of the statistical analysis showed that GLPG0634 exposures (both in term of C_{max} and AUC_{0-24h}) increased dose proportionally over the 30 mg to 300 mg dose range. However, these results should be interpreted with caution, due to the high variability observed in PK parameters and the small number of subjects per dose level which could result in non-statistical significance. The potential covariate(s) responsible for the variability in GLPG0634 exposure as well as the dose proportionality of GLPG0634 PK will be further investigated using a Population PK approach and reported separately.

Conversely to the parent, the variability in G254445 PK was low to moderate, with the highest variability being associated with the lowest dose (CV%: 48.6% -52.2% for 30 mg/day) and PK of G254445 was dose proportional over the entire dose range.

The potential of drug-drug interaction of GLPG0634 on MTX PK was assessed by pooling data from all subjects regardless of the GLPG0634 dose. Exposure to MTX (both C_{max} and AUC_{0-z}) was not impacted by the co-administration with GLPG0634 (up to 300 mg daily dose). Although this investigation was not powered to assess the potential of interaction using the 90% CI approach, the interval boundaries for both MTX parameters were close to, or even fell within, the 80%–125% bioequivalence range: 98.76% (85.43%-114.17%) and 102.72% (84.02%-125.58%), for C_{max} and AUC_{0-z} respectively. These data suggested that there was no clinically relevant PK interaction of GLPG0634 or G254445 with MTX in RA subjects.

Pharmacodynamics: Pharmacodynamic evaluations will be done at a later date and the results will be presented in a separate report.

Safety:

The number (%) of subjects with any treatment-emergent adverse events (TEAEs) in the placebo, GLPG0634 30 mg/day, GLPG0634 75 mg/day, GLPG0634 150 mg/day, GLPG0634 300 mg/day, and the total GLPG0634 groups were 3/17 (17.6%), 7/17 (41.2%), 7/22 (31.8%), 4/15 (26.7%), 9/20 (45.0%), and 27/74 (36.5%), respectively. Thus, less than 50% of subjects in each treatment group experienced at least 1 TEAE. The incidence of TEAEs was higher in the active treatment groups than in the placebo group. The highest incidence was observed in the GLPG0634 300 mg/day group (45.0%), although no notable dose-response trends in the incidences of the TEAEs were observed across the active treatment groups.

In the overall total GLPG0634 group, the most common TEAEs were headache (n=5), nausea (n=3), dyspepsia (n=2), and dysgeusia (n=2).

Subjects in the placebo group had fewer TEAEs that were reported as potentially related to study drug compared to subjects in the active GLPG0634 treatment groups, although no notable trend in the incidences of the drug-related TEAEs was observed among the active GLPG0634 treatment groups.

The number (%) of subjects reporting at least 1 drug-related TEAE in the placebo, GLPG0634 30 mg/day, GLPG0634 75 mg/day, GLPG0634 150 mg/day, GLPG0634 300 mg/day, and the total GLPG0634 groups were 1/17 (5.9%), 3/17 (17.6%), 3/22 (13.6%), 1/15 (6.7%), 3/20 (15.0%), and 10/74 (13.5%), respectively.

The only related TEAE that was reported by more than 1 subject was nausea that occurred in 2 subjects, 1 subject each in the 150 mg/day and 300 mg/day GLPG0634 dose groups.

One TEAE in the system organ class (SOC) of infections and infestations was reported i.e, cystitis. This was observed in a subject of the GLPG0634 300 mg/day treatment group, and was assessed as possibly treatment related by the Investigator.

Subjects across all the groups experienced mild or moderate TEAEs. None of the subjects experienced any severe TEAE.

No subject experienced an AE which led to permanent discontinuation from the study treatment. Only 1 subject in the GLPG0634 30 mg/day group had a temporary discontinuation of the study treatment for 1 day due to nausea.

There were no serious TEAEs or deaths reported in the study.

No notable shifts from baseline in laboratory parameters evaluated were noted. However, the following observations were noted:

- Hemoglobin: There were more subjects in the placebo group whose hemoglobin shifted from normal values at

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baseline to low values during the study (6/9), compared with any of the GLPG0634 dose group.

- Neutrophils (absolute): In the placebo group, 7/17 subjects shifted from normal to high values of neutrophils during the study and 1/17 from normal to low, while most of the subjects in the GLPG0634 dose groups had normal values at baseline that remained normal.
- Lymphocytes (absolute): There were only sporadic shifts from normal to low; 1/14 subjects in the placebo group and 5/64 subjects in the total GLPG0634 group had normal lymphocytes at baseline shift to low abnormal values as worst case post baseline.
- Lipase: Normal in most of the subjects and remained normal.
- Amylase: Normal in most of the subjects and remained normal.
- Creatinine: Most of the subjects had normal values of creatinine at baseline (high end of normal range). In the placebo group, none of the subjects with normal values of creatinine at baseline shifted to high abnormal values post baseline. In the total GLPG0634 group, 13/65 subjects with normal values of creatinine at baseline had creatinine values increased slightly above 80 µmol/L post baseline. This increase had no clinical significance. These cases were distributed in all dose groups without a clear relationship with the dose.
- Cholesterol: In the placebo group, 3/13 subjects with normal values of cholesterol at baseline shifted to high abnormal values post baseline. In the total GLPG0634 group, more than half (28/51) subjects with normal values of cholesterol at baseline shifted to high abnormal values post baseline; slightly more frequently in the GLPG0634 300 mg/day and GLPG0634 30 mg/day groups.
- LDL: In the placebo group, 3/13 subjects with normal values of LDL at baseline shifted to high abnormal values post baseline. In the total GLPG0634 group, 22/55 subjects with normal values of LDL at baseline shifted to high abnormal values post baseline; slightly more frequently in the GLPG0634 300 mg/day dose group.

In this study, there were 4 clinically significant laboratory abnormalities which were reported as TEAEs i.e., anemia (n=1; GLPG0634 75 mg/day group), AST increased (n=1, GLPG0634 30 mg/day group), blood triglycerides increased (n=1, GLPG0634 30 mg/day group), and hypercholesterolemia (n=2, one each from GLPG0634 75 mg/day and placebo groups). Out of these abnormal laboratory AEs, 2 AEs (AST increased [GLPG0634 30 mg/day group] and hypercholesterolemia [placebo group]) were transient deterioration of abnormal baseline values.

Hormones tested in the male study subjects were not affected by the study drug.

No notable trends were observed between the treatment groups in the vital signs during the course of the study. Only 1 TEAE of hypertension was reported (GLPG0634 30 mg/day group).

None of the subjects had treatment-emergent clinically significant ECG recordings during the study. There were no notable trends observed between the treatment groups in QTcF or QT interval prolongations recorded on the ECGs. Cardiac disorder TEAEs included angina pectoris and first degree atrioventricular block.

No clinically significant physical examination findings were observed in any subject during the course of the study, except for one subject in the GLPG0634 300 mg/day group with right ankle fracture.

CONCLUSIONS:

- Efficacy of GLPG0634 was demonstrated in this short duration study of 4 weeks.
- Based on the overall efficacy results, GLPG0634 doses from 75 mg/day to 300 mg/day appear to be effective. Overall, a dose response was evident with increasing doses. GLPG0634 30 mg/day dose appeared to be suboptimal.
- Some imbalances among treatment groups in terms of demographic and disease characteristics as well the limited size of each treatment group may have affected the results and may possibly explain the relatively high placebo ACR20 response rate and the apparent lower response rate of the 150 mg/day GLPG0634 dose group.
- Overall, more consistent and dose-related results across treatment groups were observed for objective measures of disease activity, like serum CRP, and for physician's assessment of disease (SJC, TJC, and physician's global assessment), compared with subjects' subjective assessments (subject's global and pain assessment, HAQ-DI). This

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discrepancy was particularly evident in the GLPG0634 150 mg/day dose group, and was possibly the reason for the worse ACR responses observed in this group. In this dose group, the subjects had a higher SJC and TJC at baseline, and may have less perceived improvement in pain and global VAS, leading to a poor ACR response.

- GLPG0634 was safe and well tolerated at all dosages. The safety profile in this study was not different to the previous studies conducted on GLPG0634.
- Results of the statistical analysis showed that GLPG0634 and G254445 exposures (both in term of C_{max} and AUC_{0-24h}) increased dose proportionally over the 30 mg to 300 mg dose range. Conversely to the parent, the variability in G254445 PK is low to moderate, with the highest variability being associated to the lowest dose (CV%: 48.6% -52.2% for 30 mg/day).
- No clinically relevant PK interaction of GLPG0634 (up to 300 mg/day dose) with MTX was observed in RA subjects.

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