CLINICAL STUDY PROTOCOL
AMENDMENT 5 – US ONLY

Randomized, double-blind, placebo-controlled, multicenter, phase IIb dose finding study of GLPG0634 administered for 24 weeks as monotherapy to subjects with moderately to severely active rheumatoid arthritis who have an inadequate response to methotrexate alone

Protocol Number:	GLPG0634-CL-204
EudraCT Number:	2012-003654-86
Country:	United States of America
[redacted]**:**	[redacted]
Test Drug/Investigational Product:	GLPG0634
Phase:	phase IIb
Sponsor:	Galapagos NV Generaal De Wittelaan L11A3 2800 Mechelen Belgium
Date of Original Protocol:	14 March 2013
Date of Amendment 1:	11 April 2013
Date of amendment 2:	17 April 2013
Date of Amendment 3:	02 August 2013
Date of Amendment 4 – US Only:	11 November 2013
Date of Amendment 5:	23 May 2014
Date of Amendment 5 – US Only	27 May 2014

Protocol Amendment 5 – US Only

Rationale

Protocol amendment #5 introduces the following changes: i) an adjustment of the inclusion/exclusion criteria to better represent the current rheumatoid arthritis (RA) population without compromising the study objective, ii) an adjustment of the individual subject withdrawal criteria, and iii) a refinement of general study procedures (calendar days, re-screening and retesting guidelines, …) to provide further guidance to investigators.

In addition, the protocol amendment includes an update of the background information on GLPG0634 and the benefit/risk section in accordance with the current version of the IB (version 7.0, February 2014). This update includes for example the results from a 39-week chronic toxicology study in dogs.

Minor changes were also made to other relevant sections, where appropriate (e.g., synopsis, abbreviations).

Changes to Protocol Amendment 4 – US Only

Amended text has been included in underlined text format and deleted text in ~~strikethrough~~ in the following sections:

Applicable for all sections in the protocol

"day(s)" changed to "calendar day(s)"

CRO Personnel: Medical Monitor

Name: [redacted]
Title: [redacted]
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Telephone No.: [redacted]

Section 6.3.1 Physical, Chemical, and Pharmaceutical Properties and Formulations

The chemical name of GLPG0634 is N-(5-(4-((1,1-dioxidothiomorpholin-4-yl)methyl)phenyl)-[1,2,4]triazole[1,5-a]pyridin-2-yl)cyclopropanecarboxamide hydrochloride trihydrate.

Two clinical formulations with various strengths are currently available: an oral capsule (10-100 mg per capsule) filled with the hydrochloride (HCl) salt of GLPG0634; and a film-coated tablet (25-100 mg per tablet) of the HCl salt of GLPG0634. ~~The clinical formulation is an oral capsule of various strengths (10 to 100 mg per capsule) filled with the hydrochloride salt of GLPG0634.~~

Section 6.3.2.1 Primary and Secondary Pharmacology

GLPG0634 is an adenosine triphosphate (ATP)-competitive inhibitor of JAK1. It is highly selective for inhibition of JAK1 among 451 unique kinase gene products tested *in vitro*. In cellular assays, it inhibits biological processes involving JAK1 from 179 nM onwards, with a 30-fold selectivity over JAK2 in human whole blood. A high potency is observed in the rat collagen-induced arthritis (CIA) model.

Metabolite G254445 exhibits a similar JAK1 selectivity profile while being approximately 10-fold less potent as compared to parent GLPG0634, ~~both~~ *in vitro* ~~and in the rat CIA model~~. In the rat CIA model, while being less potent than the parent molecule, G254445 displays a good curative effect against established arthritis.

Section 6.3.4.1 General Toxicology

[redacted]

…

[redacted]

[redacted]

Section 6.4 Background - Preliminary Clinical Data

[redacted]

[redacted]

Section 6.5. Clinical Risks/Benefits

Pre-clinical safety

[redacted]

[redacted]

Clinical safety

[redacted]

Section 8.1 Overall Study Design and Plan

At completion of the 24-week treatment period, subjects will be offered the option to enter a Long Term Follow-up study (GLPG0634-CL-205). This Long Term Follow-up study is subject to separate approval from Regulatory Agencies and Ethics Committees.

Section 8.3.2 Inclusion Criteria

4. Screening serum CRP ≥ 0.7~~1.2~~ x upper limit of the normal (reference) laboratory range (ULN).
7. If taking oral steroids, these should be at a dose ≤10 mg/day of prednisone or prednisone equivalent and stable for at least 4 weeks prior to ~~Screening~~Baseline.
8. If taking non-steroidal anti-inflammatory drugs (NSAIDs), these must be at a stable dose for at least 2 weeks prior to ~~Screening~~Baseline.
9. The results of the following laboratory tests performed at the central laboratory at Screening must be within the limits specified below:
   a) Hemoglobin ≥10 g/dL (International System of Units [SI]: ≥100 g/L);
   b) WBCs ≥3.0 x 10^3 cells/mm^3 (SI: ≥3.0 x 10^9 cells/L);
   c) Neutrophils ≥2.0 x 10^3 cells/mm^3 (SI: ≥2.0 x 10^9 cells/L);
   d) Lymphocytes ≥1.0 x 10^3 cells/mm^3 (SI: ≥1.0 x 10^9 cells/L);
   e) Platelets ≥100 x 10^3 cells/mm^3 (SI: ≥100 x 10^9 cells/L);
   f) Serum ALT and aspartate aminotransferase (AST) ≤1.5 x ULN;
   g) Total bilirubin level ≤1.25 x ULN;
   h) Alkaline phosphatase ≤1.5ULN;
   i) Lipase ≤1.5 x ULN and amylase ≤1.5 x ULN;
   j) Creatinine clearance >60 mL/min ~~and blood urea nitrogen (BUN) within normal ranges~~. Creatinine clearance will be calculated using the Cockroft-Gault formula.

Section 8.3.3 Exclusion Criteria

1. Current therapy with any non-biological DMARD, including oral or injectable gold, sulfasalazine, azathioprine, or D penicillamine within 4 weeks prior to Baseline, cyclosporine within 8 weeks prior to Baseline, and leflunomide within 3 months prior to Baseline or a minimum 4 weeks prior to Baseline if after 11 calendar days of standard cholestyramine therapy, with the exception of antimalarials, which must be at a stable dose for at least 12 weeks prior to ~~Screening~~Baseline.
4. Previous use of JAK ~~or SYK~~ inhibitors.

Section 8.3.4 Removal of Subjects from Therapy or Assessments

Subjects may stop study medication for any of the following reasons:

- Subject request.
- Use of nonpermitted concurrent therapy.
- Noncompliance with the study medication (see Section 8.5.9.)
- Noncompliance with the study procedures (see Section 8.5.9 and Section 8.6)
- Lost to follow-up.
- Occurrence of AEs not compatible with the continuation of subject participation in the study, in the investigator's opinion. This also includes any clinically significant laboratory results, ECGs, and vital signs.

- Investigator request.
- Sponsor request.
- Treatment failure deemed by the investigator as lack of improvement or worsening of the disease symptoms or occurrence of intolerable AEs.

Treatment with GLPG0634 will be discontinued and the patient withdrawn from this study for:

- …
- Two sequential ~~D~~decreases from the baseline of inhibin B by 50% or Testosterone by 50% with concurrent increases in FSH or LH respectively.[3]

After becoming aware of any of the above described abnormal laboratory changes occurring at any one time, an unscheduled visit (i.e. second sequential) must occur to retest within 3 to 5 days. ~~The retesting for laboratory parameters should occur within 3 to 5 days~~.

[1] In each case, there is a need for additional investigations, such as review of ethanol, recreational drug and dietary supplement consumption; testing for acute hepatitis A, B or C infection and biliary tract imaging should be promptly discussed with the Study Medical Monitor.

[2] At the time of study completion or discontinuation, if a patient should exhibit elevations in serum creatinine ≥33% above the average of screening and baseline values, they should be re-tested every 1 to 2 weeks until the serum creatinine elevation is fully reversed to within 10% of the average of screening and baseline values.

[3] In each case, hormones in male subjects should be monitored monthly and if no positive dynamics is seen after 3 months from stopping GLPG0634, referral to an andrologist should be considered.

Section 8.5.8 Prior and Concomitant Therapy

Concomitant therapies taken for the long term treatment of preexisting conditions can continue during the study provided they are in accordance with the inclusion and exclusion criteria. It is preferred that these medications be stabilized ~~prior to study entry~~ and continued without variation of dose or regimen during the study.

In case new therapies need to be administered during the study, the risk/benefit to the subject should be carefully assessed and consideration given to the timing of any necessary introduction of new medications.

Permitted concomitant medications at Screening and during the study include:

- Antimalarials, which must be at a stable dose for at least 12 weeks prior to ~~Screening~~Baseline.
- NSAIDs, provided that the dose is stable for at least 2 weeks prior to ~~Screening~~Baseline and, if possible, is kept constant during the study;
- Oral steroids, provided that the dose is stable, is ≤10 mg/day prednisone or equivalent for at least 4 weeks prior to ~~Screening~~Baseline, and is kept stable for the study duration; and
- Analgesics, other than NSAIDs, up to the maximum recommended doses may be used for pain as required. However, subjects must not take analgesics within 24 hours before a visit where clinical efficacy assessments are performed and recorded.

Female subjects of childbearing potential will use highly effective birth-control methods as outlined in the inclusion criteria and agree to continue their use during the study and for at least 12 weeks after the last dose of study medication. The use of hormonal contraceptives will be recorded in the Concomitant Therapy section of the eCRF. Applicable procedures and treatment guidance based on package inserts will be respected.

…

Previous use of JAK ~~or SYK~~ inhibitors is prohibited.

Section 8.5.9 Treatment Compliance and Drug Accountability

For each dose taken, the date, the time of intake, and the number of capsules taken should be recorded on the subject diary card.

The investigator or designated study personnel will maintain a log of all drug dispensed and returned. Drug supplies for each subject will be inventoried and accounted for throughout the study.

Subjects with a poor compliance (<80% or >120%) will be retained by the study site. If study drug compliance remains <80% or >120% between study visits, or if the subject missed more than 2 visits, the subject will be evaluated for potential discontinuation. Any discontinuation should be done in consultation with the Medical Monitor.

Section 8.6.1.1 Screening Period (Visit 1, Day -29 to Day -2)

- Each subject will receive a patient number by using the IXRS system.

Note 1: Retesting during the Screening period is only allowed once for abnormal lab values except for positive QuantiFERON-TB Gold, Hepatitis B, Hepatitis C, HIV or pregnancy test in a female of childbearing potential AND only in case it is still possible to randomize the patient within the per protocol defined Screening period of 28 calendar days.

Note 2: Rescreening is only allowed in specific situations and after having obtained written sponsor approval.

Section 8.6.2.8 Week 24 (Visit 10) or Early Discontinuation Visit (EDV)

The Week 24 visit (Visit 10) will take place on Day 169 ± 2 calendar days relative to the start of study medication intake. Subjects who have discontinued from the study early and subjects who attend the Week 24 visit will complete the following assessments. This visit needs to be entered in IXRS.

Section 8.7.1.5 Flow chart

IXRS call was added to the D169/W24 and EDV visits in the flow chart.

Section 8.9.2 Monitoring.

Data for each subject will be recorded on an eCRF. Data collection must be completed for each subject who signs an ICF ~~and is administered study medication~~.

1 Protocol Approval Signatures

Protocol Title: Randomized, double-blind, placebo-controlled, multicenter, phase IIb dose finding study of GLPG0634 administered for 24 weeks as monotherapy to subjects with moderately to severely active rheumatoid arthritis who have an inadequate response to methotrexate alone

Protocol Number: GLPG0634-CL-204

This study will be conducted in compliance with the clinical study protocol (and amendments), International Conference on Harmonization (ICH) guidelines for current Good Clinical Practice (GCP) and applicable regulatory requirements.

Sponsor Signatory

[redacted]

Signature

28 May 2014

Date

[redacted]

[redacted]

2 Study Personnel

Sponsor Personnel

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3 Synopsis

Protocol Number:	GLPG0634-CL-204
Title:	Randomized, double-blind, placebo-controlled, multicenter, phase IIb dose finding study of GLPG0634 administered for 24 weeks as monotherapy to subjects with moderately to severely active rheumatoid arthritis who have an inadequate response to methotrexate alone
Test Drug/Investigational Product:	GLPG0634
Number of Study Centers:	International multicenter. Approximately 90 sites.
Phase:	IIb
Objectives:	The primary objective is to evaluate the efficacy in terms of the percentage of subjects achieving an American College of Rheumatology (ACR) 20 response, of different doses of GLPG0634 given once daily compared with placebo at Week 12. The secondary objectives are to evaluate the efficacy in terms of the percentage of subjects achieving an ACR20, ACR50, ACR70, ACR-N, the disease activity score based on 28 joints (DAS28 [c-reactive protein {CRP}]), European League Against Rheumatism (EULAR) response and ACR/EULAR remission, clinical disease activity index (CDAI), and simplified disease activity index (SDAI) with different doses of GLPG0634 given once daily compared with placebo at every visit; to evaluate the safety and tolerability of different doses of GLPG0634 in comparison with placebo; to characterize the population pharmacokinetics (PK) and pharmacodynamics (PD) of GLPG0634 and its metabolite (G254445) in subjects with rheumatoid arthritis (RA) and investigate the relationship between exposure and efficacy/safety/PD; and to evaluate the effects of different doses of GLPG0634 administration on subjects' disability, fatigue, and quality of life.
Study Design:	This will be a double-blind, placebo-controlled, monotherapy study in subjects with moderately to severely active RA who have an inadequate response to methotrexate (MTX) (oral or parenteral). A total of 280 subjects will each be randomized to one of 3 doses of GLPG0634 or to placebo, given once daily (q.d.). Treatment duration will be 24 weeks.
Number of Subjects:	280 subjects to be randomized.

Treatment:	Twelve weeks of treatment with GLPG0634 50 mg, 100 mg, or 200 mg q.d. or placebo. [redacted] At Week 12, all subjects on placebo and the subjects on the 50 mg dose who have not achieved 20% improvement in swollen joint count (SJC66) and tender joint count (TJC68) will be assigned (automatically via interactive voice/web response system [IXRS]) to 100 mg q.d. in a blinded fashion and will continue treatment until Week 24. Subjects in the other groups will maintain their randomized treatment until Week 24. Subjects will be offered the possibility of entering a separate LongTerm Follow-up study (GLPG0634-CL-205) at the end of Week 24. This Long Term Follow-up study is subject to separate approval from Regulatory Agencies and Ethics Committees. Subjects who decline the LongTerm Follow-up study or those who discontinue early will have a Follow-up visit 7 to 10 calendar days after the last dose of study medication.
Study Duration:	Approximately 29 weeks: Up to 28 calendar days for Screening, up to 24 weeks of treatment and up to 10 calendar days for follow-up.
Study Population:	Main inclusion criteria: • male or female subjects who are ≥18 years of age on the day of signing informed consent, • have a diagnosis of RA since at least 6 months prior to Screening and meeting the 2010 ACR/EULAR criteria of RA and ACR functional class I-III, • have ≥6 swollen joints (from a 66-joint count) and ≥8 tender joints (from a 68-joint count) at Screening and at Baseline, • Screening serum c-reactive protein ≥ 0.7 x upper limit of laboratory normal range (ULN), • have shown an inadequate response in terms of either lack of efficacy or toxicity to MTX, • have agreed to be washed out from MTX for a period of at least 4 weeks before or during the Screening period. Main exclusion criteria: • current therapy with any non-biological disease modifying anti-rheumatic drug (DMARD), including oral or injectable gold, sulfasalazine, azathioprine, or D penicillamine within 4 weeks prior to Baseline, cyclosporine within 8 weeks prior to Baseline, and leflunomide within 3 months prior to Baseline or a minimum 4 weeks prior to Baseline if after 11 calendar days of standard cholestyramine therapy, with the exception of antimalarials, which must be at a stable dose for at least 12 weeks prior to Baseline,

Study Population (continued):	• current or previous RA treatment with a biologic DMARD, with the exception of biologic DMARDs: administered in a single clinical study setting, and; more than 6 months prior to Screening (12 months for rituximab or other B cell depleting agents), and; where the biologic DMARD was effective, and if discontinued, this should not be due to lack of efficacy, • previous treatment at any time with a cytotoxic agent, other than MTX, before Screening.
Primary Endpoint:	Percentage of subjects achieving an ACR20 response at Week 12
Secondary Endpoints:	Percentage of subjects achieving ACR20 response at Week 24, percentage of subjects achieving ACR50, ACR70, ACR-N, the DAS28(CRP), EULAR response and ACR/EULAR remission, CDAI, SDAI, the change from Baseline in Quality of Life (functional assessment of chronic illness therapy [FACIT] and Short Form-36 [SF-36]) scores at Weeks 1, 2, 4, 8 12, and 24, as appropriate.
Efficacy analysis:	The efficacy analysis will be performed on all subjects who used the study medication at least once and have post-Baseline efficacy data. Efficacy data (ACR20, ACR50, ACR70, ACR-N, EULAR response and ACR/EULAR remission, DAS28[CRP], components of the ACR, and DAS28, CDAI, and SDAI at each post-dosing visit) will be analyzed descriptively. Between-group comparisons will also be done for each dose group versus the placebo group. The effects of different doses of GLPG0634 administration on subject's disability, fatigue, and quality of life will also be evaluated. Hommel's closed-testing correction procedure will be applied to adjust for multiplicity. This study is not powered for any formal comparison among the GLPG0634 dose groups. Differences will be explored descriptively. No adjustment for multiplicity will be done for these exploratory differences.
Safety analysis:	Assessment of adverse events, laboratory parameters, vital signs, physical examination, and electrocardiograms. The safety analysis will be performed for all subjects who used the study medication at least once.
Pharmacokinetics:	Blood samples will be collected for analysis of GLPG0634 and G254445 plasma concentrations. Nonlinear mixed-effects modelling will be used to determine the population PK parameters as well as the impact of covariates influencing the PK in subjects with RA. The correlation between exposures and selected efficacy and safety endpoints will also be investigated.

Pharmacodynamics:	Serum will be collected for analysis of modulation of analytes (proteins such as cytokines, chemokines, and signaling molecules) previously identified as RA disease-linked, inflammation-related, and/or janus kinase (JAK) pathway-dependent biomarkers. In addition, analysis of the expression of genes sensitive to JAK pathways or disease-related, relative to housekeeping genes, will be evaluated in whole blood. In parallel, micro ribonucleic acid (miRNA) profiling may be performed on serum and whole blood to measure the level of miRNAs impacted by inflammation and/or JAK pathway disturbances. [redacted]

4 Table of Contents

5 List of Abbreviations and Definition of Terms

Abbreviations

ACR	=	American College of Rheumatology
AE	=	adverse event
ALT	=	alanine aminotransferase
AST	=	aspartate aminotransferase
ATP	=	adenosine triphosphate
AUC	=	area under the curve
$AUC_{0\text{-}24h}$	=	area under the curve from time 0 to 24 hours
b.i.d.	=	bis in die (twice daily)
BUN	=	blood urea nitrogen
CCP	=	cyclic citrullinated peptide
CD	=	Crohn's disease
CDAI	=	Clinical Disease Activity Index
CES	=	carboxylesterases
CFR	=	Code of Federal Regulations
CIA	=	collagen-induced arthritis
CMV	=	cytomegalovirus
CNS	=	central nervous system
CRP	=	c-reactive protein
CYP	=	cytochrome P450
DAS28	=	Disease Activity Score based on 28 joints
DMARD	=	disease-modifying antirheumatic drug
DSMB	=	Data Safety Monitoring Board
ECG	=	electrocardiogram
eCRF	=	electronic case report form
EDC	=	electronic data capture
EDV	=	early discontinuation visit
EULAR	=	European League Against Rheumatism
FACIT	=	Functional Assessment of Chronic Illness Therapy
FDA	=	Food and Drug Administration
FSH	=	follicle stimulating hormone
GCP	=	Good Clinical Practice
GGT	=	gamma glutamyltransferase
GH	=	general health
GI	=	gastrointestinal
HAQ-DI	=	Health Assessment Questionnaire–Disability Index
HCl	=	hydrochloride
HDL	=	high-density lipoprotein
hERG	=	human ether-a-go-go related gene
HIV	=	human immunodeficiency virus
HR	=	heart rate
IB	=	investigator's brochure
ICF	=	informed consent form
ICH	=	International Conference on Harmonization
IEC	=	Independent Ethics Committee
IL	=	interleukin
IRB	=	Institutional Review Board
ITT	=	intent-to-treat
IV	=	intravenous
IXRS	=	interactive voice/web response system

JAK	=	janus kinase
LDL	=	low density lipoprotein
LH	=	luteinizing hormone
[redacted]	=	[redacted]
miRNA	=	micro ribonucleic acid
MTX	=	methotrexate
NOAEL	=	no observed adverse effect level
NOEL	=	no-observed-effect-level
NONMEM	=	nonlinear mixed-effects modeling
NSAID	=	non-steroidal anti-inflammatory drug
NYHA	=	New York Heart Association
OATs	=	organic anion transporters
PD	=	pharmacodynamic
PK	=	pharmacokinetic
PRL	=	prolactin
q.d.	=	quaque die (once daily)
RA	=	rheumatoid arthritis
RBC	=	red blood cell
RF	=	rheumatoid factor
SAE	=	serious adverse event
SDAI	=	Simplified Disease Activity Index
SF-36	=	36-item Short Form Health Survey
SI	=	International System of Units
SJC	=	swollen joint count
SOP	=	Standard operating procedure
SQRT	=	square root
STAT	=	signal transducer and activation of transcription
SYK	=	spleen tyrosine kinase
$t_{1/2}$	=	terminal eliminationhalf-life
TB	=	tuberculosis
TJC	=	tender joint count
t_{max}	=	time to maximum plasma concentration
TNF	=	tumor necrosis factor
TYK	=	tyrosine kinase
ULN	=	upper limit of the normal (reference) laboratory range
VAS	=	visual analog scale
WBC	=	white blood cell

6 Introduction

6.1 Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory and joint degenerative disease that affects almost 1% of the adult population worldwide, with onset classically between the ages of 30 and 50 and a higher prevalence in women. The disease is characterized by pain, stiffness, and restricted mobility due to a persistent symmetrical inflammation of the synovial membrane of multiple joints that ultimately results in irreversible damage of the joint cartilage and bone.[1,2,3]

Development of the disease involves an inflammatory response of the synovial membrane that is accompanied by infiltration of a variety of immune cells, which leads to the build-up and maintenance of a cytokine network. One of the cytokines central to this network is tumor necrosis factor α (TNF-α), as is clearly demonstrated by the clinical success of the TNF-α blockers in treating RA. TNF-α and other proinflammatory cytokines contribute to cartilage and bone erosion by inducing release of degradative enzymes such as the matrix metalloproteinases and stimulating the release of receptor activator for nuclear factor κ B ligand which triggers differentiation of hematopoietic cells into bone-resorbing osteoclasts. When left untreated, the disease leads to significant disability associated with high economic costs.

In recent years, the therapeutic management of subjects with RA has seen a major revolution. Ten years ago, therapeutic approaches relied on disease-modifying antirheumatic drugs (DMARDs) such as methotrexate (MTX) and sulfasalazine that had only partial clinical benefit and were associated with significant toxicity. A considerable advance in the treatment of RA came from the introduction of the biological therapeutics like etanercept, infliximab, adalimumab, and, more recently, certolizumab pegol, which neutralize TNF-α. Spurred by their therapeutic success, more biologicals aimed at targeting other molecules involved in RA pathology are being developed. An anti-CD20 antibody (rituximab) directed at depleting B cells, a fusion protein targeting T-cell costimulation (abatacept), and tocilizumab, targeting the interleukin 6 receptor, have all recently been approved for the treatment of RA.[4]

Due to the high production costs, inconvenience of parenteral administration, increased risk for infections, and potential immunogenicity of biologicals, there is still a need for less expensive and orally active drugs. Hence, various companies are pursuing the development of small-molecule inhibitors, targeting disease-relevant signal transduction pathways, e.g., janus kinase (JAK) inhibitors (tofacitinib, Pfizer; INCB28050, Incyte; VX 509, Vertex) or the spleen tyrosine kinase (SYK) inhibitor R788 (Rigel).

In November 2012, tofacitinib (Xeljanz®) became the first JAK inhibitor to receive Food and Drug Administration (FDA) approval for the treatment of adult patients with RA. Tofacitinib is a small molecule suitable for oral administration, has strong binding affinity for JAK1 and JAK3, and weaker affinity for JAK2. The extensive pre-clinical and phase I, II, and III clinical development programs demonstrated its mechanisms of action via antiinflammatory and immunosuppressive effects. The drug proved to be efficacious in treating the signs and symptoms of RA and was well tolerated. Overall, the side-effects and risk profiles of tofacitinib are similar to those of several conventional antirheumatic agents with cytopaenias, elevated levels of liver function enzymes, increased level of low-density lipoprotein (LDL), high density lipoprotein (HDL) cholesterol[5], and small increased risk for infections including serious and opportunistic infections seen during the studies. INCB28050, a molecule with strong binding affinity for JAK1 and 2, has been through extensive phase I and II testing and currently undergoing large scale phase III studies. In phase II clinical studies, VX-509

specifically targeted JAK3. Both these molecules have demonstrated efficacy roughly similar to tofacitinib with an equally manageable side-effect profile.

6.2 Background on GLPG0634

Janus kinases are intracellular cytoplasmic tyrosine kinases (TYKs) that transduce cytokine signaling from membrane receptors to the nucleus of cells. JAK inhibitors block the signaling of various cytokines, growth factors and hormones, including the pro-inflammatory cytokine interleukin (IL)-6. Four different types of JAKs are known which (co-)interact with different sets of membrane receptors: JAK1, JAK2, JAK3 and TYK2. Inhibition of JAKs is a promising therapeutic option for a range of inflammatory conditions including RA and Crohn's disease (CD).

GLPG0634 is a potent and selective inhibitor of JAK1. The compound is currently in phase II development for RA and CD and has shown good preliminary efficacy in RA patients. No typical JAK2 side effects such as anemia were observed in clinical studies. The anticipated therapeutic daily dose range is 50 to 200 mg.

GLPG0634 is metabolized to form one major active metabolite, G254445. Though the potency of this metabolite is lower than the parent molecule, the overall exposure and peak plasma concentration in humans is higher. As a consequence, dedicated pharmacology and toxicology studies have been performed with G254445. Results from pharmacodynamics (PD) testing in healthy volunteers suggest that the clinical activity of GLPG0634 could result from the combination of the parent molecule and the metabolite.

More information on the study drug along with references to support the cited data are presented in the Investigator's Brochure (IB).[6] A summary is provided hereafter.

6.3 Background – Pre-clinical Studies

6.3.1 Physical, Chemical, and Pharmaceutical Properties and Formulations

The chemical name of GLPG0634 is N-(5-(4-((1,1-dioxidothiomorpholin-4-yl)methyl)phenyl)-[1,2,4]triazole[1,5-a]pyridin-2-yl)cyclopropanecarboxamide hydrochloride trihydrate.

Two clinical formulations with various strengths are currently available: an oral capsule (10-100 mg per capsule) filled with the hydrochloride (HCl) salt of GLPG0634; and a film-coated tablet (25-100 mg per tablet) of the HCl salt of GLPG0634.

6.3.2 Nonclinical Pharmacology

6.3.2.1 Primary and Secondary Pharmacology

GLPG0634 is an adenosine triphosphate (ATP)-competitive inhibitor of JAK1. It is highly selective for inhibition of JAK1 among 451 unique kinase gene products tested *in vitro*. In cellular assays, it inhibits biological processes involving JAK1 from 179 nM onwards, with a 30-fold selectivity over JAK2 in human whole blood. A high potency is observed in the rat collagen-induced arthritis (CIA) model.

Metabolite G254445 exhibits a similar JAK1 selectivity profile while being approximately 10-fold less potent as compared to parent GLPG0634, *in vitro*. In the rat CIA model, while being less potent than the parent molecule, G254445 displays a good curative effect against established arthritis.

6.3.2.2 Safety Pharmacology

[redacted]

6.3.3 Nonclinical Pharmacokinetics and Product Metabolism

[redacted]

6.3.4 Toxicology

[redacted]

6.3.4.1 General Toxicology

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

6.3.4.2 Reproductive Toxicology

[redacted]

[redacted]

6.4 Background - Preliminary Clinical Data

[redacted]

[redacted]

[redacted]

[redacted]

6.5 Clinical Risks/Benefits

JAK/signal transducer and activation of transcription (STAT) signaling pathways are ubiquitous in humans and animals, and are activated by cytokines, growth factors and hormones. RA is associated with the overproduction of IL-6, IL-12, IL-15, IL-23, granulocyte-macrophage colony stimulating factor and interferons. Targeting selected cytokine signaling via JAK/STAT pathway is therefore an effective approach to down regulate immune inflammatory reaction and represents a novel therapeutic option for the treatment of RA.

GLPG0634 is a selective JAK1 inhibitor with a 30-fold selectivity for inhibition of JAK1 over JAK2 *in vitro* human whole blood assays. Tofacitinib (former CP-690,550, the first JAK inhibitor that was studied in RA patients) on the other hand inhibits JAK1, JAK2, and JAK3 *in vitro*, with functional cellular specificity for JAK1 and JAK3 over JAK2 (pan-JAK inhibitor). The relative contribution of the different JAKs (JAK1, JAK3) in RA and the utility of selective blockade remain to be determined.

Major side effects of tofacitinib include serious infections, (bacterial, mycobacterial, fungal and viral), GI perforations, lymphoma and other malignancies and change in various laboratory parameters (including hematology parameters, liver enzymes, lipids and creatinine). It is possible that immunosuppressive effects of a JAK1 inhibitor may be enhanced by inhibition of JAK3, which is not a target for GLPG0634. This higher selectivity of GLPG0634 for JAK1 is expected to favor better tolerability while maintaining good efficacy in treating signs and symptoms of active RA.

Clinical benefit

[redacted]

Pre-clinical safety

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Clinical safety

[redacted]

[redacted]

[redacted]

[redacted]

Risk mitigation

In the forthcoming study patient risk will be minimized by implementing conservative eligibility criteria. Subjects with increased risk for GI perforations and lymphoproliferative disorders are excluded from the study. Any potential negative effects of GLPG0634 on hematological, clinical chemistry and hormonal parameters will be carefully assessed through regular physical assessments and laboratory monitoring that will happen at each and every visit. Individual stopping criteria have been generated by Galapagos and these provide guidance to the investigators throughout the study. Subjects will also be strictly monitored for occurrence of infections in the course of the study, while subjects at risk of severe infections (including subjects who have recently required parenteral antibiotics or recent infection with herpes zoster), tuberculosis, human immunodeficiency virus (HIV) positive subjects or hepatitis B or C subjects are excluded from enrolment. Special attention to the male reproductive system is applied throughout the study with hormones (testosterone, FSH, LH, PRL and inhibin B) being carefully monitored. An independent Data Safety Monitoring Board (DSMB) will regularly review safety data.

Overall benefit/risk conclusions

Galapagos believes that taking into account the benefits demonstrated during the clinical development of GLPG0634 and the potential risks associated with selective JAK1 inhibition and by providing an appropriate study eligibility criteria and monitoring strategy, the overall risk/benefit ratio of the compound remains favorable.

6.6 Rationale for the Study

Over the last decade changes in RA treatment strategies, accompanied by advances in drug development and the addition of targeted biological therapies, have greatly improved the outcomes for patients with RA. Despite these developments, therapeutic challenges have remained since current conventional and biological DMARDs sometimes fail or produce only partial response. Therefore there is still a need for orally administered novel therapies with a different mechanism of action that can effectively modify the disease course and that are safe and well tolerated.

GLPG0634 is a small molecule for oral daily administration that has shown promising results as a potentially safe and effective RA treatment. Study GLPG0634-CL-204 is an exploratory phase IIb dose-finding study to compare 3 doses (50 mg, 100 mg and 200 mg) of GLPG0634 versus placebo to be administered daily for 24 weeks in subjects with established RA, who have moderately to severely active disease despite MTX treatment. The aims of the current study are to evaluate the efficacy of varying doses of GLPG0634 as monotherapy, to identify the minimally and optimally effective dose, and to assess the safety and tolerability, as well as to describe the PK and PD parameters of the compound in this subject population.

Many biologic therapies are routinely administered in combination with nonbiologic DMARDS, especially MTX. MTX has a known side-effect profile and is not universally well tolerated. It is thought that for JAK inhibitors, 24-week treatment duration as monotherapy agents allows sufficient time for improvement in manifestations of active disease to be

demonstrated and confirms that clinical benefit is sustained over time. Limited use of placebo in the clinical studies has remained important, especially to characterize placebo response and to prove efficacy of the study drug. Withholding subjects with sub-optimally treated disease from more effective treatments for a maximum of 12 weeks is considered clinically and ethically acceptable.

The ACR criteria for 20%, 50%, and 70% improvement in disease activity (ACR20, ACR50, and ACR70) responses and the Disease Activity Score based on 28 joints (DAS28) are considered reliable measures of response to treatment and disease activity, respectively. Comparison between the treatment arms of the proportion of subjects achieving an ACR20 response at Week 12, which is the study's primary efficacy endpoint, allows for straightforward interpretation of a positive clinically meaningful result and has been shown to achieve high discriminatory capacity, and it is therefore considered an adequate primary endpoint for dose-finding studies. The evaluation of ACR50 and ACR70 responses (secondary endpoints) further allows for a preliminary assessment of the study drug as a potentially effective treatment for RA and will provide useful information for planning and adequately sizing future confirmatory phase III clinical studies.

Evaluation of continuous outcome measures of DAS28 and ACR-N as secondary endpoints enables the demonstration of improvement and magnitudes of benefit for study subjects. The European League Against Rheumatism (EULAR) response criteria classify subjects as non-, moderate-, or good responders, depending on the extent of change and the level of disease activity reached. These criteria are useful when describing clinically meaningful therapeutic targets. The Clinical Diagnostic Activity Index (CDAI) and the Simplified Diagnostic Activity Index (SDAI) are simple formulae that were developed primarily for use in clinical practice, but have been widely used in clinical studies to demonstrate the impact of a study drug on controlling disease activity. Assessing quality of life (measured by Functional Assessment of Chronic Illness Therapy [FACIT] and the 36-item Short Form Health Survey [SF-36]) at Baseline and during the course of study treatment provides further insight into the effects on modifying disease course and its impact on everyday life.

6.7 Rationale of Choice of the Dose and Dosing Interval

For the current study, enrolled subjects will be randomized to receive 3 different daily doses of GLPG0634 (50 mg, 100 mg or 200 mg) or placebo as monotherapy. [redacted]

The choice for the maximum (200 mg [redacted]) and minimum (50 mg) daily doses of GLPG0634 for the current study is based on efficacy, tolerability and safety data derived from 3 completed phase I studies and 2 completed phase IIa studies. [redacted]

[redacted]

[redacted]

[redacted]

In addition, information obtained from 2 modeling exercises was used. A model-based meta-analysis of comparative effectiveness (ACR20/50/70) of JAK inhibitors on RA patients included GLPG0634 data and publically available data on other JAK inhibitors (16 trials, 5,477 patients) was used. In addition, results from PK/PD modeling of biomarker response (signal transducer and activator of transcription 1 inhibition) relating to GLPG0634 and G25445 exposures to assess the magnitude of inhibition at the selected doses was utilized.

Model-based meta-analysis supported the conclusion that a daily dose of 50 mg should demonstrate clinical efficacy. In addition, results from modeling of biomarker response revealed that relevant JAK1 inhibition should be observed from the 50 mg daily dose upward.

In addition, the 3 selected daily dose levels of 50 mg, 100 mg and 200 mg (increase of 2-fold increments between the doses) would enable sufficient exposure variability to distinguish efficacy differences between the treatment groups.

Two JAK inhibitors with short $t_{1/2}$ (tofacitinib, Pfizer; baricitinib Incyte/Eli Lilly) show good activity under q.d. dosing regimens. GLPG0634 with an apparent $t_{1/2}$ of 5 to 11 hours has the same potential to be active as a once daily dosing regimen, as confirmed by the high-level efficacy observed at different dose levels in the proof-of-concept phase IIa studies in subjects with RA.

7 Study Objectives

7.1 Primary Objective

The primary objective of the study is to evaluate the efficacy in terms of the percentage of subjects achieving an ACR20 response, of different doses of GLPG0634 given once daily compared with placebo at Week 12.

7.2 Secondary Objectives

The secondary objectives of the study are:

- To evaluate the efficacy in terms of the percentage of subjects achieving an ACR20, ACR50, ACR70, ACR-N, DAS28(CRP), EULAR response and ACR/EULAR remission, CDAI, and SDAI with different doses of GLPG0634 given once daily compared with placebo at every visit.
- To evaluate the safety and tolerability of different doses of GLPG0634 in comparison with placebo.
- To characterize the population PK and PD of GLPG0634 and its metabolite (G254445) in subjects with rheumatoid arthritis and investigate the relationship between exposure and efficacy/safety/PD.
- To evaluate the effects of different doses of GLPG0634 administration on subjects' disability, fatigue, and quality of life.

8 Investigational Plan

8.1 Overall Study Design and Plan

This is a multicenter phase IIb, double-blind, placebo-controlled, monotherapy study in subjects with moderately to severely active RA who have an inadequate response to MTX alone. A total of 280 subjects will be randomized to one of 3 q.d. dose regimens of GLPG0634 (50 mg q.d., 100 mg q.d., 200 mg q.d.) or to placebo. [redacted] Treatment duration will be 24 weeks. At Week 12, all subjects on placebo and the subjects on the 50 mg dose who have not achieved a 20% improvement in swollen joint count (SJC66) and tender joint count (TJC68) will be assigned (automatically via interactive voice/web response system [IXRS]) to 100 mg q.d. in a blinded fashion and will continue the study until Week 24. Subjects in the other groups will maintain their randomized treatment until Week 24.

To enhance the safety and integrity of the study data a DSMB consisting of independent experts will be convened to periodically review the accumulating safety data for the study.

There will be an unblinded interim analysis after all subjects have completed Week 12. This will be done by an independent statistician so that the regular study team will remain blinded. The interim analysis is intended to support preliminary dose selection for the phase III development program.

At completion of the 24-week treatment period, subjects will be offered the option to enter a Long Term Follow-up study (GLPG0634-CL-205). This Long Term Follow-up study is subject to separate approval from Regulatory Agencies and Ethics Committees.

Subjects participating in the study will be requested to attend a total of 11 visits throughout the study: Screening visit (up to 28 calendar days before Baseline visit), Baseline visit, Week 1 visit, Week 2 visit, Week 4 visit, Week 8 visit, Week 12 visit, Week 16 visit, Week 20 visit, Week 24 visit, and for the subjects not entering the Long Term Follow-up study (GLPG0634-CL-205), a Follow-up visit 7 to 10 calendar days after end of study treatment.

Consequently, each subject will remain in the study for approximately 29 weeks (from Screening visit to Follow-up visit).

A diagram of the study design can be found below:

Week 1 – 12	**Week 13 – 24**
Randomized to placebo q.d.	All **assigned** to 100 mg q.d.
Randomized to 50 mg q.d.	Responders **remain** on 50 mg q.d.
	Nonresponders **assigned** to 100 mg q.d.
Randomized to 100 mg q.d.	**Remain** on 100 mg q.d.
Randomized to 200 mg q.d.*	**Remain** on 200 mg q.d.*

[redacted]

8.2 Discussion of Study Design

The discussion of study design is presented in Section 6.7.

8.3 Selection of Study Population

8.3.1 Number of Planned Subjects

Sufficient subjects will be screened to ensure that 280 subjects will be randomized to one of the 3 treatment arms with GLPG0634 or placebo. Details of the statistical considerations for the number of subjects are presented in Section 8.8.2.

8.3.2 Inclusion Criteria

To be eligible for study entry subjects must fulfil all of the following criteria:

1. Male or female subjects who are ≥18 years of age on the day of signing informed consent.
2. Diagnosis of RA since at least 6 months prior to Screening and meeting the 2010 ACR/EULAR criteria of RA and ACR functional class I-III.
3. Have ≥6 swollen joints (from a 66-joint count) and ≥8 tender joints (from a 68-joint count) at Screening and Baseline.
4. Screening serum CRP ≥ 0.7 x upper limit of the normal (reference) laboratory range (ULN).
5. Have shown an inadequate response in terms of either lack of efficacy or toxicity to MTX.
6. Have agreed to be washed out from MTX for a period of at least 4 weeks before or during the Screening period.
7. If taking oral steroids, these should be at a dose ≤10 mg/day of prednisone or prednisone equivalent and stable for at least 4 weeks prior to Baseline.
8. If taking non-steroidal anti-inflammatory drugs (NSAIDs), these must be at a stable dose for at least 2 weeks prior to Baseline.
9. The results of the following laboratory tests performed at the central laboratory at Screening must be within the limits specified below:
   a) Hemoglobin ≥10 g/dL (International System of Units [SI]: ≥100 g/L);
   b) WBCs ≥3.0 x 10^3 cells/mm^3 (SI: ≥3.0 x 10^9 cells/L);
   c) Neutrophils ≥2.0 x 10^3 cells/mm^3 (SI: ≥2.0 x 10^9 cells/L);
   d) Lymphocytes ≥1.0 x 10^3 cells/mm^3 (SI: ≥1.0 x 10^9 cells/L);
   e) Platelets ≥100 x 10^3 cells/mm^3 (SI: ≥100 x 10^9 cells/L);
   f) Serum ALT and aspartate aminotransferase (AST) ≤1.5 x ULN;
   g) Total bilirubin level ≤1.25 x ULN;
   h) Alkaline phosphatase ≤1.5ULN;
   i) Lipase ≤1.5 x ULN and amylase ≤1.5 x ULN;
   j) Creatinine clearance >60 mL/min. Creatinine clearance will be calculated using the Cockroft-Gault formula.
10. Female subjects must have a negative pregnancy test unless they are surgically sterile or have been post-menopausal for at least one year (12 consecutive months without menses); in case of doubt a determination of serum FSH can be done with FSH levels above 35 mIU/mL being confirmative for menopause.

11. Women of childbearing potential must use a highly effective method of birth control and agree to continue its use during the study and for at least 12 weeks after the last dose of study medication. Highly effective methods of birth control include implantable methods, intrauterine devices, tubal ligation (if performed more than one year before Screening), and double barrier contraception. In case an oral, patch or injectable contraceptive method is used, this should be done together with a male partner using a condom (addition of spermicide jelly is advisable). In the case of a vasectomized male partner the procedure must have been performed at least 12 weeks prior to screening and an absence of sperm in the ejaculate have been recorded in the medical documentation prior to screening. Total sexual abstinence may be considered acceptable at the discretion of the investigator.
12. Sexually active men must agree to use a highly effective method of contraception (double barrier) during the study and continue its use for at least 12 weeks after the last dose of study medication. Vasectomized males do not need to use additional forms of contraception providing that the procedure was performed at least 12 weeks prior to screening and an absence of sperm in the ejaculate have been documented prior to screening. Total sexual abstinence may be considered acceptable at the discretion of the investigator.
13. Able and willing to sign the informed consent as approved by the Independent Ethics Committee (IEC)/Institutional Review Board (IRB), prior to Screening evaluations and agree to the schedule of assessments.
14. Judged to be in good health, except for their RA, as determined by the investigator based upon the results of medical history, laboratory profile, physical examination, chest X-ray, and a 12-lead ECG performed during Screening.

8.3.3 Exclusion Criteria

Subjects will be excluded from the study if one or more of the following statements are applicable:

1. Current therapy with any non-biological DMARD, including oral or injectable gold, sulfasalazine, azathioprine, or D penicillamine within 4 weeks prior to Baseline, cyclosporine within 8 weeks prior to Baseline, and leflunomide within 3 months prior to Baseline or a minimum 4 weeks prior to Baseline if after 11 calendar days of standard cholestyramine therapy, with the exception of antimalarials, which must be at a stable dose for at least 12 weeks prior to Baseline.
2. Current or previous RA treatment with a biologic DMARD, with the exception of biologic DMARDs:
    - administered in a single clinical study setting, and;
    - more than 6 months prior to Screening (12 months for rituximab or other B-cell depleting agents), and;
    - where the biologic DMARD was effective, and if discontinued, this should not be due to lack of efficacy.
3. Previous treatment at any time with a cytotoxic agent, other than MTX, before Screening. These agents include, but are not limited to chlorambucil, cyclophosphamide, nitrogen mustard, or other alkylating agents.
4. Previous use of JAK inhibitors.
5. Receipt of an intra-articular or parenteral corticosteroid injection within 4 weeks prior to Screening.
6. Known hypersensitivity to study medication ingredients or a significant allergic reaction to any drug as determined by the investigator, such as anaphylaxis requiring hospitalization.

7. Positive serology for HIV 1 or 2 or hepatitis B or C or any history of hepatitis from any cause with the exception of hepatitis A.
8. Immunocompromised subjects who in the opinion of the investigator are at an unacceptable risk for participating in the study.
9. Previous history of symptomatic herpes zoster or herpes simplex infection within 12 weeks prior to Screening or have a history of disseminated/complicated herpes zoster infection (multi-dermatomal involvement, ophthalmic zoster CNS involvement or postherpetic neuralgia).
10. Known active infection of any kind (excluding fungal infection of nail beds), or any major episode of infection requiring hospitalization or treatment with parenteral (intramuscular or IV) anti-infectives (antibiotics, antiviral, anti-fungals or anti-parasitic agents) within 4 weeks of the Screening Visit or completion of oral anti-infectives within 2 weeks of the Screening Visit.
11. Currently on any therapy for chronic infection (such as pneumocystis, cytomegalovirus (CMV), herpes simplex, herpes zoster and atypical mycobacteria).
12. History of any inflammatory rheumatological disorder other than RA except secondary Sjögren Syndrome.
13. Any surgical procedure, including bone/joint surgery/synovectomy (including joint fusion or replacement) within 24 weeks prior to the Screening Visit.
14. History of moderate to severe congestive heart failure (New York Heart Association [NYHA] class III or IV), recent (within 24 weeks prior to study entry) cerebrovascular accident and any other condition that in the opinion of the investigator, would put the subject at risk by participation in the study.
15. History or current symptoms of GI tract ulceration and/or diverticulitis.
16. History of malignancy within the past 5 years (except for basal cell carcinoma of the skin or cervical carcinoma *in situ* that has been treated with no evidence of recurrence).
17. History of lymphoproliferative disease; or signs and symptoms suggestive of possible lymphoproliferative disease including lymphadenopathy or splenomegaly
18. History of active or latent tuberculosis (TB) infection as determined by either:
    a) positive QuantiFERON-TB Gold test result OR
    b) chest radiograph (both posterior-anterior and lateral views), taken within 3 months prior to Screening and read by a qualified radiologist, with evidence of current active TB or old inactive TB symptoms of clinically significant illness in the 3 months before the initial study medication administration.
19. History of invasive infection (e.g., listeriosis and histoplasmosis).
20. Treatment with any drug known to have a well-defined potential for toxicity to a major organ in the last 3 months preceding the initial study drug administration.
21. Administration of a live vaccine within 90 calendar days or an attenuated vaccine within 30 calendar days prior to the initial study medication administration.
22. Participation in any investigational drug/device clinical study within 4 weeks prior to Screening.
23. History within the previous 2 years or current evidence of drug or alcohol abuse.
24. If applicable to national or local legislation: history of being admitted to an institution under an administrative or court order.
25. Breastfeeding during the study.
26. Any condition or circumstances that, in the opinion of the investigator, may make a subject unlikely or unable to complete the study or comply with study procedures and requirements.
27. Significant blood loss (including blood donation [> 500 mL]) or a transfusion of any blood product within 12 weeks prior to the initial study medication administration.

8.3.4 Removal of Subjects from Therapy or Assessments

Subjects may stop study medication for any of the following reasons:

- Subject request.
- Use of nonpermitted concurrent therapy.
- Noncompliance with the study medication (see Section 8.5.9).
- Noncompliance with the study procedures (see Section 8.5.9 and Section 8.6).
- Lost to follow-up.
- Occurrence of AEs not compatible with the continuation of subject participation in the study, in the investigator's opinion. This also includes any clinically significant laboratory results, ECGs, and vital signs.
- Investigator request.
- Sponsor request.
- Treatment failure deemed by the investigator as lack of improvement or worsening of the disease symptoms or occurrence of intolerable AEs.

Treatment with GLPG0634 will be discontinued and the patient withdrawn from this study for:

- Serious infections (those requiring parenteral antimicrobial therapy or hospitalization).
- Any opportunistic infections.
- Complicated herpes zoster infection (multi-dermatomal, disseminated, ophthalmic or CNS involvement).
- Two sequential total white cell counts <2000 cells/mm^3 (SI: <2.0 x 10^9 cells/L).
- Two sequential neutrophil counts <1000 neutrophils/mm^3 (SI: <1.0 x 10^9 cells/L).
- Two sequential lymphocyte counts <750 lymphocytes/mm^3 (SI: <0.75 x 10^9 cells/L).
- Two sequential hemoglobin <8.0 g/dL (SI: <80 g/L).
- Two sequential platelet counts <75,000 platelets/mm^3 (SI: <75.0 x 10^9 cells/L).
- Two sequential AST or ALT elevations >3 times the upper limit of normal with at least one total Bilirubin value >2 times the upper limit of normal[1].
- Two sequential AST or ALT elevations >3 times the upper limit of normal accompanied by symptoms consistent with hepatic injury[1].
- Two sequential AST or ALT elevations >3 times the upper limit of normal accompanied by elevated INR.
- Two sequential AST or ALT elevations >5 times the upper limit of normal, regardless of total Bilirubin or accompanying symptoms[1].
- Two sequential increases in serum creatinine >50% over the average of screening and baseline values[2].
- Two sequential decreases from the baseline of inhibin B by 50% or Testosterone by 50% with concurrent increases in FSH or LH respectively.[3]

<u>After becoming aware of any of the above described abnormal laboratory changes occurring at any one time, an unscheduled visit (i.e. second sequential) must occur to retest within 3 to 5 days</u>. [1] In each case, there is a need for additional investigations, such as review of ethanol, recreational drug and dietary supplement consumption; testing for acute hepatitis A, B or C infection and biliary tract imaging should be promptly discussed with the Study Medical Monitor.

[2] At the time of study completion or discontinuation, if a patient should exhibit elevations in serum creatinine ≥33% above the average of screening and baseline values, they should be re-tested every 1 to 2 weeks until the serum creatinine elevation is fully reversed to within 10% of the average of screening and baseline values.

[3] In each case, hormones in male subjects should be monitored monthly and if no positive dynamics is seen after 3 months from stopping GLPG0634, referral to an andrologist should be considered.

Subjects who stop study medication for any reason will not be replaced. Subjects withdrawing from the study will be encouraged to complete the same final evaluations as subjects completing the study according to the protocol, particularly safety evaluations in the subject's interest, so that data can be recorded in the same way as for subjects who completed the study. Subjects are free to withdraw from the study at any time without providing reason(s) for withdrawal and without prejudice to further treatment. The reason(s) for withdrawal will be documented in the electronic case report form (eCRF).

Reasonable efforts will be made to contact subjects who are lost to follow-up. These must be documented in the subject's file.

The sponsor has the right to terminate the study at any time in case of safety concerns or if special circumstances concerning the study medication or the company itself occur, making further treatment of subjects impossible. In this event, the investigator(s) and relevant authorities will be informed of the reason for study termination.

8.4 Data Safety Monitoring Board

To enhance the safety and integrity of the study data a DSMB consisting of independent experts will be convened to periodically review the accumulating safety data for the study. The first safety review by the DSMB will occur after the first 25% of subjects have been randomized and received study drug to review accumulating safety data and to provide a recommendation on study continuation or termination early in case there is a concern regarding safety. From here on the DSMB will be convened every 3 months for periodic safety reviews. The specific responsibilities and composition of the DSMB are outlined in a separate document, the DSMB Charter. Also the details of outputs provided for the meetings are referenced in this separate DSMB Charter.

8.5 Investigational Products

8.5.1 Investigational Products Administered

The study medication will consist of 25, 50 and 100 mg capsules of GLPG0634 for oral administration or matching placebo.

The following doses will be evaluated:

- GLPG0634 50 mg q.d.: 2 capsules of 25 mg GLPG0634 in the morning.
- GLPG0634 100 mg q.d.: 2 capsules of 50 mg GLPG0634 in the morning.
- GLPG0634 200 mg q.d.: 2 capsules of 100 mg GLPG0634 in the morning.
- Placebo: 2 placebo capsules in the morning.

[redacted]

At Week 12, all subjects on placebo and the subjects on the 50 mg dose who have not achieved a 20% improvement in SJC66 and TJC68 will be assigned (automatically via IXRS) to 100 mg q.d. in a blinded fashion and will continue the study until Week 24. Subjects in the other groups will maintain their randomized treatment until Week 24.

8.5.2 Identity of Investigational Products

The GLPG0634 study medication will be presented as a Swedish Orange oral hard gelatin capsule (size 0) containing GLPG0634 as hydrochloride salt equivalent to 25 mg, 50 mg, or 100 mg of GLPG0634, croscarmellose sodium, colloidal anhydrous silica, microcrystalline cellulose, and magnesium stearate.

The placebo study medication will be presented as a Swedish Orange oral hard gelatin capsule (size 0) containing croscarmellose sodium, colloidal anhydrous silica, microcrystalline cellulose, and magnesium stearate.

The GLPG0634 and placebo study medications will be identical in appearance and taste.

8.5.3 Packaging, Labelling and Distribution

A contract drug supplier (Belgium) will provide the GLPG0634 and placebo capsules.

The study packaging will be performed by , Belgium.

All manufacturing, packaging and labeling operations will be performed according to Good Manufacturing Practice for Medicinal Products and the relevant regulatory requirements.

The study medication is to be dispensed according to the protocol. The distribution will only occur after the required documentation including study approval by Competent Authorities and the IECs/IRBs, is obtained.

Sites are to store their study medication supplies in a secure area at 2°C to 8°C (36°F-46°F). Sites will be required to keep a temperature log, completed each working day, to establish a record of compliance with these storage conditions. The investigator will instruct subjects on how the study medication should be stored after it is dispensed.

8.5.4 Method of Assigning Subjects to Treatment Groups

Subjects will be randomly allocated to treatment according to a prespecified randomization scheme prepared by an independent statistician within . Upon qualification for the study, subjects will be randomized using a computerized IXRS system (Belgium) to placebo or one of 3 doses of GLPG0634 (50 mg, 100 mg, and 200 mg) in an approximate 1:1:1:1 ratio, stratified by region and previous use of a biological DMARD during a single clinical study setting.

A total of 280 subjects will be randomized (N=70 for each treatment group).

For each subject at each visit, the clinic will contact the IXRS system for the appropriate kit number to be dispensed. The kit will contain the relevant study medication up until the next visit.

At Week 12, all subjects on placebo and the subjects on the 50 mg dose who have not achieved 20% improvement in SJC66 and TJC68 will be assigned (automatically via IXRS) to 100 mg q.d. in a blinded fashion and will continue the study until Week 24. Subjects in the other groups will maintain their randomized treatment until Week 24.

8.5.5 Selection of Doses in the Study

Details of the selection of doses in the study are presented in Section 6.7.

8.5.6 Selection and Timing of Dose for Each Subject

The study medication will be administered daily with a glass of water in the morning.

Each subject's dose will be selected by random allocation according to randomization procedures.

If a subject misses a dose (e.g., because he/she forgot to take the medication), he/she should take the missed dose within 5 hours after the planned intake time. If the study medication is not taken within 5 hours after the planned time, the missed dose should be skipped. For each dose taken, the number of capsules taken should be recorded on the subject's diary card. Additional to the number of capsules taken, the date and time of the very first intake, and for selected visits, the 2 most recent intakes prior to the visits will be recorded on the subject's diary card. During each visit, the investigator will record a summary of the study medication intake data in the eCRF.

Dose reduction during the study is not allowed. Instead, the subject should either temporarily stop all intake or permanently stop study medication. Every effort should be made to contact the medical monitor before stopping study medication (temporarily or permanently).

8.5.7 Blinding

This is a randomized, double-blind study. The subject, the investigator, the study coordinator, the sponsor, and the entire study processing team will remain blinded to treatment assignment. The blind can be broken only if the investigator deems it necessary for the safe treatment of a subject, and whenever possible the medical monitor and sponsor should be consulted before breaking the blind.

If the blind is broken for any reason during the course of the study, the moment on which the blind was broken and all other relevant information will be documented by the investigative site, [redacted], and other sponsor designees, as appropriate. The reason for breaking the blind will be indicated and justified in the source documentation and in the eCRF. The blind can be broken by the investigator via the IXRS system.

All subjects who are unblinded while on the study will be withdrawn at the moment of unblinding, with the reason for unblinding given as the reason for discontinuation from the study. If an AE leads to unblinding, the AE should be given as the reason for unblinding and the AE should also be recorded in the eCRF. All subjects who are unblinded should, where possible, complete the early discontinuation visit (EDV). Any AEs should be followed until resolution.

An unblinded interim analysis will be performed when all subjects have completed the Week 12 visit. Details are provided in Section 8.8.1.5.

8.5.8 Prior and Concomitant Therapy

Concomitant therapies taken for the long term treatment of preexisting conditions can continue during the study provided they are in accordance with the inclusion and exclusion criteria. It is preferred that these medications be stabilized and continued without variation of dose or regimen during the study.

In case new therapies need to be administered during the study, the risk/benefit to the subject should be carefully assessed and consideration given to the timing of any necessary introduction of new medications.

Permitted concomitant medications at Screening and during the study include:

- Antimalarials, which must be at a stable dose for at least 12 weeks prior to Baseline.
- NSAIDs, provided that the dose is stable for at least 2 weeks prior to Baseline and, if possible, is kept constant during the study;
- Oral steroids, provided that the dose is stable, is ≤10 mg/day prednisone or equivalent for at least 4 weeks prior to Baseline, and is kept stable for the study duration; and
- Analgesics, other than NSAIDs, up to the maximum recommended doses may be used for pain as required. However, subjects must not take analgesics within 24 hours before a visit where clinical efficacy assessments are performed and recorded.

Female subjects of childbearing potential will use highly effective birth-control methods as outlined in the inclusion criteria and agree to continue their use during the study and for at least 12 weeks after the last dose of study medication. The use of hormonal contraceptives will be recorded in the Concomitant Therapy section of the eCRF. Applicable procedures and treatment guidance based on package inserts will be respected.

Hormone replacement therapy will be allowed in post-menopausal women if ongoing at the time of Screening. The use of hormone replacement therapy will be recorded in the Concomitant Therapy section of the eCRF. Applicable procedures and treatment guidance based on package inserts will be respected.

Prohibited medication during the study include any non-biological DMARDS.

Current or previous RA treatment with a biologic DMARD is prohibited, with the exception of biologic DMARDs administered in a single clinical study setting more than 6 months prior to Screening (12 months for rituximab or other B-cell depleting agents), where the biologic DMARD was effective, and if discontinued, this should not be due to lack of efficacy.

Previous treatment at any time with a cytotoxic agent, other than MTX, before Screening, is prohibited. These agents include, but are not limited to chlorambucil, cyclophosphamide, nitrogen mustard, and other alkylating agents.

Previous use of JAK inhibitors is prohibited.

Receipt of an intra-articular or parenteral corticosteroid injection within 4 weeks prior to Screening is prohibited.

Vaccine Guidelines:

Vaccination with live components is prohibited during the study and for 6 weeks after the last dose of study drug. Also routine household contact with persons vaccinated with live vaccine components should be avoided. These vaccines include varicella, oral polio and inhaled flu vaccine. General guidelines suggest that exposure should be avoided following vaccination with these vaccines for the stated time period:

- Varicella or attenuated typhoid fever vaccination for 4 weeks following vaccination;
- Oral polio vaccination for 6 weeks following vaccination;
- Attenuated rotavirus vaccine for 10 calendar days following vaccination;
- Inhaled flu vaccine for 1 week following vaccination.

When inactivated flu vaccines are to be used during the study, it should be borne in mind that vaccination responses have not been studied during the administration of GLPG0634. Currently, there are no available data on continuous use of GLPG0634 and its impact on immune responses following vaccination.

8.5.9 Treatment Compliance and Drug Accountability

For each dose taken, the date, the time of intake, and the number of capsules taken should be recorded on the subject diary card.

The investigator or designated study personnel will maintain a log of all drug dispensed and returned. Drug supplies for each subject will be inventoried and accounted for throughout the study.

Subjects with a poor compliance (<80% or >120%) will be retained by the study site. If study drug compliance remains <80% or >120% between study visits, or if the subject missed more than 2 visits, the subject will be evaluated for potential discontinuation. Any discontinuation should be done in consultation with the Medical Monitor.

8.5.10 Subject Diary Card

Subjects will record any changes in concomitant illnesses, new AEs and any change in AEs or their concomitant medication in their diary card. AEs and changes in concomitant medication will be transcribed into the eCRF by the investigator. Details of dosing with study medication will be recorded in the subject diary and summarized in the eCRF by the investigator.

The subject diary card will be considered source information. The data from the subject diary card will not be entered into the study database.

8.6 Study Procedures

All planned study assessments are presented in the flow chart in Section 8.7.1.5.

8.6.1 Pre-treatment

Written informed consent will be obtained before any study-related procedures and/or assessments are performed.

8.6.1.1 Screening Period (Visit 1, Day -29 to Day -2)

- Each subject will receive a patient number by using the IXRS system.
- Each subject will be assessed for eligibility against the inclusion and exclusion criteria.
- Subjects taking MTX will be washed out over a 4-week period.
- The subject's full medical history, including concomitant illnesses/diseases and concomitant medications will be documented.
- Demographic data will be recorded.
- Baseline disease characteristics will be recorded.
- A physical examination will be performed, including body weight and height, and the results will be documented.
- Vital signs (blood pressure, heart rate [HR], and oral temperature) will be measured.
- TB test (QuantiFERON-TB Gold test) and chest X-ray will be performed (chest X-ray is to be performed only if not performed in the previous 3 months (results must be available at the site for any chest X-ray performed in the previous 3 months).
- Serology (including hepatitis B and C, HIV 1 and 2, rheumatoid factor [RF] and anti-cyclic citrullinated peptide [CCP] tests) will be performed on a sample collected at this visit.
- A 12-lead ECG will be performed.
- Hematology, clinical chemistry, and urinalysis tests (dipstick and microscopy) will be performed on samples collected at this visit. A serum pregnancy test will be performed on women of childbearing potential.
- Serum CRP will be measured.
- SJC66 and TJC68 evaluations will be performed.
- The subject will complete the Patient's Global Assessment of Disease Activity.

Note 1: Retesting during the Screening period is only allowed once for abnormal lab values except for positive QuantiFERON-TB Gold, Hepatitis B, Hepatitis C, HIV or pregnancy test in a female of childbearing potential AND only in case it is still possible to randomize the patient within the per protocol defined Screening period of 28 calendar days.

Note 2: Rescreening is only allowed in specific situations and after having obtained written sponsor approval.

8.6.1.2 Baseline Visit (Visit 2)

The Baseline visit (Visit 2) will take place 1 to 28 calendar days after the Screening visit (Visit 1).

- Visit 2 will take place when the laboratory test results from the Screening period are available.
- Each subject will be reassessed for eligibility against the inclusion and exclusion criteria.
- Any changes in concomitant diseases and illnesses since signing the informed consent form (ICF) will be documented as AEs.
- Changes in concomitant medication will be documented, and linked to AEs if relevant.
- Vital signs will be measured.
- A physical examination will be performed.
- Hematology, clinical chemistry, and urinalysis (dipstick and microscopy) tests will be performed on samples collected at this visit. A urine pregnancy test will be performed on females of childbearing potential.
- Blood samples for measurement of PD parameters will be collected.

- Serum CRP will be measured.
- SJC66 and TJC68 evaluations will be performed.
- Physician's and Patient's Global Assessments of Disease Activity will be completed.
- The subject will complete the Health Assessment Questionnaire – Disability Index (HAQ-DI).
- The subject will complete the FACIT fatigue scale and the SF-36 questionnaire.
- The subject will be randomly assigned to treatment (upon qualification for the study) using IXRS.
- A subject diary card will be dispensed.

When all the Baseline procedures have been performed and the investigator has confirmed the subject's eligibility for the study, the study medication will be dispensed to the subject according to the information provided using the IXRS system. The subject will start taking the study medication on the morning of Day 1, the day after the Baseline visit (Day -1).

8.6.2 Treatment Period

8.6.2.1 Week 1 (Visit 3)

The Week 1 visit (Visit 3) will take place on Day 8 ± 2 calendar days relative to the start of the study medication intake.

- Any remaining study medication as well as empty study medication containers will be returned to the investigator and an accountability check will be performed.
- Any AEs that have occurred since signing the ICF will be documented, and any changes in concomitant medication will be reported.
- Vital signs will be measured.
- Blood samples for measurement of PD parameters will be collected.
- The subject diary card will be collected, a summary will be recorded in the eCRF, and a new subject diary card will be dispensed.
- Serum CRP will be measured.
- SJC66 and TJC68 evaluations will be performed.
- Physician's and Patient's Global Assessments of Disease Activity will be completed.
- The subject will complete the HAQ-DI.
- Hematology, clinical chemistry, and urinalysis (dipstick and microscopy) tests will be performed on samples collected at this visit. A urine pregnancy test will be performed on females of childbearing potential.

When all of these procedures have been performed, the study medication will be dispensed according to the information provided using IXRS and all subsequent visits will be scheduled.

8.6.2.2 Week 2 (Visit 4)

The Week 2 visit (Visit 4) will take place on Day 15 ± 2 calendar days relative to the start of study medication intake.

- Any remaining study medication as well as empty study medication containers will be returned to the investigator and an accountability check will be performed.
- Any AEs that have occurred since signing the ICF will be documented and any changes in concomitant medication will be reported.
- Vital signs will be measured.

- The subject diary card will be collected. a summary will be recorded in the eCRF,and a new subject diary card will be dispensed.
- Serum CRP will be measured.
- SJC66 and TJC68 evaluations will be performed.
- Physician's and Patient's Global Assessments of Disease Activity will be completed.
- The subject will complete the HAQ-DI.
- Hematology, clinical chemistry, and urinalysis (dipstick and microscopy) tests will be performed on samples collected at this visit. A urine pregnancy test will be performed on females of childbearing potential.

When all of these procedures have been performed, the study medication will be dispensed according to the information provided using IXRS and the date of the next visit will be confirmed.

8.6.2.3 Week 4 (Visit 5)

The Week 4 visit (Visit 5) will take place on Day 29 ± 2 calendar days relative to the start of study medication intake.

- Any remaining study medication as well as empty study medication containers will be returned to the investigator, and an accountability check will be performed.
- Any AEs that have occurred since signing the ICF will be documented and any changes in concomitant medication reported.
- Vital signs will be measured.
- The subject diary card will be collected, a summary will be recorded in the eCRF,and a new subject diary card will be dispensed.
- Blood samples for measurement of PK and PD parameters will be collected.
- Serum CRP will be measured.
- SJC66 and TJC68 evaluations will be performed.
- Physician's and Patient's Global Assessments of Disease Activity will be completed.
- The subject will complete the HAQ-DI.
- The subject will complete the FACIT fatigue scale and SF-36 questionnaire.
- Hematology, clinical chemistry, and urinalysis (dipstick and microscopy) tests will be performed on samples collected at this visit. A urine pregnancy test will be performed on females of childbearing potential.

When all of these procedures have been performed, the study medication will be dispensed according to the information provided using IXRS and the date of the next visit will be confirmed.

8.6.2.4 Week 8 (Visit 6)

The Week 8 visit (Visit 6) will take place on Day 57 ± 2 calendar days relative to the start of study medication intake.

- Any remaining study medication as well as empty study medication containers will be returned to the investigator, and an accountability check will be performed.
- Any AEs that have occurred since signing the ICF will be documented, and any changes in concomitant medication will be reported.
- Vital signs will be measured.
- The subject diary card will be collected, a summary will be recorded in the eCRF, and a new subject diary card will be dispensed.

- Serum CRP will be measured.
- SJC66 and TJC68 evaluations will be performed.
- Physician's and Patient's Global Assessments of Disease Activity will be completed.
- The subject will complete the HAQ-DI.
- Hematology, clinical chemistry, and urinalysis (dipstick and microscopy) tests will be performed on samples collected at this visit. A urine pregnancy test will be performed on females of childbearing potential.

When all of these procedures have been performed, the study medication will be dispensed according to the information provided using IXRS and the date of the next visit will be confirmed.

8.6.2.5 Week 12 (Visit 7)

The Week 12 visit (Visit 7) will take place on Day 85 ± 2 calendar days relative to the start of study medication intake.

- Any remaining study medication as well as empty study medication containers will be returned to the investigator, and an accountability check will be performed.
- Any AEs that have occurred since signing the ICF will be documented and any changes in concomitant medication will be reported.
- Vital signs will be measured.
- A 12-lead ECG will be performed.
- A physical examination will be performed.
- The subject diary card will be collected, a summary will be recorded in the eCRF, and a new subject diary card will be dispensed.
- Blood samples for measurement of PK and PD parameters will be collected.
- Serum CRP will be measured.
- SJC66 and TJC68 evaluations will be performed.
- Physician's and Patient's Global Assessments of Disease Activity will be completed.
- The subject will complete the HAQ-DI.
- The subject will complete the FACIT fatigue scale and SF-36 questionnaire.
- Hematology, clinical chemistry, and urinalysis (dipstick and microscopy) tests will be performed on samples collected at this visit. A urine pregnancy test will be performed on females of childbearing potential.

At Visit 7, all subjects on placebo and the subjects on the 50 mg dose who have not achieved a 20% improvement in SJC66 and TJC68 will be assigned (automatically via IXRS) to 100 mg q.d. in a blinded fashion and will continue the study until Week 24. Subjects in the other groups will maintain their randomized treatment until Week 24.

When all of these procedures have been performed, the study medication will be dispensed according to the information provided using IXRS and the date of the next visit will be confirmed.

8.6.2.6 Week 16 (Visit 8)

The Week 16 visit (Visit 8) will take place on Day 113 ± 2 calendar days relative to the start of study medication intake.

- Any remaining study medication as well as empty study medication containers will be returned to the investigator, and an accountability check will be performed.

- Any AEs that have occurred since signing the ICF will be documented and any changes in concomitant medication will be reported.
- Vital signs will be measured.
- The subject diary card will be collected, a summary will be recorded in the eCRF, and a new subject diary card will be dispensed.
- Serum CRP will be measured.
- SJC66 and TJC68 evaluations will be performed.
- Physician's and Patient's Global Assessments of Disease Activity will be completed.
- The subject will complete the HAQ-DI.
- Hematology, clinical chemistry, and urinalysis (dipstick and microscopy) tests will be performed on samples collected at this visit. A urine pregnancy test will be performed on females of childbearing potential.

When all of these procedures have been performed, the study medication will be dispensed according to the information provided using IXRS and the date of the next visit will be confirmed.

8.6.2.7 Week 20 (Visit 9)

The Week 20 visit (Visit 9) will take place on Day 141 ± 2 calendar days relative to the start of study medication intake.

- Any remaining study medication as well as empty study medication containers will be returned to the investigator, and an accountability check will be performed.
- Any AEs that have occurred since signing the ICF will be documented and any changes in concomitant medication will be reported.
- Vital signs will be measured.
- The subject diary card will be collected, a summary will be recorded in the eCRF, and a new subject diary card will be dispensed.
- Serum CRP will be measured.
- SJC66 and TJC68 evaluations will be performed.
- Physician's and Patient's Global Assessments of Disease Activity will be completed.
- The subject will complete the HAQ-DI.
- Hematology, clinical chemistry, and urinalysis (dipstick and microscopy) tests will be performed on samples collected at this visit. A urine pregnancy test will be performed on females of childbearing potential.

When all of these procedures have been performed, the study medication will be dispensed according to the information provided using IXRS and the date of the next visit will be confirmed.

8.6.2.8 Week 24 (Visit 10) or Early Discontinuation Visit

The Week 24 visit (Visit 10) will take place on Day 169 ± 2 calendar days relative to the start of study medication intake. Subjects who have discontinued from the study early and subjects who attend the Week 24 visit will complete the following assessments. This visit needs to be entered in IXRS.

- Any remaining study medication as well as empty study medication containers will be returned to the investigator, and an accountability check will be performed.
- Any AEs that have occurred since signing the ICF will be documented and any changes in concomitant medication will be reported.

- Vital signs will be measured.
- A 12-lead ECG will be performed.
- A physical examination will be performed.
- The subject diary card will be collected and a summary will be recorded in the eCRF.
- Blood samples for measurement of PK and PD parameters will be collected.
- Serum CRP will be measured.
- SJC66 and TJC68 evaluations will be performed.
- Physician's and Patient's Global Assessments of Disease Activity will be completed.
- The subject will complete the HAQ-DI.
- The subject will complete the FACIT fatigue scale and SF-36 questionnaire.
- Hematology, clinical chemistry, and urinalysis (dipstick and microscopy) tests will be performed on samples collected at this visit. A serum pregnancy test will be performed on females of childbearing potential.

8.6.3 Follow-up (Visit 11)

A Follow-up visit (Visit 11) will be performed only for subjects discontinuing prematurely from the study and for subjects not entering the LongTerm Follow-up Study GLPG0634-CL-205. This will take place 7 to 10 calendar days after either the EDV or the Week 24 visit.

- Any AEs that have occurred since signing the ICF will be documented and any changes in concomitant medication will be reported.
- Vital signs will be measured.
- A 12-lead ECG will be performed.
- A physical examination will be performed.
- Hematology, clinical chemistry, and urinalysis (dipstick and microscopy) tests will be performed on samples collected at this visit. A urine pregnancy test will be performed on females of childbearing potential.

8.6.4 Duration of Treatment

Subjects participating in the study will be requested to attend a total of 11 visits throughout the study: Screening visit (up to 28 calendar days before Baseline visit), Baseline visit, Week 1 visit, Week 2 visit, Week 4 visit, Week 8 visit, Week 12 visit, Week 16 visit, Week 20 visit, Week 24 visit, and for the subjects not entering the Long Term Follow-up study (GLPG0634-CL-205), a Follow-up visit 7 to 10 calendar days after end of study treatment.

Consequently, each subject will remain in the study for approximately 29 weeks (from Screening visit to Follow-up visit). Treatment will last for 24 weeks.

8.7 Efficacy, Pharmacokinetics, Pharmacodynamics, and Safety Variables

The flow chart in Section 8.7.1.5 shows the planned study assessments.

8.7.1 Efficacy, Pharmacokinetics, Pharmacodynamics and Safety Measurements Assessed and Flow Chart

8.7.1.1 Efficacy Assessments

8.7.1.1.1 Evaluation of Disease Activity

Efficacy assessments will be carried out at Screening (joint counts and Patient's Global Assessment of Disease Activity only); Baseline (Day -1); Weeks 1, 2, 4, 8, 12, 16, 20, and 24; and the EDV (if applicable).

Each of 68 joints will be evaluated for tenderness, and each of 66 joints will be evaluated for swelling (Appendix 13.2).

A joint assessor with adequate training and experience in performing joint assessments will be designated at each study site to perform all joint assessments. The joint assessor should preferably be a rheumatologist; however, if a rheumatologist is not available, it should be a health care worker with at least one year's experience in performing joint assessments. The assessor should remain the same throughout the study per subject, as much as possible. It is required that the designated joint assessor identify an appropriate back-up assessor to provide coverage if the designated joint assessor is absent.

8.7.1.1.2 Patient's Global Assessment of Disease Activity

The Patient's Global Assessment of Disease Activity will be recorded on a 0 to 100 visual analog scale (VAS), with 0 indicating "very well" and 100 indicating "very poor" in answer to the question "Considering all the ways arthritis affects you, how well are you doing today?" (Appendix 13.3).

8.7.1.1.3 Physician's Global Assessment of Disease Activity

The Physician's Global Assessment of Disease Activity will be recorded on a 0 to 100 mm VAS, with 0 indicating "no disease activity" and 100 indicating "extreme disease activity". The evaluating physician and the subject must complete the global assessments independently of each other (Appendix 13.4).

8.7.1.1.4 Health Assessment Questionnaire - Disability Index (HAQ-DI)

The functional status of the subject will be assessed using the HAQ-DI. This 20-question instrument assesses the degree of difficulty a person has in accomplishing tasks in 8 domains (dressing, arising, eating, walking, hygiene, reaching, gripping, and errands/chores). Responses are scored on a 4-point Likert scale from 0, indicating no difficulty, to 3, indicating inability to perform a task in that area. The need for aids/devices or help from another person will also be recorded. The HAQ-DI total score ranges from 0 to 3 with higher scores indicating greater dysfunction (Appendix 13.5).

As part of the HAQ-DI, subjects will be asked to assess their average pain during the last week on a 0 to 100 mm VAS, with 0 indicating "no pain" and 100 indicating "severe pain". This assessment should be completed before the joint examination. This pain score will be used to drive the ACR20/50/70.

8.7.1.1.5 FACIT Fatigue Scale

The FACIT fatigue scale (version 4) measures an individual's level of fatigue during their usual daily activities over the past week. It consists of 13 questions with a 7-day recall period on a 5-point Likert scale, with 0 indicating "not at all" and 4 indicating "very much". The total score ranges from 0 to 52. The higher the score, the better the quality of life (Appendix 13.6).

8.7.1.1.6 36-Item Short-form Health Survey (SF-36)

The health–related quality of life of the subject will be assessed using the SF-36 (version 2) with a 4-week recall period. This consists of 36 questions belonging to 8 domains in 2 components:

- Physical well-being: 4 domains: physical functioning (10 items), role physical (4 items), bodily pain (2 items), and general health perceptions (5 items).
- Mental well-being: 4 domains: vitality (4 items), social functioning (2 items), role emotional (3 items), and mental health (5 items).

The remaining item (health transition) is not part of the above domains but is kept separately (Appendix 13.7).

These scales will be rescaled from 0 to 100 (converting the lowest possible score to 0 and the highest possible score to 100), with higher scores indicating a better quality of life.

8.7.1.2 Pharmacokinetic Assessments

One blood sample (2 mL) for analysis of GLPG0634 and its metabolite (G254445) in plasma will be collected at Weeks 4, 12, and 24 or the EDV, if applicable, by venipuncture (or indwelling cannula) in the forearm into tubes containing lithium heparin and will be immediately chilled (ice bath), processed, and frozen as plasma at -20°C (-4°F).

8.7.1.3 Pharmacodynamic Assessments

Blood samples for PD assessments will be collected in all subjects at Baseline (Day -1), Week 1, Week 4, Week 12 and Week 24 or the EDV, if applicable.

Two blood samples of 2.5 mL each will be collected in 2 PAX-gene tubes. Immediately after collection, the tubes will be gently inverted 8 to 10 times and stored at room temperature for a minimum of 2 hours and a maximum of 72 hours before freezing at -20°C (-4°F) for storage until further analysis (gene expression in circulating leukocytes and messenger ribonucleic acid as well as micro ribonucleic acid [miRNA] profiling).

Additionally, 1 blood sample of 8.5 mL will be collected in a SST tube. The sample will be allowed to clot in the tube for 30 minutes at room temperature, after which the tube will be centrifuged. Serum will be extracted, divided over 4 aliquots, and frozen at -80°C (-112°F) until further analysis (analytes and miRNA profiling).

8.7.1.4 Safety Assessments

8.7.1.4.1 Adverse Event Definitions and Reporting

8.7.1.4.1.1 Definitions

ICH and European guidance will be followed for AE reporting.

Adverse Event

An AE is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or noninvestigational) product. An AE does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or noninvestigational) product, whether or not related to that medicinal (investigational or noninvestigational) product.

This includes any occurrence that is new in onset or aggravated in intensity or frequency from the baseline condition (signing the ICF) or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Serious Adverse Event

A SAE is any untoward medical occurrence that at any dose meets any of the following conditions:

- results in death.
- is life-threatening: the subject is at risk of death at the time of the event. It does not refer to an event that hypothetically might cause death if it were more severe.
- requires inpatient hospitalization or prolongation of existing hospitalization.
- results in persistent or significant disability or incapacity.
- is a congenital anomaly or birth defect.
- is a medically significant event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definitions above.

Unexpected Adverse Event/Reference Safety Information

An AE is considered unexpected if the nature or intensity is not consistent with the applicable product reference safety information. For an investigational product, the expectedness of an AE will be determined by whether or not it is listed in the IB.

Intensity of an Adverse Event

Each AE must be rated on a 3-point scale of increasing intensity:

- Mild: Transient or mild discomfort; no limitation in activity; no medical intervention/therapy required.
- Moderate: Mild to moderate limitation in activity; some assistance may be needed; no or minimal medical intervention/therapy required.
- Severe: Marked limitation in activity; some assistance usually required; medical intervention/therapy required, hospitalization possible.

If there is a change in intensity of an ongoing AE, it must be recorded as a separate event.

Causality Assessment

The following decision choice will be used by the investigator to describe the causality assessment between the reported event and the investigational medicinal product.

- Unrelated: No relationship between the AE and the administration of investigational product; related to other etiologies such as concomitant medications or subject's clinical state.
- Unlikely: Event or laboratory test abnormality with a time to study medication intake that makes a relationship improbable (but not impossible). Disease or other drugs provide plausible explanations.
- Possible: Event or laboratory test abnormality with reasonable time relationship to study medication intake which could also be explained by disease or other drugs. Information on drug withdrawal may be lacking or unclear.
- Probable: Event or laboratory test abnormality with reasonable time relationship to study medication intake. Event unlikely to be attributed to disease or other drugs. Response to withdrawal is clinically reasonable and rechallenge not required.
- Certain: Event or laboratory test abnormality, with plausible time relationship to study medication intake that cannot be explained by disease or other drugs. Response to withdrawal is plausible (pharmacologically, pathologically). Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognized pharmacological phenomenon). Rechallenge satisfactory, if necessary.

Action Taken Regarding Investigational Product

The action taken must be described by choosing among:

- Dose not changed: No action is taken regarding the study medication.
- Study medication permanently withdrawn: Subject is permanently withdrawn from the study.
- Study medication temporarily withdrawn: Study drug is temporarily withdrawn.
- Not applicable: Other situations (e.g., AE started after the last study medication administration)

Outcome

Each AE must be rated by choosing among:

- Recovered/resolved.
- Recovered/resolved with sequelae.
- Not recovered/not resolved.
- Fatal.
- Recovering/resolving.
- Unknown.

8.7.1.4.1.2 Recording Adverse Events

AEs will be recorded from the signature of ICF until the final Follow-up visit. If an AE is ongoing at that time, it will be followed up until resolution or until stabilization, according to the investigator's medical judgement.

It is the responsibility of the investigator to collect all AEs (both serious and nonserious) derived by spontaneous, unsolicited reports of subjects, by observation, and by routine open questioning (such as "How do you feel?").

Any adverse or unusual event occurring during or after the clinical study (until the Follow-up visit or the moment of rollover to the Follow-up study GLPG0634-CL-205), whether observed by the investigator or investigational staff, or spontaneously reported by the subjects will be recorded in the eCRF.

8.7.1.4.1.3 Managing Serious Adverse Events

Subjects experiencing an SAE or an emergency situation will be examined by a physician as soon as possible. The physician in attendance will do whatever is medically needed for the safety and well-being of the subject. The subject will remain under observation as long as medically indicated. Appropriate laboratory studies will be conducted until all parameters return to normal or are otherwise explained or stable. The subject will be followed until the SAE resolves or until the subject is medically stabilized.

8.7.1.4.1.4 Reporting Serious Adverse Events to [redacted]

All SAEs, whether or not deemed study medication-related, must be recorded in the eCRF and SAE form and reported by the investigator to [redacted] Belgium) within 24 hours by facsimile. Other means of transmission can be decided where facsimile is not possible. The SAE should include a clearly written narrative describing signs, symptoms, and treatment of the event, diagnostic procedures, as well as any relevant laboratory data and any sequelae.

Follow-up and outcomes should be reported for all subjects that experience an SAE. It is critical that the information provided on the [redacted] SAE form matches the information recorded on the eCRF for the same event. In addition, the same information is to be recorded in the source documents.

Copies of additional laboratory tests, consultation reports, post-mortem reports, hospital case reports, autopsy reports, and other documents should be sent when requested and applicable. Follow-up reports relative to the subject's subsequent course must be submitted to [redacted] until the event has subsided or, in the case of permanent impairment, until the condition stabilizes.

The contact persons are:

Name and Title	Telephone no.	Fax no.	E-mail
[redacted]	[redacted]	[redacted]	[redacted]
[redacted] Medical Safety Officer*	[redacted]	[redacted]	[redacted]

* The Medical Safety Officer at Galapagos is the sponsor liaison for [redacted] assessment of SAEs.

8.7.1.4.1.5 Pregnancy

All initial reports of pregnancy in a subject and pregnancies in partners of male subjects included in the study must be reported to [redacted] by the investigator using a pregnancy form within 24 hours of knowledge of the event. Any subject who becomes pregnant during the study must be promptly withdrawn from the study (not applicable if the subject is male). Spontaneous abortion is considered an SAE and will be reported as such.

The investigator will contact the subject at the expected time of delivery for follow-up on the pregnancy outcome. Abnormal pregnancy outcomes are considered SAEs and must be reported using the SAE form.

8.7.1.4.1.6 Reporting Serious Adverse Events to Competent Authorities/ Ethics Committees

[redacted] assumes responsibility for appropriate reporting of AEs to the regulatory authorities. [redacted] will also report to the investigator(s) all SAEs that are unlisted (unexpected) and associated with the use of the study medication. The investigator(s) (or [redacted] where required) must report these events to the appropriate IEC/IRB that approved the protocol unless otherwise required and documented by the IEC/IRB.

AE reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

After termination of the clinical study (last subject last contact in the study), any unexpected safety issue that changes the risks benefit analysis and is likely to have an impact on the subjects who have participated in it, will be reported by the sponsor/[redacted] as soon as possible to the competent authority(ies) concerned together with proposed actions.

8.7.1.4.2 Clinical Laboratory Evaluation

The hematology, clinical chemistry, and urinalysis laboratory analyses will be performed at a central laboratory ([redacted]). Reference ranges will be supplied by the central laboratory and used by the investigator to assess the laboratory data for clinical significance and pathological changes.

The total amount of blood to be taken during the study will not exceed 600 mL.

The following laboratory safety tests will be performed at every visit:

Hematology

Hemoglobin, hematocrit, WBC count (total and differential), RBC count, differential lymphocyte count (by flow cytometry; CD3, CD19, CD4, CD8, CD3-/CD16+, and CD56+), platelet count, activated partial thromboplastin time, and prothrombin time.

Clinical Chemistry

Creatinine, blood urea nitrogen (BUN), AST, ALT, gamma glutamyltransferase (GGT), alkaline phosphatase, total bilirubin, amylase, lipase, albumin, total protein, sodium, potassium, chloride, glucose, uric acid, total cholesterol, HDL and LDL, triglycerides, calcium, phosphorus, and CRP.

Serum pregnancy test for females of childbearing potential at Screening and Week 24 only or EDV only.

Hormone tests (for male subjects only)

Testosterone (total and free), LH, FSH, prolactin, and inhibin B.

Urinalysis

pH, glucose, ketone bodies, indicators of blood and WBC, and protein (quantitative).

Urine pregnancy test for females of childbearing potential at all visits, excluding Screening and Week 24 or EDV.

8.7.1.4.3 Other Laboratory Variables

Serology

Hepatitis B and C, HIV 1 and 2, RF and anti-CCP at Screening only.

Other

TB (QuantiFERON-TB Gold) test at Screening only.

8.7.1.4.4 Vital Signs

Vital signs (blood pressure, HR and oral temperature) will be recorded as described in the schedule of observations in a standardized manner, i.e., after the subject has rested in the sitting position for 5 minutes.

8.7.1.4.5 Physical Examination

A physical examination will be performed at times as described in the schedule of observations. Any changes from the Baseline assessment will be recorded. Height and weight will be measured at Screening only.

8.7.1.4.6 Other Safety Assessments

12-lead Electrocardiogram

A resting 12-lead ECG will be performed at times presented in the schedule of observations.

Subjects should rest for at least 5 minutes in the supine position before ECG evaluation.

Parameters to be recorded in the eCRF include: HR, RR, QRS, uncorrected QT interval, morphology, and rhythm analysis. QT interval corrected by Friderica's formula will be derived during the statistical analysis. ECGs will be interpreted by the investigator for clinical significance and results will be entered into the eCRF.

Chest X-ray

A chest X-ray (both anterior-posterior and lateral views) will be taken during the Screening period and reviewed by a qualified radiologist. If chest radiographs have been taken within 3 months of the Screening visit (documented evidence is needed) then the chest radiographs do not need to be repeated (as long as they demonstrate no clinically significant abnormality, and no signs or symptoms suggestive of lung disease including current active or latent TB, which would exclude the subject from the study). The results must be entered into the eCRF.

8.7.1.5 Flow Chart

Event	Screening	Baseline[1]	Treatment period[2]									FU visit[3]
Study days (D) /weeks (W)	**D-29 to D-2**	**D -1**	**D8/ W1**	**D15/ W2**	**D29/ W4**	**D57/ W8**	**D85/ W12**	**D113/ W16**	**D141/ W20**	**D169/ W24**	**EDV[4]**	**W24 or EDV + 7-10 days**
Informed consent	Written informed consent will be obtained before any study-related procedures and/or assessments are performed.											
Inclusion/ exclusion criteria	X	X[5]										
Demographic data and baseline disease characteristics	X											
Medical history/ concomitant illnesses	X											
Physical examination	X[6]	X					X			X	X	X
Serology[7]	X											
TB test and chest X-ray[8]	X											
Pregnancy test[9]	X	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG	X						X			X	X	X
Vital signs[10]	X	X	X	X	X	X	X	X	X	X	X	X
Clinical laboratory tests[11]	X	X	X	X	X	X	X	X	X	X	X	X
PK blood samples[12]					X		X			X	X	
PD blood samples[13]		X	X		X		X			X	X	

[1] Subjects will begin to take their treatment on the next morning (Day 1) following randomization.
[2] During the treatment period, a visit time window of ± 2 calendar days is allowed.
[3] Follow-up visit will be performed only for subjects discontinuing prematurely from the study and for subjects not entering the Long Term Follow-up study GLPG0634-CL-205.
[4] Early discontinuation visit.
[5] Eligibility criteria check based on the laboratory results from the Screening visit.
[6] At Screening, includes height and weight.
[7] Includes Hepatitis B and C, HIV 1 and 2, RF, and anti-CCP.
[8] X-ray should be performed if results from an X-ray performed in the previous 3 months are not available at the site.
[9] For female subjects only. To be performed on serum at Screening and Week 24/EDV and on urine for other visits.
[10] Vital signs are defined as blood pressure (systolic and diastolic), HR, and oral temperature.
[11] Refer to Section 8.7.1.4.2.
[12] PK samples: 1 blood sample (2 mL) for analysis of GLPG0634 and its main metabolite (G254445) in plasma.
[13] PD samples: 4 blood samples (2x4 mL for serum preparation and 2x2.5 mL in PAXgene tubes) will be collected for analysis of serum (analytes and miRNA profiling) and whole blood (gene expression in circulating leukocytes, mRNA and miRNA profiling).

Event	**Screening**	**Baseline**[14]	**Treatment period**[15]									**FU visit**[16]
Study days (D) /weeks (W)	**D-29 to D-2**	**D -1**	**D8/ W1**	**D15/ W2**	**D29/ W4**	**D57/ W8**	**D85/ W12**	**D113/ W16**	**D141/ W20**	**D169/ W24**	**EDV**[17]	**W24 or EDV + 7-10 days**
Randomization		X[18]					X[19]					
IXRS call	X	X	X	X	X	X	X	X	X	X	X	
Dispense study medication		X	X	X	X	X	X	X	X			
Subject diary card dispensation[20]		X	X	X	X	X	X	X	X			
Subject diary card collection			X	X	X	X	X	X	X	X	X	
Drug accountability check			X	X	X	X	X	X	X	X	X	
Study medication dosing			→	→	→	→	→	→	→	→		
Serum CRP	X	X	X	X	X	X	X	X	X	X	X	
SJC66	X	X	X	X	X	X	X	X	X	X	X	
TJC68	X	X	X	X	X	X	X	X	X	X	X	
Physician's Global Assessment		X	X	X	X	X	X	X	X	X	X	
Patient's Global Assessment	X	X	X	X	X	X	X	X	X	X	X	
HAQ-DI		X	X	X	X	X	X	X	X	X	X	
FACIT fatigue scale		X			X		X			X	X	
SF-36 questionnaire		X			X		X			X	X	
AE assessment	→	→	→	→	→	→	→	→	→	→	→	→
Concomitant medications	→	→	→	→	→	→	→	→	→	→	→	→

[14] Subjects will begin to take their treatment on the next morning (Day 1) following randomization.
[15] During the treatment period, a visit time window of ± 2 calendar days is allowed.
[16] Follow-up visit will be performed only for subjects discontinuing prematurely from the study and for subjects not entering the Long Term Follow-up study GLPG0634-CL-205.
[17] Early discontinuation visit.
[18] Upon qualification for the study.
[19] At Week 12, all subjects on placebo and the subjects on the 50 mg dose who have not achieved a 20% improvement in SJC66 and TJC68 will be assigned (automatically via IXRS) to 100 mg q.d. in a blinded fashion and will continue in the study until Week 24.
[20] Subject diary card will be dispensed to subjects on D -1 and at every following visit; subjects should be instructed to bring their diary card along with them to all visits.

8.7.2 Appropriateness of Measurements

The efficacy and safety assessments are widely used and generally recognized as reliable, accurate, and relevant to the disease condition.

8.8 Statistical Methods

8.8.1 Statistical and Analytical Plans

A detailed statistical analysis plan will be created and finalized prior to the interim database lock and the final database lock.

8.8.1.1 Datasets or Populations Analyzed

All randomized subjects who received at least one dose of study medication and have at least one post-Baseline efficacy assessment will be included in the efficacy analysis (intent-to-treat [ITT]).

A secondary per-protocol analysis will be performed to confirm the ITT analysis, excluding subjects with major protocol deviations (such as Baseline CRP within normal range, Baseline TJC68 <8, Baseline SJC66 <6, <80% study medication compliance, or use of forbidden concomitant medications). Full details of the major protocol deviations will be described in the statistical analysis plan, with adherence to analysis sets agreed upon prior to database lock and unblinding.

All randomized subjects who received at least one dose of study medication will be included in the safety analysis.

All randomized subjects who received at least one dose of GLPG0634 and who have at least one PK measurement will be included in the PK analysis.

Reasons for study termination will be tabulated.

8.8.1.2 Demographic and Other Baseline Characteristics

Demographic characteristics will be listed. Demographic characteristics will be summarized using appropriate descriptive statistics, as applicable. Details of the summaries to be produced will be included in the statistical analysis plan.

8.8.1.3 Efficacy Variables

Definition of Primary Efficacy Endpoint – ACR20 at Week 12

The primary endpoint is the percentage of subjects achieving an ACR20 response at Week 12. Other time points will be regarded as secondary endpoints.

The ACR response is a measurement of improvement in multiple disease assessment criteria. The ACR20 response is defined as:

≥20% improvement from Baseline in SJC66 (66 joints) and TJC68 (68 joints)

AND

≥20% improvement from Baseline in at least 3 of the following 5 assessments

- Pain (VAS) in cm (from HAQ-DI).
- Patient's Global Assessment of Disease Activity (VAS) in cm.
- Physician's Global Assessment of Disease Activity (VAS) in cm.
- Patient's Assessment of Physical Function as measured by HAQ-DI.
- CRP in mg/dL or mg/L.

Definition of Secondary Efficacy Endpoints

ACR50 and ACR70

ACR50 and ACR70 are defined similarly to ACR20, except the improvement threshold from Baseline is 50% and 70%, respectively.

ACR-N

The ACR-N[8] is the smallest percentage improvement in swollen and tender joints and the median of the remaining 5 core parameters, and is expected to be more sensitive to change than the ACR20, ACR50 or ACR70.

ACR-N = MIN [%improvement in TJC68,
%improvement in SJC66,
MED %improvement in (Patient's Global Assessment, Physician's Global Assessment, HAQ-DI, CRP)]

ACR/EULAR Remission

A subject's disease activity status can be defined as being in remission:

when scores on the TJC28, SJC28, CRP (actual value in mg/dL) and Patient Global Assessment of Disease Activity (cm) are all ≤1.

Simplified Disease Activity Index (SDAI)

The SDAI[9] is the numerical sum of 5 outcome parameters: TJC28, SJC28, Patient Global Assessment of Disease Activity (in cm), Physician's Global Assessment of Disease Activity (in cm) and CRP (mg/dL).

SDAI = TJC28 + SJC28 + Patient's Global Assessment of Disease Activity (VAS in cm) + Physician's Global Assessment of Disease Activity (VAS in cm) + CRP (mg/dL)

The SDAI can be categorized:

- High disease activity: SDAI >26
- Moderate disease activity: [11,26]
- Low disease activity: [3.3,11]
- Remission: ≤3.3

Clinical Disease Activity Index (CDAI)

The CDAI[10] is the SDAI modified to exclude CRP.

CDAI = TJC28 + SJC28 + Patient's Global Assessment of Disease Activity (VAS in cm) + Physician's Global Assessment of Disease Activity (VAS in cm)

The CDAI can also be categorized:

- High disease activity: >22
- Moderate disease activity: [10,22]
- Mild disease activity: [2.8,10]
- Remission: ≤2.8

Disease Activity Score Based on 28 Joints Corrected for C-reactive Protein (DAS28[CRP])

The DAS28(CRP)[11] is a statistically derived index combining tender joints (28 joints), swollen joints (28 joints), CRP, and Patient's Global Assessment of Disease Activity (general health, GH). DAS28(CRP) is defined as follows:

DAS28(CRP) = 0.56 x SQRT(TJC28) + 0.28 x SQRT(SJC28) + 0.36 x Ln(CRP+1) + 0.014 x GH + 0.96,

Where:

TJC28 is 28-joint count for tenderness
SJC28 is 28-joint count for swelling.
Ln(CRP1+1) is the natural logarithm of (CRP value [mg/L] + 1)
SQRT is square root
GH is the Patient's Global Assessment of Disease Activity on a 100 mm VAS

Categorization of the DAS28(CRP) scores:

High disease activity: >5.1
Moderate disease activity: [3.2,5.1]
Low disease activity: [2.6,3.2]
Remission: <2.6

EULAR Response

A second categorization of the DAS28(CRP) will be done according to the following table[12]:

Actual DAS28(CRP)	Improvement in DAS28(CRP) from Baseline:		
	> 1.2	> 0.6, ≤ 1.2	≤ 0.6
≤ 3.2	Good	Moderate	None
> 3.2, ≤ 5.1	Moderate	Moderate	None
> 5.1	Moderate	None	None

Quality of Life - FACIT Fatigue Scale and SF-36

Quality of life will be assessed using the FACIT fatigue scale and the SF-36 questionnaire. The appropriate (sub)totals will be derived according to the scale's scoring algorithm.

Methods of Analysis

Efficacy data (ACR20, ACR50, ACR70, ACR-N, DAS28[CRP]), EULAR response, and ACR/EULAR remission, and components of the ACR, CDAI and SDAI at each post-dosing visit) will be analyzed descriptively.

Between-group comparisons will be done for each dose group versus the placebo group. Hommel's closed-testing correction procedure (as implemented in SAS PROC MULTTEST) will be applied to adjust for multiplicity.

This study is not powered for any formal comparison among the GLPG0634 dose groups. However, differences between the dose groups will be calculated and presented with a 95% confidence interval. No adjustment for multiplicity will be done for these exploratory differences.

All subjects from the placebo group and nonresponding subjects from the 50 mg group who are reassigned to 100 mg at Week 12 will be handled as follows:

- Their Week 12 value will be carried forward in the original treatment group to all further time points (and between-group comparisons) after Week 12.
- Their actual assessments on Weeks 16, 20, and 24 will be analyzed descriptively as these represent their response after 12 weeks of GLPG0634 exposure after first having received placebo or failed on a low dose.

Analysis methods per post-Baseline time point:

- Binary parameters: logistic regression model with factors treatment, region and previous use of biologics.
- Continuous parameters: changes from Baseline and percent changes from Baseline: using an analysis of (co)variance model with factors treatment, baseline value, region and previous use of biologics.
- Time to response (ACR20/50/70) will be analyzed using Kaplan-Meier survival techniques, and groups will be compared against placebo using a Cox proportional hazards regression model with factors treatment, region and previous use of biologics.

Other applicable factors, if any, will also be included in the models. Quality of life data (FACIT fatigue scale and SF-36 questionnaire) will be analyzed descriptively. Exploratory between-group comparisons will also be done at each post-Baseline time point using analysis of (co)variance models on the changes from Baseline with factors treatment, Baseline value, region and previous use of biologics.

Handling of discontinued subjects during the 24-week treatment period:

- Subjects who discontinue within the first week so that ACR20/50/70 responses cannot be determined will be classified as nonresponders.
- For all discontinued subjects, their last observed non-missing result will be used in the subsequent visits (last observation carried forward algorithm) and for the ACR20/50/70 responses as part of the secondary/supportive analyses.

A descriptive sensitivity analysis by country, geographic region and previous use of biologics will be performed for the ACR criteria response rates.

Further exploratory analyses may be added when deemed useful to understand the data.

Graphical presentations may be added to facilitate the overall interpretation of the study results.

8.8.1.4 Safety Variables

Clinical safety will be evaluated by assessing treatment-emergent AEs, physical examinations, laboratory assessments, ECGs, and vital signs results in a descriptive manner. Original results and changes from Baseline or from Screening, for the ECG, will be summarized for the laboratory data, vital signs, and ECG values. Values will be categorized as low/normal/high according to normal ranges, and shift tables versus baseline will be created to determine treatment-emergent abnormalities.

8.8.1.5 Interim Analyses

A fully unblinded interim analysis will be performed when all subjects have reached Week 12. The statistical analysis of the unblinded data will be handled by a statistician who is independent from the regular study team. The lead statistician and corresponding biometrics team will remain blinded and will not be involved in the interim analyses, to preserve blinding when assessing the final results at Week 24.

This interim analysis output will comprise summary tables and plots, but no listings. These summary results will be viewed by the sponsor, but no individual subject data (such as listings or datasets) will be exchanged. The analysis will summarize demographics, reason for early discontinuation from the study, efficacy (i.e., ACR20, ACR50, ACR70, ACR-N, DAS28(CRP) with low disease activity, CDAI/SDAI with low disease activity, CRP, and HAQ-DI) and safety (i.e., AE, SAE, and selected laboratory tests).

The interim analysis is intended to support preliminary dose selection for the GLPG0634 phase III program. Because this efficacy analysis matches the full Week 12 primary analysis, there is no inflation of the type-I error rate, and therefore no statistical correction is applied.

8.8.1.6 Pharmacokinetic Analyses

GLPG0634 and G254445 plasma concentrations will be analyzed by nonlinear mixed-effects modeling (NONMEM program) to determine the population PK parameters as well as the covariates influencing the PK in RA subjects. The population PK analysis will be reported separately.

8.8.1.7 Pharmacodynamic Analyses

PD from analyte and/or gene expression/miRNA profiling modulation data will be analyzed descriptively. Exploratory between-group comparisons will be done.

8.8.1.8 Pharmacokinetic, Efficacy, Safety, and Pharmacodynamic Correlations

Exposure-efficacy response relationship between GLPG0634 and G254445 concentrations and selected efficacy endpoints such as CRP and DAS28 will be explored. Correlation with safety parameters (i.e., neutrophils, and LDL, or others) will be explored if altered by the treatments. More parameters may be used for the correlation if deemed necessary. [redacted]

[redacted]

The results of PK/PD, -efficacy, and –safety analyses will be reported separately.

8.8.2 Determination of Sample Size

The sample size calculation is based on the expected ACR20 response rates at Week 12.

Assuming:

- 4 treatment arms with an equal (1:1:1:1) group allocation, and
- n=70 in each of the study arms, with a total of N=280 in the study, and
- Alpha = 5%/3 = 1.67% per comparison versus placebo, and
- a 15% to 40% placebo ACR20 response at Week 12.

Then the study has 90% power to detect a 28% (=43% - 15%) to 30% (=70% - 40%) treatment difference versus placebo, depending on the placebo response rate. This is considered clinically meaningful.

The study also has 80% power to detect a 24% (=39% - 15%) to 27% (=67% - 40%) treatment difference versus placebo, depending on the placebo response rate.

Calculations were performed using a chi-square approach in nQuery 7.0.

Note that the type-I error rate was Bonferroni-adjusted for the 3 comparisons versus the placebo group. No further correction of the type-I error rate is required for the Week 12 interim analysis because it matches the primary efficacy analysis (ACR20 at Week 12).

8.9 Quality Assurance and Quality Control

8.9.1 Audit and Inspection

Study centers and study documentation may be subject to Quality Assurance audit during the course of the study by [redacted], the sponsor, or the sponsor's nominated representative. In addition, inspections may be conducted by regulatory authorities at their discretion.

8.9.2 Monitoring

Data for each subject will be recorded on an eCRF. Data collection must be completed for each subject who signs an ICF.

In accordance with GCP and ICH guidelines, the study monitor will carry out source document verification at regular intervals to ensure that the data collected in the eCRF are accurate and reliable. The frequency of monitoring visits will be determined by the rate of subject recruitment.

The following will be reviewed at these visits:

- Compliance with the protocol.
- Consent procedure.
- Source documents.
- AE procedures.
- Storage and accountability of materials.

The monitoring visits also provide the sponsor with the opportunity to ensure the investigator's obligations and all applicable ICH or health authority regulation requirements are being fulfilled.

The investigator must permit the monitor, the IEC/IRB, the sponsor's internal auditors and representatives from regulatory authorities direct access to all study-related documents and pertinent hospital or medical records for confirmation of data contained within the eCRFs. Subject confidentiality will be protected at all times.

8.9.3 Data Management and Coding

[redacted] will be responsible for activities associated with the data management of this study. This will include setting up a relevant database and data transfer mechanisms, along with appropriate validation of data and resolution of queries. Data generated within this clinical study will be handled according to the relevant standard operating procedures (SOPs) of the data management and biostatistics departments of [redacted]

Study centers will enter data directly into the electronic data capture (EDC) system by completing the eCRF via a secure internet connection. Data entered into the eCRF must be verifiable against source documents at the study center. Data to be recorded directly on the eCRF (without prior written or electronic record) will be identified, and the eCRF will be considered the source document. Any changes to the data entered into the EDC system will be recorded in the audit trail and will be FDA Code of Federal Regulations (CFR) 21 Part 11 compliant.

Data entered into the eCRF will be validated as defined in the data validation plan. External data checks will be programmed where appropriate (e.g. for laboratory data, and ECGs) as well as for cross table checking between eCRFs (e.g., AE and concomitant medication forms).

Medical coding will use the *Medical Dictionary for Regulatory Activities* for concomitant diseases and AEs and World Health Organization Drug for medications.

Missing or inconsistent data will be queried in writing to the investigator for clarification. Subsequent modifications to the database will be documented.

9 Records and Supplies

9.1 Drug Accountability

On receipt of the study medication, the investigator (or deputy) will conduct an inventory of the supplies and verify that study medication supplies are received intact and in the correct amounts before completing a supplies receipt. The investigator will retain a copy of this receipt at the study center and return the original receipt to the study monitor. The inventory of supplies at each study center may be checked at any time during the study by the monitor.

It is the responsibility of the study monitor to ensure that the investigator (or deputy) has correctly documented the amount received, dispensed, and returned of the study medication on the dispensing log that will be provided. A full drug accountability log will be maintained at the study center at all times. The study monitor will arrange collection/destruction of unused study medication returned by the subject. The study monitor will also perform an inventory of study medication at the close-out visit to the study center. All discrepancies must be accounted for and documented.

9.2 Financing and Insurance

Financing and insurance of this study will be outlined in a separate agreement between [redacted] and the sponsor.

10 Ethics

10.1 Independent Ethics Committee or Institutional Review Board

Before initiation of the study at each study center, the protocol, the ICF, other written material given to the subjects, and any other relevant study documentation will be submitted to the appropriate IEC/IRB. Written approval of the study and all relevant study information must be obtained before the study center can be initiated or the study medication is released to the investigator. Any necessary extensions or renewals of IEC/IRB approval must be obtained for changes to the study such as modification of the protocol, the ICF, or other study documentation. The written approval of the IEC/IRB together with the approved ICF must be filed in the study files.

The investigator will report promptly to the IEC/IRB any new information that may adversely affect the safety of the subjects or the conduct of the study. The investigator will submit written summaries of the study status to the IEC/IRB as required. On completion of the study, the IEC/IRB will be notified that the study has ended.

10.2 Regulatory Authorities

The protocol, name, and study center of the investigators, the votes of the IEC(s)/IRB(s), as well as other relevant study documentation will be submitted to the Regulatory Authorities of the participating countries, according to local/national requirements, for review and approval before the beginning of the study. On completion of the study, the Regulatory Authorities will be notified that the study has ended.

10.3 Ethical Conduct of the Study

The investigator(s) and all parties involved in this study should conduct the study in adherence to the ethical principles based on the Declaration of Helsinki, GCP, ICH guidelines, and the applicable national and local laws and regulatory requirements.

10.4 Informed Consent

The process of obtaining informed consent must be in accordance with applicable regulatory requirement(s), and must adhere to GCP.

The investigator is responsible for ensuring that no subject undergoes any study related examination or activity before that subject has given written informed consent to participate in the study.

The investigator or designated personnel will inform the subject of the objectives, methods, anticipated benefits and potential risks and inconveniences of the study. The subject should be given every opportunity to ask for clarification of any points he does not understand and, if necessary, ask for more information. At the end of the interview, the subject will be given ample time to consider the study. Subjects will be required to sign and date the ICF. After signatures are obtained, the ICF will be kept and archived by the investigator in the investigator's study file. A signed and dated copy of the subject ICF will be provided to the subject or their authorized representative.

It should be emphasized to the subject that he or she is at liberty to refuse to enter the study or to withdraw from the study at any time, without consequences for their further care or penalty or loss of benefits to which the subject is otherwise entitled. Subjects who refuse to

give or who withdraw written informed consent should not be included or continue in the study.

If new information becomes available that may be relevant to the subject's willingness to continue participation in the study, a new ICF will be approved by the IEC(s)/IRB(s) (and Regulatory Authorities if required). The study subjects will be informed about this new information and re consent will be obtained.

10.5 Subject Confidentiality

Monitors, auditors, and other authorized agents of the sponsor and/or its designee, the IEC(s)/IRB(s) approving this research, and the United States FDA, as well as that of any other applicable agency(ies) in other countries, will be granted direct access to the study subjects' original medical records for verification of clinical study procedures and/or data, without violating the confidentiality of the subjects to the extent permitted by the law and regulations. In any presentations of the results of this study or in publications, the subjects' identity will remain confidential.

11 Reporting and Publication, Including Archiving

The name of the coordinating investigator will be documented separately. During the study, the sponsor will contact some of the participating investigators and assess their interest in taking up the role of the coordinating investigator. Once selected the coordinating investigator will help review and sign-off the final clinical study report.

Essential documents are those documents that individually and collectively permit evaluation of the study and quality of the data produced. After completion of the study, all documents and data relating to the study will be kept in an orderly manner by the investigator in a secure study file. This file will be available for inspection by the sponsor or its representatives. Essential documents should be retained for 2 years after the final marketing approval in an ICH region or for at least 2 years since the discontinuation of clinical development of the test drug/investigational product or according to local regulation if they state otherwise. . It is the responsibility of the sponsor to inform the study center of when these documents no longer need to be retained. The investigator must contact the sponsor before destroying any study related documentation. In addition, all subject medical records and other source documentation will be kept for the maximum time permitted by the hospital, institution, or medical practice.

The sponsor must review and approve any results of the study or abstracts for professional meetings prepared by the investigator(s). Published data must not compromise the objectives of the study. Data from individual study centers in multi-center studies must not be published separately.

12 References

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6. Investigator Brochure of GLPG0634. Version 7, 21 Feb 2014.

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8. Jeffrey N. Siegel, Bo-Guang Zhen, Arthritis & Rheumatism. 2005 Jun. 52; 6:1637–1641.

9. American College of Rheumatology/European League Against Rheumatism Provisional Definition of Remission in Rheumatoid Arthritis for Clinical Trials David T. Felson, Josef S. Smolen, George Wells, et al. Arthritis & Rheumatism. 2011 Mar. 63; 3:573–586.

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11. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Arthritis Rheum. 1995 Jan;38(1):44-8.

12. The Disease Activity Score and the EULAR response criteria. J. Fransen, P.L.C.M. van Riel. Clin Exp Rheumatol 2005; 23 (Suppl. 39):S93-S99.

13 Appendices

13.1 Investigator Signature Page

Protocol Title: Randomized, double-blind, placebo-controlled, multicenter, phase IIb dose finding study of GLPG0634 administered for 24 weeks as monotherapy to subjects with moderately to severely active rheumatoid arthritis who have an inadequate response to methotrexate alone

Protocol Number: GLPG0634-CL-204

Confidentiality and GCP Compliance Statement

I, the undersigned, have reviewed this protocol, including appendices, and I will conduct the study as described in compliance with this protocol, GCP, and relevant ICH guidelines.

Once the protocol has been approved by the IEC/IRB, I will not modify this protocol without obtaining prior approval of Galapagos NV and of the IEC/IRB. I will submit the protocol modifications and/or any ICF modifications to Galapagos NV and IEC/IRB, and approval will be obtained before any modifications are implemented.

I understand that all information obtained during the conduct of the study with regard to the subjects' state of health will be regarded as confidential. No subjects' names will be disclosed. All subjects will be identified by assigned numbers on all eCRFs, laboratory samples or source documents forwarded to the sponsor. Clinical information may be reviewed by the sponsor or its agents or regulatory agencies. Agreement must be obtained from the subject before disclosure of subject information to a third party.

Information developed in this clinical study may be disclosed by Galapagos NV to other clinical investigators, regulatory agencies, or other health authority or government agencies as required.

_____ _____

Investigator Signature Date

_____

Printed Name

_____

Institution

13.2 66/68 Joint Count

Joints Assessed (left and right):

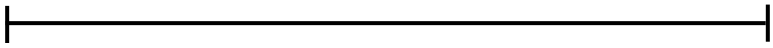
Temporomandibular
Sternoclavicular
Acromioclavicular
Shoulder
Elbow
Wrist
Metacarpophalangeal
  First
  Second
  Third
  Fourth
  Fifth
Proximal interphalangeal
  First
  Second
  Third
  Fourth
  Fifth
Distal interphalangeal
  Second
  Third
  Fourth
  Fifth
Hip #
Knee
Ankle
Tarsus
Metatarsophalangeal
  First
  Second
  Third
  Fourth
  Fifth
Proximal interphalangeal (toe)
  First
  Second
  Third
  Fourth
  Fifth

#Assessed for tenderness only

13.3 Patient's Global Assessment of Disease Activity Questionnaire

Instructions:

Considering all the ways arthritis affects you, how well are you doing today? Please indicate by making a vertical line (I) through the line below.



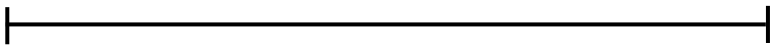
Very Well Very Poor

Note: The VAS Scale must be 100 mm long.

13.4 Physician's Global Assessment of Disease Activity Questionnaire

Instructions:

Please indicate your assessment of the subject's overall disease activity by marking a vertical line (I) through the line below.



No Disease Activity Extreme Disease Activity

Note: The VAS Scale must be 100 mm long.

13.5 Health Assessment Questionnaire - Disability Index (HAQ-DI)

HEALTH ASSESSMENT QUESTIONNAIRE

Name_____ **Date**_____

In this section we are interested in learning how your illness affects your ability to function in daily life.

Please tick the response which best describes your usual abilities OVER THE PAST WEEK:

	Without ANY Difficulty	With SOME Difficulty	With MUCH Difficulty	UNABLE To Do
DRESSING & GROOMING				
Are you able to:				
- Dress yourself, including tying shoelaces and doing up buttons?				
- Wash your hair?	_____	_____	_____	_____
RISING				
Are you able to:				
- Stand up from a straight chair?	_____	_____	_____	_____
- Get in and out of bed?				
EATING				
Are you able to:				
- Cut up your meat?	_____	_____	_____	_____
- Lift a full cup or glass to your mouth?	_____	_____	_____	_____
- Open a new milk carton?	_____	_____	_____	_____
WALKING				
Are you able to:				
- Walk outdoors on flat ground?	_____	_____	_____	_____
- Climb up five steps?				

Please tick any of the following AIDS OR EQUIPMENT that you usually use for any of the activities mentioned above:

_____ Walking stick
_____ Walking frame
_____ Crutches
_____ Wheelchair
_____ Aids used for dressing (button hook, zip-puller, long-handled shoe horn, etc.)
_____ Specially adapted utensils (such as for eating and cooking)
_____ Specially adapted chair
_____ Other (Please specify:_____)

Please tick any of the following categories for which you usually need HELP FROM ANOTHER PERSON:

_____ Dressing and Grooming
_____ Rising
_____ Eating
_____ Walking

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Please tick the response which best describes your usual abilities OVER THE PAST WEEK:

	Without ANY Difficulty	With SOME Difficulty	With MUCH Difficulty	UNABLE To Do
HYGIENE				
Are you able to:				
- Wash and dry your body?				
- Have a bath?	____	____	____	____
- Get on and off the toilet?	____	____	____	____
REACH				
Are you able to:				
- Reach up for and take down a 5 lb object (e.g. a bag of potatoes) from just above your head?	____	____	____	____
- Bend down to pick up clothing from the floor?				
GRIP				
Are you able to:				
- Open car doors?	____	____	____	____
- Open jars which have been previously opened?	____	____	____	____
- Turn taps on and off?				
ACTIVITIES				
Are you able to:				
- Go shopping?				
- Get in and out of a car?	____	____	____	____
- Do chores such as vacuuming or gardening?	____	____	____	____

Please tick any of the following AIDS OR EQUIPMENT that you usually use for any of the activities mentioned above:

____Raised toilet seat
____Bath seat
____Jar opener (for jars previously opened)
____Bath rail
____Long-handled appliances for reaching things
____Long-handled appliances in bathroom (eg: a long-handled brush)
Other (Please specify:)

Please tick any of the following categories for which you usually need HELP FROM ANOTHER PERSON:

____Hygiene
Reaching
____Gripping and opening things
Shopping and housework

We are also interested in learning whether or not you are affected by pain because of your illness.

How much pain have you had because of your illness IN THE PAST WEEK:

PLACE A VERTICAL (I) MARK ON THE LINE TO INDICATE THE SEVERITY OF THE PAIN.

NO PAIN 0 ——————————————— SEVERE PAIN 100

13.6 FACIT Fatigue Scale

FACIT Fatigue Scale (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

		Not at all	A little bit	Some-what	Quite a bit	Very much
HI7	I feel fatigued	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble starting things because I am tired	0	1	2	3	4
An4	I have trouble finishing things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4

13.7 36-Item Short-Form Health Survey (SF-36)

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. ***Thank you for completing this survey!***

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. <u>Compared to one year ago</u>, how would you rate your health in general <u>now</u>?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d Climbing several flights of stairs	☐ 1	☐ 2	☐ 3
e Climbing one flight of stairs	☐ 1	☐ 2	☐ 3
f Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g Walking more than a mile	☐ 1	☐ 2	☐ 3
h Walking several hundred yards	☐ 1	☐ 2	☐ 3
i Walking one hundred yards	☐ 1	☐ 2	☐ 3
j Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Were limited in the kind of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Had difficulty performing the work or other activities (for example, it took extra effort)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Did work or other activities less carefully than usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

6. **During the <u>past 4 weeks</u>, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?**

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. **How much <u>bodily</u> pain have you had during the <u>past 4 weeks</u>?**

None	Very mild	Mild	Moderate	Severe	Very severe
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

8. **During the <u>past 4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?**

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks…

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Did you feel full of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Have you been very nervous?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f Have you felt downhearted and depressed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h Have you been happy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a. I seem to get sick a little easier than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!