Generaal De Wittelaan L11 A3
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Belgium

PROTOCOL AMENDMENT SUMMARY OF CHANGES

PROTOCOL AMENDMENT 4

STUDY GLPG0634-CL-205

A multicenter, open-label, long-term follow-up safety and efficacy study of GLPG0634 treatment in subjects with moderately to severely active rheumatoid arthritis

Original Protocol Date:	23 August 2013
Amendment 1 Date:	13 March 2014
Amendment 2 Date:	07 October 2016
Amendment 3 Date:	15 March 2018
Amendment 4 Date:	13 May 2021

Rationale:	Herein is a summary of the major changes made to the Protocol Amendment 3, dated 15 March 2018 and reflected in the Protocol Amendment 4, dated 13 May 2021. The purpose of Protocol Amendment 4, dated 13 May 2021 is as follows: • To change sponsorship from Gilead Sciences, Inc. to Galapagos NV Additional formatting and grammatical updates and corrections were made throughout the document, which are not explicitly outlined in the changes below. New and updated text is indicated by ***bold italicization*** and deleted text by ~~strikethrough~~.

Global Changes:	• Contact details have been updated due to changes in Medical Monitor, Study Personnel, and the contract research organization [redacted] • Safety monitoring components, including information for the Data Safety Monitoring Board, were updated to align with current practices and safety standards. • Clarification was made to a study drug discontinuation criterion regarding serious infections. • Information regarding packaging, labelling, and distribution was updated to align with change in sponsorship. • Administrative, editorial, and formatting updates, changes, corrections, and clarifications were made, where appropriate, throughout the protocol.

Section:	Section 6.5 Risk/Benefit Assessment for the Study, Section 8.5 Data Safety Monitoring Board, Section 8.9.1.5 Interim Analyses
Original Text:	A Data Safety Monitoring Board (DSMB) consisting of independent experts will be convened to periodically review the accumulating safety data for the study and provide a recommendation on study continuation or early termination in case there is a concern regarding safety. The specific responsibilities and composition of the DSMB are outlined in a separate document, the DSMB Charter. Also the details of timing of the meetings and outputs provided for the meetings are referenced in this separate DSMB Charter.
Revised Text:	A ~~Data Safety Monitoring Board~~ ~~(~~DSMB~~)~~ consisting of independent experts ~~will be~~ ***was*** convened to periodically review the accumulating safety data for the study and provide a recommendation on study continuation or early termination in case there ~~is a concern regarding~~ ***were*** safety ***concerns***. The specific responsibilities and composition of the DSMB ~~are~~ ***were*** outlined in a separate document, the DSMB Charter. ~~Also~~ ***As of 01 April 2021,*** the ~~details of timing~~ ***independent DSMB reviews were discontinued as ongoing review*** of ~~the meetings~~ ***safety*** and ~~outputs provided for~~ ***efficacy data by the sponsor's clinical study team was considered sufficient by*** the ~~meetings are referenced in this separate DSMB Charter~~ ***sponsor, based on the current development status of filgotinib and the open-label design of the study.***.
Rationale:	Text was added to clarify that the DSMB have performed their final review and the DSMB reviews were discontinued.

Section:	Section 8.4.2 Study Drug Discontinuation Considerations
Original Text:	• Any serious infection that requires antimicrobial therapy or hospitalization, or any infection that meets SAE reporting criteria.
Revised Text:	• Any serious infection that requires ***parenteral/intravenous*** antimicrobial therapy or hospitalization, or any infection that meets SAE reporting criteria.
Rationale:	Text was added to clarify this discontinuation criterion and align with the presentation of current filgotinib protocols.

Section:	Section 8.6.3 Packaging, Labelling and Distribution
Original Text:	Filgotinib 100 mg HCl salt tablets are packaged in high density polyethylene (HDPE) bottles with a polypropylene closure, and grouped in a carton box for shipment. Filgotinib 100 mg maleate salt tablets are packaged in white, HDPE bottles. Each bottle contains 30 tablets, silica gel desiccant and polyester packing material. Each bottle is enclosed with a white, continuous thread, child-resistant polypropylene screw cap fitted with an induction-sealed, aluminium-faced liner. Study drugs to be distributed to centers in the US and other participating countries shall be labeled to meet applicable requirements of the United States Food and Drug Administration (FDA), EU Guideline to Good Manufacturing Practice – Annex 13 (Investigational Medicinal Products), and/or other local regulations. Filgotinib 100 mg tablets should be stored at controlled room temperature of 25°C (77°F); excursions are permitted between 15°C and 30°C (59°F to 86°F). Storage conditions are specified on the label. Until Sponsor change becomes effective and the subsequent tablet switch, the filgotinib 100 mg HCl salt tablets will be packaged [redacted]. In case of temperature excursions, the Sponsor should immediately be contacted for evaluation of the excursion and further use of the study drug. After the tablet switch, Gilead (or its designee) will package and distribute the filgotinib 100 mg maleate salt tablets. Until dispensed to the subjects, all drug products should be stored in a securely locked area, accessible only to authorized site personnel. To ensure the stability of the study drug and to ensure proper product identification, the drug product should not be stored in a container other than the container in which it is supplied. Consideration should be given to handling, preparation, and disposal through measures that minimize drug contact with the body. Appropriate precautions should be followed to avoid direct eye contact or exposure when handling.

Revised Text:	Filgotinib 100 mg HCl salt tablets are packaged in high density polyethylene (HDPE) bottles with a polypropylene closure, and grouped in a carton box for shipment. Filgotinib 100 mg maleate salt tablets are packaged in white, HDPE bottles. Each bottle contains 30 tablets, silica gel desiccant and polyester packing material. Each bottle is enclosed with a white, continuous thread, child-resistant polypropylene screw cap fitted with an induction-sealed, aluminium-faced liner. Study drugs to be distributed to centers in the US and other participating countries shall be labeled to meet applicable requirements of the United States Food and Drug Administration (FDA), EU Guideline to Good Manufacturing Practice – Annex 13 (Investigational Medicinal Products), and/or other local regulations. Filgotinib 100 mg tablets should be stored at controlled room temperature of 25°C (77°F); excursions are permitted between 15°C and 30°C (59°F to 86°F). Storage conditions are specified on the label. ~~Until Sponsor change becomes effective and the subsequent tablet switch, the filgotinib 100 mg HCl salt tablets will be packaged~~ [redacted]. In case of temperature excursions ***(outside the permitted range mentioned above)***, the Sponsor should immediately be contacted for evaluation of the excursion and further use of the study drug. ~~After the tablet switch, Gilead (or its designee) will package and distribute the filgotinib 100 mg maleate salt tablets.~~ Until dispensed to the subjects, all drug products should be stored in a securely locked area, accessible only to authorized site personnel. To ensure the stability of the study drug and to ensure proper product identification, the drug product should not be stored in a container other than the container in which it is supplied. Consideration should be given to handling, preparation, and disposal through measures that minimize drug contact with the body. Appropriate precautions should be followed to avoid direct eye contact or exposure when handling.
Rationale:	Text regarding previous sponsor change was removed because it was irrelevant in the current protocol.

"I have read and understand the above, and agree to this protocol amendment as written."
Principal Investigator **Date**

CLINICAL STUDY PROTOCOL

AMENDMENT 4

A multicenter, open-label, long-term follow-up safety and efficacy study of GLPG0634 treatment in subjects with moderately to severely active rheumatoid arthritis

Protocol Number:	GLPG0634-CL-205
EudraCT Number:	2012-003655-11
Clinical Trials.gov Identifier	NCT02065700
[redacted]	[redacted]
Test Drug/Investigational Product:	Filgotinib (GS-6034, GLPG0634)
Phase:	Phase 2
Sponsor:	Galapagos NV Generaal De Wittelaan L11 A3 2800 Mechelen Belgium
Protocol Version/Date:	Original: 23 August 2013 Amendment 1: 13 March 2014 Amendment 2: 07 October 2016 Amendment 3: 15 March 2018 Amendment 4: 13 May 2021

1 Protocol Approval Signatures

Protocol Title: A multicenter, open-label, long-term follow-up safety and efficacy study of GLPG0634 treatment in subjects with moderately to severely active rheumatoid arthritis

Protocol Number: GLPG0634-CL-205

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

Sponsor Signatory

[redacted]
Generaal De Wittelaan L11 A3
2800 Mechelen
Belgium

[redacted]
18 May 2021
Date

2 Study Personnel

Sponsor Personnel

Galapagos Medical Leader

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CRO Personnel

Medical Monitor

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

3 Synopsis

Protocol Number:	GLPG0634-CL-205
Title:	A multicenter, open-label, long-term follow-up safety and efficacy study of filgotinib treatment in subjects with moderately to severely active rheumatoid arthritis
Test Drug/Investigational Product:	Filgotinib (GS-6034, GLPG0634)
Number of Study Centers:	International multicenter. 116 sites.
Phase:	2
Objectives:	The primary objective is to evaluate the long-term safety and tolerability of filgotinib for the treatment of rheumatoid arthritis (RA). The secondary objectives are to evaluate the long-term efficacy of filgotinib and to evaluate the long-term effects of filgotinib administration on subject's disability, fatigue, and quality of life.
Study Design:	This will be an open-label, long-term follow-up safety and efficacy study in subjects with RA. Subjects will be enrolled in the study after they have completed one of the 2 core studies (GLPG0634-CL-203 or GLPG0634-CL-204) if, in the opinion of the investigator, they will continue to benefit from treatment in the extension study. Subjects will start the study at the same dose level (filgotinib 200 mg per day), administered in the same dosing regimen (frequency of intake of active IMP) as during the preceding core study (200 mg once daily [q.d.] or 100 mg twice daily [b.i.d.]).
Number of Subjects:	739 subjects

Treatment:	All subjects will start the study at the same dose level (filgotinib 200 mg per day) either as 200 mg q.d. or as 100 mg b.i.d. The investigator may decide to decrease the daily dose of filgotinib to 100 mg q.d. in case of intolerance or for safety reasons. Subjects will return to filgotinib 200 mg per day after the reasons for decreasing the dose have resolved, and at the investigator's discretion. Subjects can also continue filgotinib 100 mg q.d. when deemed necessary by the investigator.
Study Duration:	Ongoing until marketing, local (if applicable) regulatory and/or pertinent local reimbursement approval.
Study Population:	Main inclusion criteria: • Male or female subjects who are ≥18 years of age, having completed one of the qualifying core studies (GLPG0634-CL-203 or GLPG0634-CL-204) and, who in the opinion of the investigator, will continue to benefit from treatment in the extension study. Main exclusion criteria: • Subjects who have been prematurely withdrawn from one of the 2 core studies (GLPG0634-CL-203 and GLPG0634-CL-204), for any reason including fulfilling the individual stopping criteria. • Subjects who are deemed not to be benefiting from the study medication based upon lack of improvement or worsening of their symptoms. Local guidelines for subject treatment to be followed. • Subjects with persistent abnormal laboratory values associated with the use of the study medication (including but not limited to hematology, liver and renal function values) during one of the 2 core studies (GLPG0634-CL-203 or GLPG0634-CL-204), according to the investigator's clinical judgment. • Subjects with diagnosis since the inclusion to GLPG0634-CL-203 or GLPG0634-CL-204 core studies of rheumatic autoimmune disease or inflammatory joint disease other than RA, except for secondary Sjögren's syndrome.
Primary Endpoint:	Safety and tolerability of long-term dosing of filgotinib 200 mg q.d. and 100 mg b.i.d.

Secondary Endpoints:	Evolution in the percentage of subjects achieving American College of Rheumatology (ACR)20, ACR50, ACR70, and ACR-N responses; European League Against Rheumatism (EULAR) responses; ACR/EULAR remission, clinical disease activity index (CDAI), simplified disease activity index (SDAI), and the disease-activity score based on 28 joints (DAS28 c-reactive protein [CRP]) every 12 weeks or until the Final Visit or the Early Discontinuation Visit (EDV). Change from Baseline in the Quality of Life (functional assessment of chronic illness therapy [FACIT] fatigue scale and 36-item short form health survey [SF-36] scores) every 48 weeks or until the Final Visit or the EDV.
Safety Analysis:	The safety analysis will be performed for all subjects who used the study medication at least once in this study. Assessment of treatment-emergent adverse events, and of changes from Baseline in laboratory parameters, vital signs, physical examination, and electrocardiograms.
Efficacy Analysis:	ACR20, ACR50, ACR70, ACR-N, EULAR response, and ACR/EULAR remission, DAS28(CRP), components of the ACR, and DAS28, CDAI, SDAI, and Quality of Life data (FACIT fatigue scale and SF-36 questionnaire) at each post dosing visit (as appropriate) will be analyzed descriptively. Changes from Baseline will be examined to check for evolution over time in treatment effect.

4 Table of Contents

LIST OF TABLES

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 concentration-time curve
AUC_{0-24}	=	area under the concentration-time curve from 0 to 24 hours
b.i.d.	=	bis in die (twice daily)
CD	=	Crohn's disease
CDAI	=	clinical disease activity index
CES	=	carboxylesterases
CIA	=	collagen-induced arthritis
eCRF	=	electronic case report form
CNS	=	central nervous system
CrCl	=	Creatinine Clearance
CRP	=	c-reactive protein
CYP	=	cytochrome P450
DAS28	=	disease-activity score based on 28 joints
DMARD	=	disease-modifying anti-rheumatic drug
DSMB	=	Data Safety Monitoring Board
ECG	=	electrocardiogram
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
GH	=	general health
GI	=	gastrointestinal
HAQ-DI	=	health assessment questionnaire – disability index
HCl	=	hydrochloride
HDL	=	high-density lipoprotein
HDPE	=	high density polyethylene
HR	=	heart rate
IB	=	investigator's brochure
ICF	=	informed consent form
ICH	=	International Council for Harmonisation
IEC	=	Independent Ethics Committee
IL	=	interleukin
IRB	=	Institutional Review Board
IXRS	=	interactive voice/web response system
JAK	=	janus kinase
LDL	=	low-density lipoprotein

LH	=	luteinizing hormone
Ln	=	natural logarithm
MTX	=	methotrexate
NOAEL	=	no-observed-adverse-effect-level
NOEL	=	no-observed-effect-level
NSAID	=	non-steroidal anti-inflammatory drug
PD	=	pharmacodynamic
PK	=	pharmacokinetic
PRL	=	prolactin
q.d.	=	quaque die (once daily)
RA	=	rheumatoid arthritis
RBC	=	red blood cell
SAE	=	serious adverse event
SDAI	=	simplified disease activity index
SF-36	=	36-item short-form health survey
SJC	=	swollen joint count
SMPC	=	Summary of Product Characteristics
SQRT	=	square root
STAT	=	signal transducer and activator of transcription
$t_{1/2}$	=	terminal half-life
TB	=	tuberculosis
TEAE	=	treatment-emergent adverse event
TJC	=	tender joint count
t_{max}	=	time to maximum plasma concentration
TNF	=	tumor necrosis factor
TYK	=	tyrosine kinase
UGT	=	uridine 5'-diphosphate glucuronosyltransferase
VAS	=	visual analog scale
WBC	=	white blood cell

Cockroft-Gault CrCl Formula = [(140-age) x (Wt in kg) x (0.85 if female)]/(72 x Cr)
Wt = Weight in Kilograms
Cr = Creatinine in mg/dL

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. A considerable advance in the treatment of RA came from the introduction of the biological therapeutics like etanercept, infliximab, adalimumab or 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 co-stimulation (abatacept), and tocilizumab, targeting the interleukin (IL)-6 receptor have all recently been approved for the treatment of RA.[4]

Despite these advances a need still exists for less expensive and orally active drugs. Hence, various companies are pursuing the development of small-molecule inhibitors, including janus kinase (JAK) inhibitors.

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 1, 2, and 3 clinical development programs demonstrated its mechanisms of action via anti-inflammatory 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 cytopenias, elevated levels of liver function enzymes, increased level of low-density lipoprotein (LDL), high-density lipoprotein (HDL) cholesterol[5], and a small increased risk for infections including serious and opportunistic infections seen during the studies. Baricitinib, a molecule with strong binding affinity for JAK1 and 2, has been through extensive phase 1 and 2 testing and is currently undergoing large scale phase

3 studies. In phase 2 clinical studies, VX-509 specifically targets JAK3. Both these molecules have demonstrated efficacy roughly similar to tofacitinib with an equally manageable side-effect profile.

6.2 Background on Filgotinib

JAKs 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 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, now referred to as filgotinib (GS-6034) is a potent and selective inhibitor of JAK1 and is being co-developed by Galapagos NV and Gilead Sciences, Inc. (Gilead). The compound is currently in phase 3 development for RA and CD and has shown good preliminary efficacy in RA patients. The anticipated therapeutic daily dose range is 100 to 200 mg.

Filgotinib is metabolized to form one major active metabolite, GS-829845 (formerly 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 GS-829845. Results from pharmacodynamics (PD) testing in healthy volunteers suggest that the clinical activity of filgotinib could result from the combination of the parent molecule and the metabolite.

More information on the study medication along with references to support the cited data is 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 filgotinib hydrochloride (HCl) trihydrate or GS-6034-01 is N-(5-(4-((1,1-dioxidothiomorpholin-4-yl)methyl)phenyl)-[1,2,4]triazole[1,5-a]pyridin-2-yl) cyclopropanecarboxamide hydrochloride trihydrate.

The chemical name of filgotinib maleate or GS-6034-02 is N-(5-{4-[(1,1-dioxidothiomorpholin-4-yl) methyl]phenyl}[1,2,4]triazolo[1,5-a]pyridin-2-yl) cyclopropanecarboxamide (2Z)-but-2-enedioate.

Two clinical tablet formulations are currently available: (1) a film-coated tablet (25-100 mg per tablet) of the HCl salt of filgotinib and (2) a film-coated tablet (100 mg per tablet) of the maleate salt of filgotinib.

6.3.2 *Nonclinical Pharmacology*

6.3.2.1 Primary and Secondary Pharmacology

Filgotinib 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 GS-829845 exhibits a similar JAK1 selectivity profile while being approximately 10-fold less potent as compared to parent filgotinib *in vitro*. In the rat CIA model, while being less potent than the parent molecule, GS-829845 displays a good curative effect against established arthritis.

6.3.2.2 Safety Pharmacology

Filgotinib and GS-829845 had no effects on the respiratory system and central nervous system (CNS) up to respectively 40- and 5-fold the human exposure in RA patients at 200 mg q.d. filgotinib.

Filgotinib and GS-829845 had no relevant effects on cardiovascular parameters (human ether-a-go-go [hERG] and dog telemetry studies), apart from a slight non-adverse increase in heart rate (HR) and arterial pressure with GS-829845 at exposures approximately 7-fold that of RA patients treated with 200 mg q.d. filgotinib. There were no relevant effects on electrocardiogram (ECG) and QT.

6.3.3 *Nonclinical Pharmacokinetics and Product Metabolism*

Filgotinib shows a good oral bioavailability in mice, rats, dogs and minipigs but less in monkeys. Plasma protein binding is low (<70%) in all species, including humans.

The pharmacokinetics (PK) of filgotinib is essentially dose proportional without gender differences. No accumulation occurs with repeated dosing. The mean terminal half-life after oral administration is 4 and 5 hours in rats and dogs, respectively.

Filgotinib showed a rapid and even distribution throughout the body in the rat. High concentrations were only observed in the gastrointestinal (GI) tract and urinary bladder. Filgotinib does not penetrate into the CNS tissues. Filgotinib distribution indicates some affinity of the test compound for melanin-containing tissues.

Excretion is nearly complete within 24 hours post-dosing. Fecal and urinary excretion accounted for 40% and 53% of the administered dose, respectively, with a bile secretion of about 15%.

In vitro metabolism studies in all species revealed one major metabolite (GS-829845). The formation of GS-829845 is mediated by carboxylesterases (CES) and is not dependent on cytochrome P450 (CYP).

In vitro experiments have shown that drug-drug interactions with filgotinib and GS-829845 are unlikely. There is no inhibition or induction of CYPs or uridine 5'-diphosphate glucuronosyltransferases (UGTs) and no relevant inhibition of key drug transporters, including the organic anion transporters (OATs) involved in the renal elimination of MTX, by filgotinib or GS-829845.

6.3.4 *Nonclinical Toxicology*

In repeat oral dose toxicity studies in both rats and dogs, the primary target tissues identified for filgotinib were the lymphoid tissues which is expected based on the pharmacology of JAK inhibition. Additional filgotinib-related findings were observed in the male reproductive organs of both species, and in the incisor teeth of rats only. Effects on the lymphoid system were fully reversible. Testicular toxicity demonstrated partial reversibility; however, sperm counts remained low. A dose of 200 mg/day of filgotinib results in an estimated mean clinical AUC of 2.80 µg•h/mL in RA subjects, which represents an exposure margin of 2.3, 1.8, and 3.4-fold when considering the mean AUC in male dogs at the no-observed-effect-levels (NOELs) in the 26 week and 39 week chronic toxicity studies, and the 39 week targeted exposure toxicity study, respectively.

GS-829845-related findings in general repeat dose toxicity studies were similar to those of the parent filgotinib, however no testicular toxicity was noted following administration of GS-829845.

Filgotinib and GS-829845 were non-genotoxic when evaluated in the bacterial mutagenicity assay, the in vitro mouse lymphoma mutagenicity assay, and the rat bone marrow micronucleus assay.

In embryofetal development studies, filgotinib and GS-829845 caused embryolethality and teratogenicity in rats and rabbits at exposures similar to the human exposure at 200 mg q.d. of filgotinib in subjects with RA. Administration of filgotinib did not affect female fertility but impaired fertility was observed in male rats at exposures approximately 15-fold the human exposure at 200 mg of filgotinib in subjects with RA. GS-829845 did not have any effects on fertility parameters in either male or female rats.

In an in vitro phototoxicity study in 3T3 cells, the metabolite GS-829845 was positive for phototoxic potential and results with filgotinib were equivocal. A follow-up in vivo rat phototoxicity assay revealed a lack of phototoxic potential for both compounds.

6.4 Clinical Trials of Filgotinib

Comprehensive data from the Phase 1 and 2 programs are available to support development into Phase 3. In general, filgotinib has been safe and well tolerated in all populations studied. A detailed description of all clinical studies can be found in the IB.

Phase 2b GLPG0634-CL-203, filgotinib with MTX in RA

In GLPG0634-CL-203, subjects with active RA on stable dose of MTX were randomized to receive either placebo or one of three total daily doses of filgotinib (50 mg, 100 mg, or 200 mg) on a once or twice daily schedule for 24 weeks. The

primary objective of the study was to evaluate the efficacy of different doses and dose regimens of filgotinib compared to placebo at Week 12.

The percentage of American College of Rheumatology (ACR) 20 responders was statistically significantly higher in the 100 mg and 200 mg once daily, and 100 mg twice daily dose groups at Week 12 and in the 100 mg and 200 mg once daily, and 50 mg and 100 mg twice daily dose groups at Week 24. The percentage of ACR50 responders was statistically significantly higher compared with placebo across all filgotinib dose groups and regimens at both Weeks 12 and 24 (Table 6-1). The percentage of ACR70 responders was statistically significantly higher in the filgotinib 200 mg once daily and 100 mg twice daily dose groups compared with placebo at Week 12 and across all filgotinib dose groups and regimens at Week 24. A dose-response was observed for all three parameters. In addition, the ACR20 response appeared to plateau at Week 8 in the majority of filgotinib treatment groups and was maintained up to Week 24. At Week 24, the ACR50 response was maintained and the ACR70 response continued to increase compared with Week 12.

Starting at week 2 response was observed for ACR20 and ACR50. No statistically significant difference was found between the once and twice daily regimens.

Table 6-1. Summary and analysis of ACR20/50/70 response at Weeks 12 and 24 (NRI [ITT Population]), GLPG0634-CL-203

Parameter	Time Point	Placebo N=86	filgotinib once daily Dose Groups			filgotinib twice daily Dose Groups		
			50 mg N=82	100 mg N=85	200 mg N=86	25 mg N=86	50 mg N=85	100 mg N=84
		n (%)						
ACR20	W12	38 (44.2)	46 (56.1)	54 (63.5)*	59 (68.6)**	49 (57.0)	51 (60.0)	66 (78.6)***
	W24	36 (41.9)	45 (54.9)	52 (61.2)*	63 (73.3)***	48 (55.8)	51 (60.0)*	67 (79.8)***
ACR50	W12	13 (15.1)	27 (32.9)*	32 (37.6)**	37 (43.0)***	24 (27.9)*	29 (34.1)*	46 (54.8)***
	W24	14 (16.3)	29 (35.4)**	40 (47.1)***	43 (50.0)***	30 (34.9)**	30 (35.3)**	46 (54.8)***
ACR70	W12	7 (8.1)	13 (15.9)	18 (21.2)	21 (24.4)*	12 (14.0)	16 (18.8)	26 (31.0)**
	W24	8 (9.3)	18 (22.0)*	28 (32.9)**	25 (29.1)**	18 (20.9)*	20 (23.5)*	33 (39.3)***

Note 1: p-values were based on a pairwise comparisons of each group vs. the placebo group using a logistic regression model with factors treatment group, geographical region, and prior use of biologics; Hommel-corrected p-value. Note 2: The denominator for the percentage calculations = the total number of subjects per group with a response (yes or no) at that time point
Note 3: Subjects who switched treatment at Week 12 were handled as if they discontinued at Week 12.
* p< 0.05; ** p< 0.01; *** p < 0.001
ACR=American College of Rheumatology; ITT=Intent-to-treat; NRI=non-responder imputation; W=week
Source: GLPG0634-CL-203

At Weeks 12 and 24 the mean decrease in Disease Activity Score for 28 joint count using c-reactive protein (DAS28[CRP]) was statistically significantly greater across all filgotinib dose groups and regimens compared with placebo. A dose-response was observed. No statistically significant difference was apparent between the once and

twice daily regimens. At Weeks 12 and 24, the mean decrease in Simplified Diagnostic Activity Index (SDAI) and Clinical Disease Activity Index (CDAI) score was statistically significantly greater across all filgotinib dose groups and regimens compared with placebo (with the exception of filgotinib 50 mg once daily dose group at Week 12). In addition, the mean SDAI and CDAI scores were maintained after Week 12 in the 50 mg daily dose groups and continued to improve up to Week 24 in the 100 mg and 200 mg daily dose groups.

No unexpected safety findings were noted. Overall, no differences were observed in the incidence of treatment emergent adverse events (TEAEs) reported for subjects in any of the dosing groups, including placebo, for the duration of the study. TEAEs were reported for 51.2% of “All Placebo Exposed” subjects (ie, all subjects combined who received placebo during either the entire 24 weeks or only during the first 12 weeks) and 51.5% of “All filgotinib Exposed” subjects (ie, all subjects combined who received filgotinib during either the entire 24 weeks or only during the last 12 weeks, irrespective of dose).

A total of 15 subjects had ≥1 serious TEAE; 4 subjects in the placebo group (4.7%) and 11 subjects (2.0%) in one of the filgotinib groups. One of these subjects with ≥1 serious TEAE, who received filgotinib 100 mg twice daily with concurrent MTX, died during the second 12 weeks of the study period due to pneumonia and septic shock. Out of the 15 subjects with a serious TEAE, 11 subjects had a serious TEAE due to which the study medication was stopped, and the subject discontinued the study. A total of 23 subjects had ≥1 AE leading to permanent discontinuation of the study medication and the study; 2 subjects (2.3%) in the placebo group and 21 subjects (3.9%) in one of the filgotinib groups (including a subject in the filgotinib 100 mg q.d. group who had a pre-dosing AE which was ongoing throughout the study, for which the study medication was permanently discontinued). Most of the serious TEAEs and the AEs leading to discontinuation (by preferred term) were experienced by a single subject.

For the duration of the study, the most common (≥10%) TEAEs reported by SOC in subjects from both the placebo and filgotinib dosing groups, were Infections and Infestations and Gastrointestinal disorders. There were no differences between subjects who received placebo or filgotinib in the severity of TEAEs (most TEAEs were mild or moderate; severe TEAEs were observed in 1.2% of “All Placebo Exposed” subjects and in 2.2% of “All filgotinib Exposed” subjects). Treatment-related TEAEs were generally reported more often for subjects in the filgotinib dosing groups than in the placebo group (9.3% with placebo and 20.3% with filgotinib); however, within the different filgotinib dosing groups, no clear dose relationships were observed.

Six serious infections were reported (1 in placebo arm, 5 in filgotinib arm). All 6 serious and one additional non-serious infection in the filgotinib group led to dosing discontinuation. Up to Week 24, herpes zoster infections were observed in 5 subjects (1 placebo treated patient and 4 filgotinib). No cases of tuberculosis, opportunistic infections, lymphoma, or cancer were reported throughout the 24-week dosing period.

Laboratory data were consistent with prior phase 2 studies and no new safety findings were observed from laboratory data. A summary of laboratory findings of interest,

including hemoglobin, neutrophil, lymphocyte, creatinine, lipid, and hormone data are summarized below.

Up to Week 12, small increases were observed in mean hemoglobin concentrations in the filgotinib 200 mg daily dose groups (increase of 4.4 g/L from baseline in the filgotinib 100 mg bid group). Thereafter, hemoglobin mean concentrations appeared to plateau and remain stable until Week 24 (increase of 4.9 g/L from baseline in the filgotinib 100 mg bid group).

Up to Week 4, dose-dependent decreases were observed in mean absolute neutrophil counts in the filgotinib treatment groups. Mean absolute neutrophil counts appeared to plateau and remained stable until Week 24. No decreases in mean absolute lymphocyte counts were observed, including lymphocyte subsets.

Up to Week 4, dose-dependent decreases were observed in mean absolute platelet counts in the filgotinib treatment groups. Mean absolute platelet counts appeared to plateau and remained stable. Dose-dependent increases in the filgotinib groups were observed in mean creatinine concentrations during the first 4 weeks of the study for most filgotinib treatment groups (up to Week 8 for the filgotinib 100 mg bid group) that subsequently plateaued and remained stable up to Week 24.

Up to Week 4, dose-dependent increases were observed in mean concentrations of total cholesterol, LDL cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides in all filgotinib treatment groups. All these lipid parameters further increased up to Week 8 in the filgotinib 200 mg daily dose groups. Thereafter, these increases appeared to plateau and maintained at stable mean concentrations up to Week 24. At Week 24, mean increases were observed of 0.7 mmol/L in total cholesterol, 0.3 mmol/L in LDL cholesterol, 0.3 mmol/L in HDL cholesterol, and 0.1 mmol/L in triglycerides in the filgotinib 100 mg bid group.

In male subjects, small non dose-dependent increases were observed in total and free testosterone during the study (at Week 24, mean increases were 3.4 nmol/L for total and 51.7 pmol/L for free testosterone in the filgotinib 100 mg bid group). For FSH, inhibin B, LH, and prolactin, small changes (both increases and decreases) were observed during the study, without any trends of larger changes in male subjects of one or more of the different treatment groups.

GLPG0634-CL-204, Filgotinib administered as monotherapy in RA Subjects

The primary objective of study GLPG0634-CL-204 was to evaluate the efficacy of three doses of filgotinib q.d. compared to placebo at Week 12.

As shown in Table 6-2 the percentage of ACR20 and ACR50 responders at week 12 was statistically significantly higher across all filgotinib dose groups compared with placebo. The percentage of ACR70 responders in the filgotinib 100 mg and 200 mg once daily dose groups was statistically significantly higher compared with placebo. At Week 24, the ACR50 response was maintained and the ACR70 response showed continued improvement. An early onset of response was observed for ACR20

(from Week 1 in the filgotinib 200 mg once daily dose group and Week 4 across all other dose groups), ACR50 (from Week 2 in the filgotinib 200 mg once daily dose group and Week 4 across all other filgotinib dose groups), and ACR70 (Week 4 in the filgotinib 200 mg once daily dose group). The time to ACR20/50/70 response was shorter in all filgotinib dose groups compared with placebo.

Table 6-2. Summary and analysis of ACR20/50/70 response at Weeks 12 and 24 (NRI [ITT Population]); GLPG0634-CL-204

Parameter	Time Point	Placebo	filgotinib once daily Dose Groups		
		N=72	50 mg N=72	100 mg N=70	200 mg N=69
		n (%)			
ACR20	W12	21 (29.2)	48 (66.7)***	46 (65.7)***	50 (72.5)***
	W24	Not applicable	41 (56.9)	55 (78.6)	46 (66.7)
ACR50	W12	8 (11.1)	25 (34.7)***	26 (37.1)***	30 (43.5)***
	W24	Not applicable	24 (33.3)	27 (38.6)	31 (44.9)
ACR70	W12	2 (2.8)	6 (8.3)	13 (18.6)**	9 (13.0)*
	W24	Not applicable	14 (19.4)	18 (25.7)	17 (24.6)

Note 1: p-values were based on a pairwise comparisons of each group vs. the placebo group using a logistic regression model with factors treatment group, geographical region, and prior use of biologics; Hommel-corrected p-value.
Note 2: The denominator for the percentage calculations = the total number of subjects per group with a response (yes or no) at that time point
Note 3: Subjects who switched treatment at Week 12 were handled as if they discontinued at Week 12.
* p< 0.05; ** p< 0.01; *** p < 0.001
ITT=Intent-to-treat; NRI=non-responder imputation; W=week
Source: GLPG0634-CL-204

At Week 12, the mean decrease in DAS28(CRP) was statistically significantly greater across all filgotinib dose groups compared with placebo. At Week 24, the mean decrease in DAS28(CRP) was maintained in the 50 mg once daily dose group and showed a small improvement in the highest dose groups. In addition, at Week 12, the percentage of subjects with DAS28(CRP) remission was higher across all filgotinib dose groups compared with placebo. Differences vs. placebo were not statistically significant for any of the filgotinib dose groups. The number of subjects with DAS28(CRP) < 2.6 and < 3.2 were higher across all filgotinib dose groups compared with placebo at Week 12; differences vs. placebo were statistically significant for the filgotinib 200 mg once daily dose group.

Safety data revealed no differences in the incidence of TEAEs reported for subjects in any of the treatment groups, including placebo, during both the first 12 weeks of treatment and the full 24 weeks of treatment. TEAEs were reported for 38.9% of “All Placebo Exposed” subjects (ie, all subjects combined who received placebo during the first 12 weeks) and 41.3% of “All filgotinib Exposed” subjects (ie, all subjects combined

who received filgotinib during either the entire 24 weeks or only during the last 12 weeks, irrespective of dose).

No deaths were reported and a total of 9 subjects had a serious TEAE; 1 subject (1.4%) during placebo dosing and 8 subjects (2.9%) during filgotinib dosing. No serious TEAE (by preferred term) was experienced by more than 1 subject, and all subjects recovered from their serious TEAEs. Out of the 9 subjects with a serious TEAE, 3 subjects had a serious TEAE for which the study medication was stopped, and the subject discontinued the study. There were no differences in incidences of AEs leading to discontinuation among all the different dosing groups, including placebo. A total of 11 subjects had ≥1 TEAE leading to discontinuation of the study medication; 4 subjects (5.6%) during placebo dosing and 7 subjects (2.5%) during filgotinib dosing.

During the whole study, the most common TEAEs reported by System Organ Class in subjects from both the placebo and filgotinib treatment groups, were 'Infections and Infestations' and 'Gastrointestinal disorders'. There were no differences between subjects who received placebo or filgotinib in the severity of TEAEs (most TEAEs were mild or moderate; severe TEAEs were observed in 1.4% of "All Placebo Exposed" subjects and in 1.1% of "All filgotinib Exposed" subjects). Treatment-related TEAEs were generally reported more often for subjects in the filgotinib treatment groups than in the placebo group (9.7% with placebo and 16.7% with filgotinib); however, within the different filgotinib treatment group, no clear dose relationships were observed.

Low numbers of infections were reported as serious (4 subjects with filgotinib) or led to discontinuation of the study medication (2 serious infections; ie, cellulitis and pneumonia) were observed during the study. Up to Week 24, 1 subject (filgotinib 50 mg q.d. group) had a herpes zoster infection. No cases of tuberculosis, opportunistic infections, lymphoma, or cancer were reported throughout the 24-week treatment period.

Laboratory data were consistent with prior studies and no new safety findings were observed.

Please refer to the IB for additional data regarding efficacy and safety.

6.5 Risk/Benefit Assessment for the Study

A detailed description of all clinical studies can be found in the IB.

Nonclinical studies in rats and dogs identified the testes and lymphoid tissue as target organs for filgotinib in long term repeat-dose toxicity studies. In both species, histopathological changes in the testes included germ cell depletion and degeneration, with reduced sperm content and increased cell debris in the epididymis and reduction in fertility in rats. The dog was determined to be the most sensitive species. A dose of 200 mg/day of filgotinib results in an estimated mean clinical AUC of 2.8 µg•h/mL, which represents an exposure margin of 2.3, 1.8, and 3.4-fold when considering the mean AUC in male dogs at the no-observed-effect-levels (NOELs) in the 26 week and 39 week chronic toxicity studies, and the 39 week targeted exposure toxicity study,

respectively. Decreased lymphocytes observed in nonclinical studies have not been shown in clinical studies.

Filgotinib has shown an increased risk of embryofetal malformations at exposures similar to human doses; the use of highly effective contraception in the subject population will be implemented in the study to mitigate this risk.

No clinically relevant impact on cardiovascular parameters (including vital signs and ECG), respiratory or neurologic function has been observed in Phase 1 and 2 trials of filgotinib. Across phase 2 trials in RA, filgotinib was well tolerated. In the RA studies (including this study), infections were reported more commonly in the filgotinib groups, including serious infections leading to hospitalization, and even death. The most common system organ classes (SOC) with AEs were infections and infestations, and gastrointestinal disorders. Dose dependent decreases in the phase 2b studies were observed in mean neutrophil counts and platelet counts (but mean changes in both remained within normal laboratory reference ranges), and there were no decreases in lymphocytes or lymphocyte subsets. Hemoglobin levels slightly improved (increased) with filgotinib treatment, confirming that no anemia was induced. Mild and clinically insignificant serum creatinine increases were noted in both Phase 2b studies, with stabilization by Week 24. Neutrophil decreases (in the RA population) and a potential increased risk of infection may be considered risks consistent with the mechanism of JAK inhibition.

Overall clinical findings and laboratory changes are consistent with selective JAK1 inhibition and based on Phase 2 data the expected benefit of using filgotinib as proposed in this study is considered to outweigh any associated risks.

As of 01 April 2021, the independent data safety monitoring board (DSMB) reviews were discontinued as ongoing review of safety and efficacy data by the sponsor's clinical study team was considered sufficient by the sponsor, based on the current development status of filgotinib and the open-label design of the study.

The overall risk:benefit balance of this study is considered favorable. For additional information about the risks of filgotinib, reference is made to the investigator brochure.

6.6 Rationale for the Study

Over the last decade changes in RA treatment strategies, accompanied with advances in drug development and the addition of targeted biological therapies, have greatly improved the outcome of patients with RA. Despite these developments, therapeutic challenges have remained, since current conventional and biological DMARDs sometimes fail or produce only a 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 are safe and well tolerated.

Filgotinib is a small molecule for oral daily administration that has shown promising results as a potentially safe and effective RA treatment. Study GLPG0634-CL-205 is a therapeutic open-label phase 2 extension study to assess the long-term safety and efficacy of a stable dose (200 mg q.d. or 100 mg b.i.d.) of filgotinib up to marketing of the

compound in subjects with established RA. The aim of the current study is to evaluate the long-term safety and tolerability of a stable filgotinib dose, the efficacy of filgotinib administration, and to evaluate the long-term effects of filgotinib administration on the subject's disability, fatigue, and quality of life.

As a follow-up study, which will begin following the subject's completion of either of the previous core phase 2b studies (GLP0634-CL-203 and GLP0634-CL-204), data will be gathered up to the submission of the compound to regulatory authorities and enable assessment of the long-term effects of filgotinib administration.

The study's primary endpoint is to assess the long-term safety and tolerability of filgotinib and will focus on the changes in safety parameters in order to detect any treatment-emergent effect related to the long-term daily administration of a stable 200 mg dose (200 mg q.d. or 100 mg b.i.d.) of filgotinib.

The secondary endpoints will focus on the efficacy over a long-term period and to evaluate the long-term effects on the subject's disability, fatigue, and quality of life. The efficacy assessments will be the same as for the previous core studies and will focus on the changes in efficacy parameters in order to detect any effects related to the long-term daily administration of a stable 200 mg daily dose of filgotinib, given as q.d. or divided b.i.d. 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. Assessment of the ACR criteria will allow for a straightforward interpretation of a positive clinically meaningful result and has been shown to achieve high discriminatory capacity and is therefore considered an adequate efficacy endpoint for long-term 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 that classify subjects as non-, moderate, or good responders are dependent on the extent of change and the level of disease activity reached. These criteria are useful when describing clinically meaningful therapeutic targets. Quality of Life (functional assessment of chronic illness therapy [FACIT] and 36-item short-form health survey [SF-36]) assessed during the course of study treatment, provides further insight into the effects on modifying the disease course and its impact on everyday life.

6.7 Rationale of Choice of the Dose and Dosing Interval

For the current study, all enrolled subjects will start the study at the filgotinib 200 mg q.d. or 100 mg b.i.d. dose depending on their dose regimen in GLPG0634-CL-203 or GLPG0634-CL-204. At subsequent visits, the investigator will be allowed to decrease the dose in subjects to 100 mg q.d. in case of intolerance or safety reasons and allowed to return to the 200 mg q.d. or 100 mg b.i.d. dose after the reasons for decreasing the dose have been resolved, and at the investigator's discretion. Subjects can also continue filgotinib 100 mg q.d. when deemed necessary by the investigator.

Ten-day dose regimens up to 450 mg q.d. have been shown to be well tolerated and safe in healthy volunteers. Four weeks of treatment with doses up to 300 mg q.d. was well tolerated by RA subjects in the 2 phase 2a studies.

The results from the 2 phase 2a clinical studies have revealed that a high level of efficacy is achieved with a 200 mg daily dose and there is no added value administering higher (300 mg) doses. In the initial proof-of-concept study, ACR20 at Week 4 was achieved by 92%, 75% and 33% of subjects in the 100 mg b.i.d., 200 mg q.d., and placebo groups, respectively. In the second completed phase 2a study, ACR20 by Week 4 was achieved by 65% of subjects in the 300 mg daily dose group compared to 41% for placebo.

Thus 200 mg daily was chosen as the dose to be administered to give optimal efficacy while maintaining appropriate safety margins based on the preclinical evaluation. To gather data on long-term safety and efficacy on both q.d. and b.i.d. treatment regimens with filgotinib, subjects will remain on the same treatment regimen as during the preceding core study (GLPG0634-CL-203: either q.d. or b.i.d.; GLPG0634-CL-204: q.d.).

7 Study Objectives

7.1 Primary Objective

The primary objective of the study is to evaluate the long-term safety and tolerability of filgotinib for the treatment of rheumatoid arthritis.

7.2 Secondary Objectives

The secondary objectives of the study are:

- To evaluate the long-term efficacy of filgotinib.
- To evaluate the long-term effects of filgotinib administration on subjects' disability, fatigue, and quality of life.

8 Investigational Plan

8.1 Overall Study Design and Plan

This is a multicenter, open-label, long-term follow-up study in subjects with RA. An approximate total of 600 subjects will be enrolled in the study after they have completed one of the previous 2 core studies (GLPG0634-CL-203 or GLPG0634-CL-204). All subjects will start the study at the same dose level (filgotinib 200 mg daily, administered either as 200 mg q.d. or as 100 mg b.i.d., depending on the dosing regimen [frequency of intake of active IMP] that was administered during the preceding core study). The investigator may decide to decrease the daily dose of filgotinib to 100 mg q.d. in case of intolerance or safety reasons. Subjects will return to the 200 mg GLPG0634 daily dose after the reasons for decreasing the dose have resolved, and at the investigator's discretion. Subjects can also continue filgotinib 100 mg q.d. when deemed necessary by the investigator. Subjects coming from the GLPG0634-CL-204 study will be allowed to start MTX treatment, if deemed necessary according to the investigator's clinical judgment.

Subjects have entered the study at Entry Visit on Day -1, which occurred on the same day as the last visit from the previous core study (GLPG0634-CL-203 or GLPG0634-CL-204). Subjects participating in the study have been requested to attend Quarterly Evaluation Visits (QEVs) every 12 weeks. If necessary, unscheduled visits can occur in between the scheduled study visits, for instance, in case the dose of study medication is to be adapted. In case of early withdrawal, an Early Discontinuation Visit (EDV) will be scheduled.

The duration of the participation and treatment for any subject in this study is expected to last for several years (from Entry visit to Follow-up Visit) and will be determined by the sponsor based on the following:

- Open label period (approximately 96 months).
- Marketing Application Approval/Withdrawal in Country of Residence.
- Applicable local reimbursement procedures are in place.

Sites will be notified once these criteria are met.

Following marketing, local (if applicable) regulatory and/or pertinent local reimbursement approval of the study medication, subjects should return to their next quarterly scheduled study visit as specified in the protocol. This visit will serve as a Final Visit and the subjects will be considered as having completed the treatment part of the study. At the end of the study, subjects will be requested to attend a Follow-up Visit approximately 2 weeks after the Final Visit.

The design of the study is presented in the following table.

Study 203		Roll over to **Study 205**
Week 1 – 12	**Week 13 – 24**	
Randomized to placebo	Responders(*) remain on placebo	Half of them are **rerandomized** to 200 mg q.d.
		Half of them are **rerandomized** to 100 mg b.i.d.
	Nonresponders: half of them are **rerandomized** to 100 mg q.d.	**Assigned** to 200 mg q.d.
	Nonresponders: half of them are **rerandomized** to 50 mg b.i.d.	**Assigned** to 100 mg b.i.d.
Randomized to 50 mg q.d.	Responders **remain** on 50 mg q.d.	**Assigned** to 200 mg q.d.
	Nonresponders **assigned** to 100 mg q.d.	**Assigned** to 200 mg q.d.
Randomized to 25 mg b.i.d.	Responders **remain** on 25 mg b.i.d.	**Assigned** to 100 mg b.i.d.
	Nonresponders **assigned** to 50 mg b.i.d.	**Assigned** to 100 mg b.i.d.
Randomized to 100 mg q.d.	**Remain** on 100 mg q.d.	**Assigned** to 200 mg q.d.
Randomized to 50 mg b.i.d.	**Remain** on 50 mg b.i.d.	**Assigned** to 100 mg b.i.d.
Randomized to 200 mg q.d.	**Remain** on 200 mg q.d.	**Remain** on 200 mg q.d.
Randomized to 100 mg b.i.d.	**Remain** on 100 mg b.i.d.	**Remain** on 100 mg b.i.d.
Study 204		Roll over to **Study 205**
Week 1 – 12	**Week 13 – 24**	
Randomized to placebo q.d.	All **assigned** to 100 mg q.d.	**Assigned** to 200 mg q.d.
Randomized to 50 mg q.d.	Responders **remain** on 50 mg q.d.	**Assigned** to 200 mg q.d.
	Nonresponders **assigned** to 100 mg q.d.	**Assigned** to 200 mg q.d.
Randomized to 100 mg q.d.	**Remain** on 100 mg q.d.	**Assigned** to 200 mg q.d.
Randomized to 200 mg q.d.	**Remain** on 200 mg q.d.	**Remain** on 200 mg q.d.

(*) responder: having a decrease of at least 20% in tender joint count (TJC)68 and swollen joint count (SJC)66 versus Baseline.

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*

739 subjects were enrolled from the previous core studies (GLPG0634-CL-203 or GLPG0634-CL-204) into this long-term follow-up study. 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 fulfill all of the following criteria:

1. Male or female subjects who are ≥18 years of age, having completed one of the qualifying core studies GLPG0634-CL-203 or GLPG0634-CL-204 and, who in the opinion of the investigator, will continue to benefit from treatment in the extension study.

2. Female subjects of childbearing potential who engage in heterosexual intercourse must agree to use protocol specified method(s) of contraception and agree to refrain from egg donation and in vitro fertilization as described in Appendix 13.8.

3. Fertile male subjects who engage in heterosexual intercourse must agree to use protocol specified method(s) of contraception and agree to refrain from sperm donation as described in Appendix 13.8.

4. Able and willing to sign the informed consent as approved by the Independent Ethics Committee (IEC)/Institutional Review Board (IRB), prior to the Entry visit and agree to the schedule of assessments.

8.3.3 *Exclusion Criteria*

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

1. Subjects who had been prematurely withdrawn from one of the 2 core studies (GLPG0634-CL-203 or GLPG0634-CL-204), for any reason, including fulfilling the individual stopping criteria.

2. Subjects who are deemed not to be benefiting from the study medication based upon lack of improvement or worsening of their symptoms. Local guidelines for subject treatment need to be followed.

3. Subjects with persistent abnormal laboratory values, associated with the use of the study medication (including but not limited to hematology, liver and renal function values) during one of the 2 core studies (GLPG0634-CL-203 and GLPG0634-CL-204), according to the investigator's clinical judgment.

4. Subjects who require immunization with live/live attenuated vaccine.

5. Subjects with diagnosis since the inclusion to GLPG0634-CL-203 or GLPG0634-CL-204 core studies of rheumatic autoimmune disease or inflammatory joint disease other than RA, except for secondary Sjögren's syndrome.

6. Subjects with symptoms suggestive of moderate to severe congestive heart failure or major cerebrovascular event since the inclusion to GLPG0634-CL-203 and GLPG0634-CL-204 core studies.

7. Subjects with symptoms suggestive of GI tract ulceration and/or active diverticulitis since the inclusion to GLPG0634-CL-203 and GLPG0634-CL-204 core studies.

8. Subjects with symptoms suggestive of possible lymphoproliferative disease including lymphadenopathy or splenomegaly since the inclusion to GLPG0634-CL-203 and GLPG0634-CL-204 core studies.

9. Subjects with symptoms suggestive of malignancy since the inclusion to GLPG0634-CL-203 and GLPG0634-CL-204 core studies.

10. If applicable to national or local legislation: history of being admitted to an institution under administrative or court order since the inclusion to GLPG0634-CL-203 and GLPG0634-CL-204 core studies.

11. History of drug and alcohol abuse since the inclusion to GLPG0634-CL-203 and GLPG0634–CL-204 core studies.

12. Any condition or circumstances which, in the opinion of the investigator, may make a subject unlikely or unable to complete the study or comply with study procedures and requirements.

8.4 Criteria for Interruption or Discontinuation of Study Treatment

8.4.1 *Study Drug Interruption Considerations:*

The medical monitor should be consulted prior to study drug interruption when medically feasible.

Study drug interruption should be considered in the following circumstances; *prior to resumption of study drug, the investigator should discuss the case with the medical monitor*:

- Intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree.

- Subject is scheduled for elective or emergency surgery (excluding minor skin procedures under local or no anesthesia); timing of study drug pausing should be determined in consultation with the *medical monitor*.

- Any subject who develops a new infection during the study should undergo prompt and complete diagnostic testing appropriate for an immunocompromised individual, and the subject should be closely monitored.

- Subjects with newly positive (converted) QuantiFERON® [or equivalent] TB test should be evaluated for active TB. Subjects who are diagnosed with latent TB (including chest X ray evaluation), should interrupt study drug dosing and initiate an adequate course of prophylaxis as per local standard of care; study drug is not to be resumed until after TB treatment has been initiated, as per local standard of care. Subjects may resume study drug only after investigator's written consultation with the *medical monitor*.

- QuantiFERON® tests with indeterminate results may be repeated one time via the central lab. If the repeat result is also indeterminate, the result will be considered positive for the purposes of this study.

  NOTE: During the time of study drug interruption for any of the above, the subject may continue to have study visits and to take part in procedures and assessments, if deemed medically appropriate by the investigator.

The medical monitor should consult the medical leader as needed.

8.4.2 ***Study Drug Discontinuation Considerations:***

The *medical monitor* should be consulted prior to study drug discontinuation when medically feasible.

Study medication should be permanently discontinued in the following instances:

- Any opportunistic infection

- Any subject with active TB

- Any **serious** infection that requires parenteral/intravenous antimicrobial therapy or hospitalization, or any infection that meets SAE reporting criteria.

- Complicated herpes zoster infection (with multi-dermatomal, disseminated, ophthalmic, or CNS involvement)

- Evidence of active HCV during the study, as evidenced by HCV RNA positivity

- Evidence of active HBV during the study, as evidenced by HBV DNA positivity

- Unacceptable toxicity, or toxicity that, in the judgment of the investigator, compromises the subject's ability to continue study-specific procedures or is considered to not be in the subject's best interest

- Treatment failure deemed by the investigator as lack of improvement or worsening of the disease symptoms or occurrence of intolerable AEs.
- Subject request to discontinue for any reason
- Subject noncompliance
- Pregnancy during the study (Section 8.8.1.2.1.5 and Appendix 13.8)
- Discontinuation of the study at the request of Galapagos, a regulatory agency or an institutional review board or independent ethics committee (IRB/IEC)
- Subject use of prohibited concurrent therapy *may* trigger study drug discontinuation; consultation should be made with the *medical monitor*.
- Laboratory criteria:

  After becoming aware of any of the below described abnormal laboratory changes occurring at any one time, an unscheduled visit (ie sequential visit) should occur to retest within 3 to 5 days (except for creatinine, which should be retested 7-14 days later, unless medically indicated sooner).

  — 2 sequential white cell counts <2000 cells/mm^3 (SI: <2.0 x 10^9 cells/L)

  — 2 sequential neutrophil counts <1000 neutrophils/mm3 (SI: <1.0 x 10^9 cells/L)

  — 2 sequential lymphocyte counts <750 lymphocytes/mm^3 (SI: <0.75 x 10^9 cells/L)

  — 2 sequential hemoglobin <8.0 g/dL (SI: <80 g/L)

  — 2 sequential platelet counts <75,000 platelets/mm3 (SI: <75.0 x 10^9 cells/L)

  — 2 sequential aspartate aminotransferase (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[a];

  — 2 sequential AST or ALT elevations >3 times the upper limit of normal accompanied by symptoms consistent with hepatic injury[a];

  — 2 sequential AST or ALT elevations >3 times the upper limit of normal accompanied by elevated INR;

  — 2 sequential AST or ALT elevations >5 times the upper limit of normal, regardless of total Bilirubin or accompanying symptoms[a];

  — 2 sequential values for estimate creatinine clearance <35mL/min based on the Cockcroft Gault formula[b];

— 2 sequential decreases from the baseline (of the core studies [GLPG0634-CL-203 or GLPG0634-CL-204]) of inhibin B by 50% with clinically relevant concurrent increase in FSH[c] per investigator judgment. Note that this study drug discontinuation criterion applies only to subjects with baseline hormone levels within normal limits;

— 2 sequential decreases from the baseline (of the core studies [GLPG0634-CL-203 or GLPG0634-CL-204]) of testosterone by 50% with clinically relevant concurrent increase in LH, per investigator judgment[c]. Note that this study drug discontinuation criterion applies only to subjects with baseline hormone levels within normal limits.

[a] 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 medical monitor.

[b] If Creatinine Clearance has not been centrally reported, use the following: 2 sequential increases in serum creatinine>50% over the averaged of screening and baseline value (of the core studies [GLPG0634-CL-203 or GLPG0634-CL-204]).

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

Subjects withdrawing from the study will be encouraged to complete the same final evaluations as subjects completing the study according to the protocol (please refer to Section 8.7.2.3 Final Visit or EDV), particularly safety evaluations in the subject's interest. The aim is to record data 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.

The medical monitor should consult the medical leader as needed.

8.5 Data Safety Monitoring Board

A DSMB consisting of independent experts was convened to periodically review the accumulating safety data for the study and provide a recommendation on study continuation or early termination in case there were safety concerns. The specific responsibilities and composition of the DSMB were outlined in a separate document, the DSMB Charter. As of 01 April 2021, the independent DSMB reviews were discontinued as ongoing review of safety and efficacy data by the sponsor's clinical study team was considered sufficient by the sponsor, based on the current development status of filgotinib and the open-label design of the study.

8.5.1 *Cardiovascular Endpoint Adjudication Committee*

A Cardiovascular Endpoint Adjudication Committee (CV-EAC) consisting of at least 2 cardiologists and governed by a Charter will be set up to perform adjudication of Major Adverse Cardiovascular Events occurring during the study. The adjudication of these events will be performed in a blinded fashion for the purposes of data analysis, and not for monitoring of subject safety.

8.6 Investigational Products

8.6.1 *Investigational Products Administered*

The study medication is provided as 100 mg strength tablets of filgotinib for oral administration. Study medication was initially provided as 100 mg tablets containing the HCl salt. Patients have now been switched to 100 mg tablets containing the maleate salt. A separate Phase 1 study in healthy volunteers demonstrated that the bioavailability of filgotinib was similar when given as either the HCl salt tablet or as the maleate salt tablet (GS-US-417-3900, see IB[6] for details). This switch to the tablets containing the maleate salt will not occur in a specific country/study center until the required approvals from both the Competent Authorities and IECs/IRBs have been received and the new tablets are available at the study center. Subjects currently taking the HCl salt tablets will switch to the maleate salt tablets at their next planned visit after the maleate salt tablets are available at their study center.

The following doses will be evaluated:

- Filgotinib 200 mg q.d.: 2 tablets of 100 mg filgotinib in the morning.
- Filgotinib 100 mg b.i.d.: 1 tablet of 100 mg filgotinib in the morning and 1 tablet of 100 mg filgotinib in the evening.
- Filgotinib 100 mg q.d.: 1 tablet of 100 mg filgotinib in the morning, for subjects decreasing the dose to 100 mg q.d. in the case of intolerance or safety reasons. Subjects can return to the 200 mg daily dose after the reasons for decreasing the dose have resolved, and at the investigator's discretion. Subjects can continue filgotinib 100 mg q.d. when deemed necessary by the investigator.

8.6.2 *Identity of Investigational Products*

The filgotinib study medication is provided as 100 mg strength tablets. Filgotinib HCl salt tablets are presented as an oral film-coated tablet containing filgotinib as HCl salt equivalent to 100 mg of filgotinib, microcrystalline cellulose, crospovidone, colloidal silicon dioxide and glycerol dibehenate. The tablets are coated with a nonfunctional film-coating using Opadry® II coating powder.

Filgotinib maleate salt tablets, 100 mg are beige, debossed with “GSI” on one side and “100” on the other, capsule-shaped, biconvex, film-coated tablets for clinical use. Each tablet contains the equivalent of 100 mg filgotinib free base in the form of filgotinib maleate. In addition to the active ingredient, filgotinib tablets contain the following inactive ingredients: microcrystalline cellulose, lactose monohydrate, fumaric acid, pregelatinized starch, silicon dioxide, magnesium stearate, macrogol/PEG 3350, polyvinyl alcohol, talc, titanium dioxide, iron oxide yellow, and iron oxide red.

8.6.3 *Packaging, Labelling and Distribution*

Filgotinib 100 mg HCl salt tablets are packaged in high density polyethylene (HDPE) bottles with a polypropylene closure and grouped in a carton box for shipment.

Filgotinib 100 mg maleate salt tablets are packaged in white, HDPE bottles. Each bottle contains 30 tablets, silica gel desiccant and polyester packing material. Each bottle is enclosed with a white, continuous thread, child-resistant polypropylene screw cap fitted with an induction-sealed, aluminium-faced liner.

Study drugs to be distributed to centers in the US and other participating countries shall be labeled to meet applicable requirements of the United States Food and Drug Administration (FDA), EU Guideline to Good Manufacturing Practice – Annex 13 (Investigational Medicinal Products), and/or other local regulations.

Filgotinib 100 mg tablets should be stored at controlled room temperature of 25°C (77°F); excursions are permitted between 15°C and 30°C (59°F to 86°F). Storage conditions are specified on the label.

In case of temperature excursions (outside the permitted range mentioned above), the sponsor should immediately be contacted for evaluation of the excursion and further use of the study drug.

Until dispensed to the subjects, all drug products should be stored in a securely locked area, accessible only to authorized site personnel. To ensure the stability of the study drug and to ensure proper product identification, the drug product should not be stored in a container other than the container in which it is supplied.

Consideration should be given to handling, preparation, and disposal through measures that minimize drug contact with the body. Appropriate precautions should be followed to avoid direct eye contact or exposure when handling.

8.6.4 *Method of Assigning Subjects to Treatment Groups*

Following completion of one of the previous core studies (GLPG0634-CL-203 or GLPG0634-CL-204), subjects who are deemed by the investigator to benefit from continued therapy with study medication, will be offered the option to enter this Long-term Follow-up study. All subjects who opt to roll over into this study will be enrolled and will start the study at the same dose (filgotinib 200 mg daily, administered as either 200 mg q.d. or as 100 mg b.i.d., depending on the q.d./b.i.d. regimen of the preceding core study). Subjects who were on 24 weeks of placebo during the core study

GLPG0634-CL-203 will be randomly assigned to either 100 mg b.i.d. or 200 mg q.d. All other subjects will switch to 200 mg daily, keeping the same regimen (q.d. or b.i.d.) they had in the preceding core study.

This will be done according to a pre-specified randomization scheme prepared by an independent statistician within [redacted]. Upon qualification for the study, subjects will be randomized using a computerized interactive voice/web response system (IXRS) [redacted] to filgotinib 200 mg q.d. or 100 mg b.i.d. in a 1:1 ratio.

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

8.6.5 *Selection of Doses in the Study*

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

8.6.6 *Selection and Timing of Dose for Each Subject*

The study medication will be administered once daily (in the morning) with a glass of water for q.d. dosing, and twice daily (in the morning and evening) with a glass of water for b.i.d. dosing.

For missed dose(s) of study medication, subjects should be instructed to take the missed dose(s) of study medication as soon as possible during the same day. If the missed dose is not taken on the original day, subjects should be cautioned not to double the next dose with the missed dose of study drug under any circumstances. In those cases, the missed dose should be returned to the study drug bottle.

Dose reduction during the study is allowed in the case of intolerance or safety reasons, where investigators will be allowed to decrease the dose from 200 mg q.d. to 100 mg q.d. or from 100 mg b.i.d. to 100 mg q.d. Subjects will then be allowed to return to the full dose of filgotinib (200 mg q.d. or 100 mg b.i.d. as appropriate) after the reasons for decreasing the dose have resolved, and at the investigator's discretion. Subjects can continue filgotinib 100 mg q.d. when deemed necessary by the investigator.

Further dose reductions during the study are not allowed. Instead, the subject should either temporarily or permanently stop the study drug in accordance with Section 8.4).

8.6.7 *Blinding*

This is an open-label study.

8.6.8 *Prior and Concomitant Therapy*

Concomitant therapies taken for the long-term treatment of pre-existing conditions can continue during the study provided they were in accordance with the inclusion and

exclusion criteria of the previous core studies. It is preferred that these medications be continued without variation of dose or regimen during the study, as much as possible.

At each study visit, the site will capture any and all medications taken by the subject since the last visit or during the visit (as applicable). Concomitant medications include prescription, non-prescription medications, therapies, dietary supplements, and minerals.

Subjects coming from the GLPG0634-CL-204 study will be allowed to restart MTX treatment, if deemed necessary according to the investigator's clinical judgment.

In case new (non-prohibited) 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 in the previous core studies and continuing during this study include:

- Non-steroidal anti-inflammatory drugs (NSAIDs) provided that the dose was stable and, if possible, is kept constant during this study;

- Subjects entering the open-label follow-up study had to be on a stable dose of ≤10 mg/day oral prednisone or its equivalent during one of the 2 core studies. The dose of the oral steroid can be reduced or tapered off during this open-label follow-up study based on the investigator's discretion;

- 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.

If subjects were taking folic acid in the previous GLPG0634-CL-203 study as a preventive measure for MTX toxicity, this should be continued at a stable dose for the duration of the study. For those subjects in the previous GLPG0634-CL-204 study who are restarting MTX therapy, folic acid may should be given at >5 mg/week total dose or as per local clinical practice and maintained at a stable dose throughout the study. All local standard-of-care practices for the administration of MTX, including laboratory testing, follow-up care and contraindications should be performed according to local standards of care throughout the study. The concomitant use of csDMARDs and medicines with known drug-drug interactions, such as the increased risk of hepatotoxicity and/or nephrotoxicity when MTX is administered with NSAIDs, salicylates, or folate antagonists, should be avoided, as much as possible, in accordance with clinical practice.

Males, and female subjects of childbearing potential, need to continue to use highly effective birth-control methods as outlined in Appendix 13.8. 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 it was ongoing in the previous core studies, or if there is a new diagnosis of menopause. 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.

Vitamin, mineral or herbal supplementations are permitted during the study per judgment of investigator and should be kept at a stable dose and regimen, as much as possible.

Prohibited concomitant medications while on study drug include:

- Any DMARDs, other than background MTX, including oral or injectable gold, sulfasalazine, azathioprine, D penicillamine, cyclosporine, and leflunomide. Subjects in the previous GLPG0634-CL-204 study who were on a stable dose of antimalarials can continue with the same treatment.

- Any cytotoxic agent, including chlorambucil, cyclophosphamide, nitrogen mustard, and other alkylating agents.

- Use of any JAK inhibitor or other small molecule immunomodulator

- Increases in dosage or dosing regimen of, or initiation of, potent P-gp inducers (e.g. rifampin, phenytoin, carbamazepine, and St. John's wort). Subjects already on stable doses should continue per investigator judgment.

Subjects may receive a maximum of 3 intra-articular injections of corticosteroid every 12 months while participating in this open-label extension study. The dose of corticosteroid injected should not exceed the anti-inflammatory equivalent dose of prednisone 40 mg suspension. The dose and volume should be adjusted downward as appropriate to the size of the joint. For the analysis of the TJC68 and SJC66, these joints will be considered "not assessable" for 3 months from the time of the intra-articular injection.

Vaccine Guidelines:

- Prior to study participation, it is recommended that the subject's vaccinations be brought up to date according to local vaccination standards.

- Live or attenuated vaccines (including, but not limited to varicella and inhaled flu vaccine) are prohibited within 30 days of Day 1, throughout the study, and for 6 weeks after the last dose of study drug.

- Subjects should be advised to avoid routine household contact with persons vaccinated with live/attenuated vaccine components. General guidelines suggest that a study subject's exposure to household contacts should be avoided for the below stated time periods:

- Varicella or attenuated typhoid fever vaccination – avoid contact for 4 weeks following vaccination
- Oral polio vaccination -- avoid contact for 6 weeks following vaccination
- Attenuated rotavirus vaccine -- avoid contact for 10 days following vaccination
- Inhaled flu vaccine -- avoid contact for 1 week following vaccination

Inactivated vaccines (such as inactivated flu vaccines) should be administered according to local vaccination standards whenever medically appropriate; however, there are no available data on the concurrent use of filgotinib and its impact on immune responses following vaccination.

8.6.9 *Treatment Compliance and Drug Accountability*

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 retrained 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*.

8.7 Study Procedures

All planned study assessments are presented in the flow chart in Section 8.8.1.3.

8.7.1 *Pre-treatment*

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

8.7.1.1 Entry Visit (Extension Visit 1, Day -1)

The Entry Visit (Visit 1) will take place on Day -1 relative to the start of the study medication intake. There will be no gap between the core studies and the open-label extension study.

- Subjects will be assessed for eligibility against the inclusion and exclusion criteria.
- Entry Visit data will be those collected at the Week 24 visit from the previous core study in which the subject has participated (GLPG0634-CL-203 or GLPG0634-CL-204) for physical examination, 12-lead ECG, vital signs, clinical laboratory tests (including serum pregnancy test), SJC66, TJC68, Physician's Global Assessment, Patient's Global Assessment, health assessment questionnaire – disability index (HAQ-DI), FACIT fatigue scale, and SF-36 questionnaire. Data on demographics, baseline characteristics, and medical history will be retrieved from the

Screening visit of the previous core studies. Data will not be re-entered in the GLPG0634-CL-205 eCRF but will be retrieved from the preceding core study database during statistical programming.

- Urine (dipstick) pregnancy test for females of childbearing potential.
- Tuberculosis (TB) blood test (QuantiFERON-TB gold test[a]) will be performed.
- Any new AEs that have occurred since signing the informed consent form (ICF) will be documented.
- Any ongoing or unresolved AEs and concomitant medications from the preceding core study will be documented on the GLPG0634-CL-205 AE and concomitant medication pages of the eCRF, respectively.
- IXRS call.

[a] In case of a positive or confirmed indeterminate result for QuantiFERON-TB gold test: 1.) Permanent withdrawal of the subject from the study; 2.) Consultation with the local infectious disease specialist is highly recommended to investigate if the patient has active or latent TB or no TB

When all the Entry Visit 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. The subject will start taking the study medication on Day 1 and subsequent visits will be scheduled.

8.7.2 *Treatment Period*

In addition to the procedures noted below, urine pregnancy tests will be done for female subjects of childbearing potential every 4 weeks during study participation through the follow-up visit using home urine pregnancy tests that will be provided to the subject. The site will call the subject every 4 weeks to obtain results of these pregnancy tests and will record the information in the source documents and CRF. If a positive urine pregnancy test is reported, the subject will be asked to return to the clinic for a confirmatory serum pregnancy test. Refer to Appendix 13.8 for more information.

8.7.2.1 Quarterly Evaluation Visit (QEV)

A QEV visit will take place every 12 weeks ±1 week relative to the start of the study medication intake.

- Subjects will be assessed for eligibility against the withdrawal criteria.
- Any remaining study medication as well as empty study medication containers will be returned to the investigator and an accountability check performed.
- A physical examination will be performed.
- Weight is measured at all visits.

- A 12-lead ECG 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.
- Hematology, clinical chemistry, hormones (for male subjects only), and urinalysis (dipstick and, in case of abnormal dipstick result, microscopy) tests will be performed on samples collected at this visit. A urine pregnancy test will be performed on females of childbearing potential.
- 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.
- IXRS call.

When all of these procedures have been performed, the study medication will be dispensed, and the date of the next visit confirmed.

8.7.2.2 Annual Visit (AV)

An annual visit (AV) will take place at 48 weeks ±1 week relative to the start of the study medication intake. All of the procedures as outlined in the QEV will be performed. In addition, the following will be performed:

- A serum pregnancy test will be performed on females of childbearing potential (ie, no urine pregnancy test will be performed).
- TB blood test (QuantiFERON-TB gold test) will be performed.
- Weight is measured.
- The subject will complete the FACIT fatigue scale and SF-36 questionnaire.

When all of the procedures have been performed, the study medication will be dispensed, and the date of the next visit confirmed.

8.7.2.3 Final Visit or Early Discontinuation Visit (EDV)

Following marketing, local (if applicable) regulatory and/or pertinent local reimbursement approval of the study medication, subjects should return to their next quarterly scheduled

study visit as specified in the protocol. This visit will serve as a Final Visit and the subjects will be considered as having completed the treatment part of the study.

- Any remaining study medication as well as empty study medication containers will be returned to the investigator and an accountability check performed.
- A physical examination will be performed.
- Weight is measured.
- A 12-lead ECG 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.
- Hematology, clinical chemistry, hormones (for male subjects only), and urinalysis (dipstick and, in case of abnormal dipstick result, microscopy) tests will be performed on samples collected at this visit. A serum pregnancy test will be performed on females of childbearing potential.
- 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.

8.7.3 *Follow-up Visit*

A Follow-up Visit will take place 2 weeks (+/- 4 days) after the Final Visit or the EDV.

- A physical examination will be performed.
- Weight is measured.
- A 12-lead ECG 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.

- Hematology, clinical chemistry (without CRP), hormones (for male subjects only), and urinalysis (dipstick and, in case of abnormal dipstick result, microscopy) tests will be performed on samples collected at this visit. A serum pregnancy test will be performed on females of childbearing potential.

8.7.4 *Duration of Treatment*

Subjects participating in the study will be requested to attend a series of visits throughout the study, including: an Entry Visit (Day -1 [Extension Visit 1]), QEVs every 12 weeks, a Final Visit, and a Follow-up Visit approximately 2 weeks after the Final Visit. In case of early withdrawal, an EDV will be scheduled. Home urine pregnancy testing will also be required for female subjects of childbearing potential every 4 weeks during study participation through the follow-up visit using home urine pregnancy tests provided to the subject (refer to Appendix 13.8).

The duration of the participation and treatment for any subject in this study is expected to last for several years (from Entry visit to Follow-up Visit) and will be determined by the sponsor based on the following:

- Open label period (approximately 96 months).
- Marketing Application Approval/Withdrawal in Country of Residence.
- Applicable local reimbursement procedures are in place.

Sites will be notified once these criteria are met.

Following marketing, local (if applicable) regulatory and/or pertinent local reimbursement approval of the study medication, subjects should return to their next quarterly scheduled study visit as specified in the protocol. This visit will serve as a Final Visit and the subjects will be considered as having completed the treatment part of the study. A Follow-up Visit will take place approximately 2 weeks after the Final Visit or the EDV.

8.8 Efficacy and Safety Variables

The flow chart in Section 8.8.1.3 shows the planned study assessments.

8.8.1 *Efficacy and Safety Measurements Assessed and Flow Chart*

8.8.1.1 Efficacy Assessments

8.8.1.1.1 Evaluation of Disease Activity

Efficacy assessments (excluding FACIT and SF-36) will be carried out at every visit, except the Follow-up Visit. FACIT and SF-36 will be carried out at the AV and the Final Visit/EDV.

Each of 68 joints will be evaluated for tenderness, and each of 66 joints will be evaluated for swelling, except upon receipt of an intra-articular injection of corticosteroid in the previous 3 months, where joints will be classed as not assessable (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 years' 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.

8.8.1.1.2 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" to the question "Considering all the ways arthritis affects you, how well are you doing today?" (Appendix 13.3).

8.8.1.1.3 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).

8.8.1.1.4 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 derive the ACR20/50/70.

8.8.1.1.5 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).

8.8.1.1.6 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 (GH) 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.

8.8.1.2 Safety Assessments

8.8.1.2.1 Adverse Event Definitions and Reporting

8.8.1.2.1.1 Definitions

ICH, FDA 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 non-investigational) 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 non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product.

Serious Adverse Event

An 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/incapacity.

- is a congenital anomaly/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 GLPG0634, the expectedness of AEs will be determined by whether or not it is an ADR 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 which cannot be explained by disease or other drugs. Response to withdrawal is plausible (pharmacologically, pathologically). Event definitive pharmacologically or phenomenologically (ie, 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: In case no action is taken regarding the study medication.
- Study medication permanently withdrawn: In case a subject is permanently withdrawn from the study.
- Study medication temporarily withdrawn: In case the study medication is temporarily withdrawn.
- Dose reduction: If a subject's daily dose is adjusted from 200 mg to 100 mg (q.d., once daily in the morning).
- Not applicable: Other situations (eg, in case an 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.

8.8.1.2.1.2 Recording Adverse Events

AEs will be recorded from the signature of ICF until the final Follow-up Visit. In case an AE is ongoing at that time, it will be followed up until resolution or until stabilization by the investigator's medical judgment.

It is the responsibility of the investigator to collect all AEs (both serious and non-serious) 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 last visit or the Follow-up Visit), whether observed by the investigator or investigational staff, or spontaneously reported by the subjects, will be recorded in the eCRF.

8.8.1.2.1.3 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.

8.8.1.2.1.4 Reporting Serious Adverse Events [redacted]

All SAEs, whether or not deemed study medication-related, must be recorded in the eCRF and SAE form and reported by the investigator [redacted] Belgium) within 24 hours by facsimile. Other means of transmission can be decided where facsimile is not possible. The SAE form 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, postmortem 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 case of permanent impairment, until the condition stabilizes.

The contact information is:

[redacted]

8.8.1.2.1.5 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 within

24 hours of knowledge of the event, using a pregnancy form. Any subject who becomes pregnant during the study must be promptly withdrawn from the study (not applicable if subjects are 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.

8.8.1.2.1.6 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 risk 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.

8.8.1.2.2 Clinical Laboratory Evaluation

The hematology and clinical chemistry 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 at the AV will not exceed 43 mL.

The total amount of blood to be taken at Entry Visit, QEV, Final Visit/EDV and Follow-up Visit will not exceed 39 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, aspartate aminotransferase, ALT, gamma-glutamyltransferase, alkaline phosphatase, total bilirubin, amylase, lipase, albumin, total protein, sodium, potassium, chloride, glucose, uric acid, total cholesterol, HDL- and LDL-cholesterol, triglycerides, calcium, and phosphorus.

Serum CRP will be measured at every visit except the Follow-up Visit.

Serum pregnancy test for females of childbearing potential is performed at the AV, Final Visit/EDV and the Follow-up Visit.

Hormone tests (for male subjects only)

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

Urinalysis

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

Urine pregnancy test for females of childbearing potential is performed at Entry Visit and QEV, and also performed every 4 weeks during the dosing period through 35 days after their last dose of study drug using home pregnancy tests that will be provided to them. Refer to Appendix 13.8 for details.

Other

TB blood (QuantiFERON-TB Gold) test at Entry Visit and AV.

8.8.1.2.3 Vital Signs

Vital signs (blood pressure [systolic and diastolic] and HR) will be recorded as described in the flow chart in a standardized manner, ie, after the subject has rested in the sitting position for 5 minutes.

8.8.1.2.4 Physical Examination

A physical examination will be performed at times as described in the flow chart. Any changes will be recorded.

8.8.1.2.5 Other Safety Assessments

12-Lead ECG

A resting 12-lead ECG will be performed at times presented in the flow chart.

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, morphology, and rhythm analysis. QTcF 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.

8.8.1.3 Flow Chart

Event	Entry Visit	Treatment period[a]			FUV
Study schedule[b]	D -1[c]	QEV (q12 weeks)	AV (q48 weeks)	FV/EDV	FV + 2 weeks Or EDV + 2 weeks
Informed consent	X				
Inclusion/ exclusion criteria	X				
Withdrawal criteria		X	X		
Physical examination		X	X	X	X
Pregnancy test[d]	X	X	X	X	X
12-Lead ECG		X	X	X	X
Vital signs[e]		X	X	X	X
TB blood test	X		X		
Clinical laboratory tests[f]		X	X	X	X
IXRS call	X	X	X	X	
Study medication dosing	→	→	→	→	
Serum CRP		X	X	X	
SJC66		X	X	X	
TJC68		X	X	X	
Physician's global assessment		X	X	X	

Event	Entry Visit	Treatment period[a]			FUV
Study schedule[b]	D -1[c]	QEV (q12 weeks)	AV (q48 weeks)	FV/EDV	FV + 2 weeks Or EDV + 2 weeks
Patient's global assessment		X	X	X	
HAQ-D		X	X	X	
FACIT fatigue scale			X	X	
SF-36 questionnaire			X	X	
AE assessment	→	→	→	→	→
Concomitant medications	→	→	→	→	→

a. During the treatment period, a visit time window of ±1 week is allowed for each quarterly visit.

b. QEV=Quarterly Evaluation Visit every 12 weeks; AV=Annual Visit every 48 weeks; FV=Final Visit; EDV=Early Discontinuation Visit; FUV=Follow-Up Visit.

c. Entry Visit data are those collected at the last visit from the previous core study in which the subject has participated (GLPG0634-CL-203 or GLPG0634-CL-204) for physical examination, 12-lead ECG, vital signs, clinical laboratory tests (including serum CRP and serum pregnancy test), SJC66, TJC68, Physician's Global Assessment, Patient's Global Assessment, HAQ-DI, FACIT fatigue scale, and SF-36 questionnaire, with the exception of demographics, baseline disease characteristics, and medical history.

d. For female subjects of childbearing potential only. Urine pregnancy test will be performed at Entry Visit and QEV and serum pregnancy test will be performed at AV, Final Visit/EDV and Follow-up Visit. In addition, home urine pregnancy testing will be performed every 4 weeks using home testing kits provided to the subject, as described in Appendix 13.8.

e. Vital signs are defined as heart rate and blood pressure (systolic and diastolic).

f. Refer to Section 8.8.1.2.2.

8.8.2 *Appropriateness of Measurements*

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

8.9 Statistical Methods

8.9.1 *Statistical and Analytical Plans*

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

8.9.1.1 Datasets or Populations Analyzed

All subjects who received at least one dose of study medication in the GLPG0634-CL-205 study will be included in the safety analysis.

All subjects who received at least one dose of study medication in the GLPG0634-CL-205 study will be included in the efficacy analysis.

As it is optional that MTX is restarted for subjects rolling over from the GLPG0634-CL-204 study, the analysis tables may keep subjects with/without MTX background therapy separated as well as pooled.

Other subgroups may be studied separately, when the sample size is considered to be of relevant size.

8.9.1.2 Demographic and Other Baseline Characteristics

Demographic characteristics will be listed. Demographic and baseline clinical characteristics; trial termination reasons; concomitant medications; and drug exposure will be summarized using appropriate descriptive statistics, as applicable.

8.9.1.3 Safety Variables

Clinical safety will be evaluated by assessing treatment-emergent AEs (TEAEs), physical examinations, laboratory assessments, ECG results, and vital signs results. The safety analysis may combine the data of all 3 studies (GLPG0634-CL-203, GLPG0634-CL-204, and GLPG0634-CL-205).

A treatment-emergent analysis of AEs will be done, based on the start date of the AE. TEAE (AE and SAE) preferred terms, intensity, frequency, relationship to study medication, dose reductions, and temporary/permanent treatment stops will all be tabulated. An additional analysis based on patient-years of exposure may be added when deemed useful.

Original results and changes from baseline will be summarized for all laboratory, vital signs, and ECG parameters, intended to detect any changes in safety parameters that could be attributed to GLPG0634 dosing. No imputations will be done for safety data in cases where subjects discontinued the study prematurely.

Further subgroup analyses (e.g., a selection of TEAEs with an onset date during the first weeks or months, or a division according to the mean actual dose) and exploratory analyses may be added when deemed appropriate.

8.9.1.4 Efficacy Variables

The efficacy analysis may combine the data of all 3 studies (GLPG0634-CL-203, GLPG0634-CL-204, and GLPG0634-CL-205).

Definition of Efficacy Endpoints

ACR20

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 and TJC68

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.

ACR50 and ACR70

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

ACR-N

The ACR-N[7] 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, patient's assessment of pain, 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's 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[9] 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 28 Joints Corrected for CRP (DAS28[CRP])

The DAS28(CRP)[10] is a statistically derived index combining tender joints (28 joints), swollen joints (28 joints), CRP, and the Patient's Global Assessment of Disease Activity (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(CRP+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[11]:

	Improvement in DAS28(CRP) from Baseline:		
Actual DAS28(CRP)	**>1.2**	**>0.6 and ≤1.2**	**≤0.6**
≤3.2	Good	Moderate	None
>3.2 and ≤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, components of the ACR, SDAI, and CDAI, and the quality of life data (FACIT fatigue scale and SF 36 questionnaire)) will be analyzed descriptively.

Details on the analysis will be specified in the statistical analysis plan. A descriptive sensitivity analysis by country and geographic region may 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.

8.9.1.5 Interim Analyses

Safety data will be reviewed by the sponsor on an ongoing basis. Details are presented in Section 8.5.

Interim analyses of efficacy and/or safety data may be added when such data are needed (e.g., when the integrated safety and efficacy analyses will be performed for the registration file). If such an interim analysis would be done, no correction for multiplicity will be applied because all analyses will be mainly descriptive.

8.9.2 *Determination of Sample Size*

It is expected that around 70% of the subjects in the previous core studies GLPG0634-CL-203 (N=595, approximately) and GLPG0634-CL-204 (N=280, approximately) will roll over into this study, corresponding to a sample size of roughly 600 subjects: 0.7 x (595 subjects in study 203 + 280 subjects in study 204) = 612.

8.10 Quality Assurance and Quality Control

8.10.1 *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 its nominated representative. In addition, inspections may be conducted by regulatory authorities at their discretion.

8.10.2 *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.

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.

8.10.3 *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 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 (eg, for laboratory data, ECGs) as well as for cross table checking between eCRFs (eg, AE and concomitant medication forms).

Medical coding will use Medical Dictionary for Regulatory Activities for concomitant diseases and AEs and World Health Organization Drug dictionary 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 pharmaceutical formulation (tablets) and 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 as needed throughout the study. The study monitor will also perform a final inventory of study medication at the close-out visit in 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 investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures. The study investigator must ensure that the potential risk of infertility is discussed with all male subjects during the informed consent process. The investigator must use the most current IRB/IEC approved consent form for documenting written informed consent. Each informed consent (or assent as applicable) will be appropriately signed and dated by the subject and the person conducting the consent discussion, and also by an impartial witness if required by IRB/ IEC or local requirements.

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.

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13 Appendices

13.1 Investigator Signature Page

Protocol Title: A multicenter, open-label, long-term follow-up safety and efficacy study of GLPG0634 treatment in subjects with moderately to severely active rheumatoid arthritis
Protocol Number: GLPG0634-CL-205

Investigator Statement

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Galapagos NV. I will discuss this material with them to ensure that they are fully informed about the drugs and the study.

Principal Investigator Name (Printed)	Signature
Date	Site Number

13.2 66/68 Joint Count

Joints Assessed (left and right)

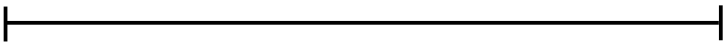
Temporomandibular
Sternoclavicular
Acromioclavicular
Shoulder
Elbow
Wrist
Metacarpophalangeal
  First
  Second
  Third
  Fourth
  Fifth
Proximal interphalangeal
  First
  Second
  Third
  Fourth
  Fifth
Distal interphalangeal
  Second
  Third
  Fourth
  Fifth
Hip #
Knee
Ankle
Tarsus
Metatarsophalangeal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

#Assessed for tenderness only
Joints will not be assessed if an intra-articular injection of corticosteroid has been given in the previous 3 months, where joints will be classed as not assessable.

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.



0 100

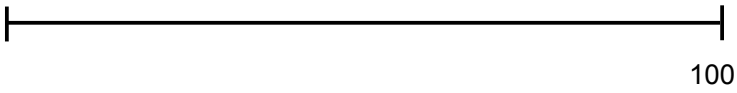
Very Well Very Poor

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.



0 100

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

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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

English (Universal)

16 November 2007
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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. Compared to one year ago, how would you rate your health in general now?

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!

13.8 Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Methods

The administration of filgotinib in embryo-fetal animal development studies resulted in decreased numbers of viable rat fetuses, increased resorptions, and visceral and skeletal malformations. Similar effects were noted in the rabbit. A safety margin relative to human exposure has not been identified. Pregnancy is contraindicated during use of filgotinib.

For participation in this study, all subjects of childbearing potential must agree to the use of *highly effective* contraception as outlined below. In addition, women of childbearing potential should have a urine pregnancy test every 4 weeks during the study.

1) Definitions

a) Definition of Childbearing Potential

For the purposes of this study, a female-born subject is considered of childbearing potential following the initiation of puberty (Tanner stage 2) until becoming post-menopausal, unless permanently sterile or with medically documented ovarian failure. Women who do not meet below criteria for being post-menopausal, are not permanently sterile, or do not have medically documented ovarian failure must have pregnancy testing as outlined by the protocol.

Women are considered to be in a postmenopausal state when they are ≧ 54 years of age with cessation of previously occurring menses for ≥12 months without an alternative cause. In addition, women of any age with amenorrhea ≥12 months may also be considered postmenopausal if their FSH level is in the postmenopausal range at Screening and they are not using hormonal contraception or hormonal replacement therapy.

Permanent sterilization includes hysterectomy, bilateral oophorectomy, or bilateral salpingectomy in a female subject of any age. Bilateral tubal ligation is not considered permanent sterilization.

b) Definition of Male Fertility

For the purposes of this study, a male-born subject is considered fertile after the initiation of puberty unless permanently sterile by bilateral orchidectomy or has medical documentation of permanent male infertility. Vasectomy is not considered permanent sterilization.

2) Contraception for Female Subjects

a) Study Drug Effects on Pregnancy and Hormonal Contraception

Filgotinib is contraindicated in pregnancy as there is a possibility of human teratogenicity/fetotoxicity in early pregnancy based on non-clinical data. Data from a

drug-drug interaction study of filgotinib and hormonal contraceptives demonstrated that filgotinib does not alter the pharmacokinetics of representative hormonal contraceptives levonorgestrel/ethinyl estradiol. For male subjects, male condom should be used; for their female partners of childbearing potential, an accepted contraceptive method should also be considered. Details are outlined below. Please refer to the latest version of the filgotinib investigator's brochure for additional information.

b) Contraception for Female Subjects of Childbearing Potential

The inclusion of female subjects of childbearing potential requires the use of highly effective contraceptive measures. Women must have a negative serum pregnancy test from Week 24 for the previous core study they participated in and a negative urine pregnancy test at the Entry Visit. Urine pregnancy tests will be performed at each Quarterly Evaluation Visit and Serum pregnancy tests will be performed at each Annual Visit and the Final Visit or Early Discontinuation Visit. In addition, urine pregnancy tests will also be performed every 4 weeks during study participation through the follow-up visit using home pregnancy urine tests that will be provided to them. The site will call the subject every 4 weeks to obtain results of these pregnancy tests and will record the information in the source documents and CRF. If a positive urine pregnancy test is reported, the subject will be asked to interrupt study drug and return to the clinic for a confirmatory serum pregnancy test. In the event of a delayed menstrual period (> one month between menstruations), a pregnancy test must be performed to rule out pregnancy. This is true even for women of childbearing potential with infrequent or irregular periods. Female subjects must agree to use one of the following methods from the Entry Visit until 35 days following the last dose of study drug, or for at least 6 months following the last dose of study drug for females of childbearing potential who were taking concurrent MTX therapy, as indicated by the SmPC of MTX.

- Complete abstinence from intercourse of reproductive potential. Abstinence is an acceptable method of contraception only when it is in line with the subject's preferred and usual lifestyle.

  Or

- Consistent and correct use of 1 of the following methods of birth control listed below.

  — Intrauterine device (IUD) with a failure rate of <1% per year

  — Tubal sterilization

  — Essure micro-insert system (provided confirmation of success 3 months after procedure)

  — Vasectomy in the male partner (provided that the partner is the sole sexual partner and had confirmation of surgical success at least 3 months after procedure, with documentation of sperm-free ejaculate)

Female subjects who wish to use a hormonally based method must agree to use it in conjunction with a barrier method (used either by the female subject or by her male partner). Female subjects who utilize a hormonal contraceptive as one of their birth

control methods must have consistently used the same method for at least three months prior to study dosing. Hormonally-based contraceptives and barrier methods permitted for use in this protocol are as follows:

- Hormonal methods (subject must agree to use with a barrier method, preferably, with a male condom)
  - Oral contraceptives (either combined estrogen/progestin or progesterone only)
  - Injectable progesterone
  - Implants of levonorgestrel
  - Transdermal contraceptive patch
  - Contraceptive vaginal ring
- Barrier methods (subject must agree to use with a hormonal method)
  - Male or female condom, with or without spermicide
  - Diaphragm with spermicide
  - Cervical cap with spermicide
  - Sponge with spermicide
- All female subjects must also agree to refrain from egg donation and in vitro fertilization during study participation and for at least 35 days after the last study drug dose, or for at least 6 months for female subjects of childbearing potential who were taking concurrent MTX therapy, as indicated by the SmPC of MTX.

Participants and their providers must agree to adhere to the respective SmPC for concomitant csDMARDs used by the subject during the study. For example, if methotrexate is used as concomitant background medication during the clinical trial, subjects and investigators must agree to adhere to the methotrexate SmPC: “Women must not become pregnant during and at least 6 months after treatment with methotrexate and must therefore practice an effective form of contraception.”

3) Contraception for Male Subjects

It is theoretically possible that a relevant systemic concentration may be achieved in a female partner from exposure to the male subject’s seminal fluid. Therefore, male subjects with female partners of childbearing potential must agree to use condoms during study participation and for 90 days after the last study drug dose, or for at least 6 months for subjects who were taking concurrent MTX therapy, as indicated by the SmPC of MTX. Female partners of male study subjects should consider using one of the above methods of contraception as well. Male subjects must also agree to refrain from sperm donation during treatment and until at least 90 days after the end of dosing, or for at least 6 months for subjects who were taking concurrent MTX therapy, as indicated by the SmPC of MTX.

4) Unacceptable Birth Control Methods

Birth control methods that are unacceptable include periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM). Female condom and male condom should not be used together.

5) Procedures to be Followed in the Event of Pregnancy

Subjects will be instructed to notify the investigator if they become pregnant at any time during the study, or if they become pregnant within 35 days of last study drug dose, or within at least 6 months for subjects who were taking concurrent MTX therapy, as indicated by the SmPC of MTX. Subjects who become pregnant or who suspect that they are pregnant during the study must report the information to the investigator and discontinue all study drug and background therapy immediately. Subjects whose partner has become pregnant or suspects she is pregnant during the study are to report the information to the investigator.

Instructions for reporting pregnancy, partner pregnancy, and pregnancy outcome are outlined in Section 8.8.1.2.1.5.