



CLINICAL STUDY PROTOCOL

Study Title: A Multicenter, Open-label, Long Term Extension Study to Assess the Safety and Efficacy of Filgotinib in Subjects with Rheumatoid Arthritis

Sponsor: Alfasigma S.p.A
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IND Number: 115,510
EudraCT Number: 2016-003630-25
EU Trial Number: 2024-513919-27-00
Clinical Trials.gov Identifier: NCT03025308

Indication: Rheumatoid Arthritis

Protocol ID: GS-US-417-0304

Medical Leader: Name: [REDACTED]

Protocol Version/Date:

Amendment 1:	10 November 2016
Amendment 2:	22 February 2018
Amendment 3:	28 March 2019
Amendment 4:	24 September 2019
Amendment 5:	24 April 2020
Amendment 6:	11 June 2021
Amendment 7:	21 January 2022
Amendment 8:	30 June 2023
Amendment 9:	10 June 2024

CONFIDENTIALITY STATEMENT

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CLINICAL STUDY PROTOCOL HISTORY

Clinical study protocol/ Amendment #	Date	Main Rationale General/Country-specific
CSP Version 1.0	23-Aug-2016	Initial CSP version General
Amendment 1	10-Nov-2016	Clarification of study procedures and update of benefit-risk General
Amendment 2	22-Feb-2018	Clarification of study procedures General
Amendment 3	28-Mar-2019	Extension of total study duration General
Amendment 4	24-Sep-2019	Study unblinding since all subjects had completed their participation in the parent studies (GS-US-417-0301 or GS-US-417-0302 or GS-US-417-0303) General
Amendment 5	24-Apr-2020	Inclusion of language on major adverse cardiovascular events adjudication; addition of guidance for subjects experiencing a thromboembolic event; change to the requirement for annual tuberculosis testing from compulsory to optional; clarification on continued data monitoring committee review of safety data; language “until commercially available” was removed to minimize confusion around the study end date across the globe. General
Amendment 6	11-Jun-2021	Change of sponsorship from Gilead to Galapagos. The Galapagos study number (GLPG0634-CL-304) was added. General
Amendment 7	21-Jan-2022	Include the option for the sponsor to terminate the study following commercialization of the study drug; change of visit schedule to 6-monthly; and extension of the visit window. General
Amendment 8	30-Jun-2023	Instructions for dose adjustments during the study were added, including a posology recommendation for elderly patients.

		Study drug interruption/discontinuation criteria for lymphopenia and neutropenia were added and instructions were added for dose reduction in case of confirmed moderate renal impairment. Contraceptive requirements for male and female subjects were adjusted. Removal of biomarker sample collection. General
Amendment 9	10 June 2024	Sponsor details have been updated in scope of the sponsorship transfer of the study from Galapagos NV to Alfasigma S.p.A. General

CSP=clinical study protocol

SUMMARY OF CHANGES

Amendment 9 (10-June-2024)
The overall reason for this amendment: The main reason for this amendment is the sponsorship transfer of the study from Galapagos NV to Alfasigma S.p.A.
The changes made to the clinical study protocol GS-US-417-0304 (GLPG0634-CL-304) Amendment 8, 30-Jun-2023, are listed below, with a brief rationale of each change and the applicable sections.
Change and Rationale: Sponsor details have been updated in scope of the sponsorship transfer of the study from Galapagos NV to Alfasigma S.p.A. and the safety reporting instructions were updated to follow Alfasigma's convention. The applicable sections have been modified to that extent. Applicable Sections: Cover page Protocol Synopsis Section 1.3 Rationale for this Study 7.3.2. Serious Adverse Events 7.7.2. Instructions for Reporting Special Situations Appendix 1. Investigator Signature Page
Change and Rationale: The new EU trial number has been added and reference is made to the European Union Clinical Trial Regulation (EU) No 536/2014 and European Data Protection Regulation (GDPR 676/2016). Applicable Sections: Cover page Protocol Synopsis 7.4. Sponsor Reporting Requirements 9.1.1. Good Clinical Practice
Change and Rationale: [REDACTED] [REDACTED] Applicable Sections: [REDACTED] [REDACTED]
Change and Rationale: The Sponsor's medical leader has been updated due to transfer of responsibilities. Applicable Sections: Cover page Signature page

Amendment 8 (30-Jun-2023)
The overall reason for this amendment: - a To add instructions for dose adjustments during the study, including an instruction for elderly patients (65 years of age and above) with well-controlled disease to use the lowest effective dose of filgotinib to align with the recommended posology for elderly patients in the Investigator's Brochure (IB). For subjects with insufficient disease control on filgotinib 100 mg once daily (QD), the possibility to allow a dose escalation to filgotinib 200 mg was added. - b To add study drug interruption/discontinuation criteria regarding lymphopenia and neutropenia in alignment with the latest IB. - c To add instructions for a dose reduction from filgotinib 200 mg to 100 mg in case of confirmed moderate renal impairment in alignment with the latest IB. - d Contraceptive requirements for male and female subjects were adjusted. ■ [REDACTED] In addition, minor updates and corrections were made.
The changes made to the clinical study protocol GS-US-417-0304 (GLPG0634-CL-304) Amendment 7, 21-Jan-2022, are listed below, reflecting a brief rationale of each change and the applicable sections.
Rationale: Instructions for dose adjustments during the study were added, including an instruction for elderly patients (65 years of age and above) with well-controlled disease to use the lowest effective dose of filgotinib to align with the recommended posology for elderly patients in the IB. For subjects with insufficient disease control on 100 mg QD, the possibility to allow a dose escalation to filgotinib 200 mg was added. Applicable sections: 3.2.1, 3.3
Rationale: A study drug interruption/discontinuation criterion for subjects with an absolute lymphocyte count <500 cells/mm³ was added. The requirement to permanently discontinue a subject after 2 sequential neutrophil counts <750 neutrophils/mm³ was removed and replaced with a study drug interruption criterion for absolute neutrophil counts <1000 neutrophils/mm³. These changes were made to align with the latest version of the IB. Applicable sections: 3.5
Rationale: Instructions were added for a dose interruption and dose reduction from filgotinib 200 mg to 100 mg in case of confirmed moderate renal impairment to align with the recommendations in the latest version of the IB. Applicable sections: 3.5

Rationale: The requirements for male subjects to use condoms and for pregnancies in female partners to be reported during this study were removed because seminal transfer is not considered to lead to relevant systemic exposure in partners of childbearing potential.

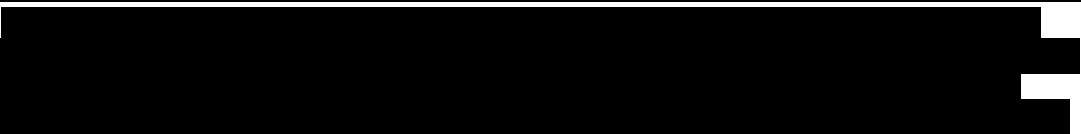
Applicable sections: Protocol Synopsis, [4.2](#), [5.3](#), [7.7.2.1](#), [Appendix 5](#)

Rationale: The contraception requirements for females were modified to remove the requirement for the use of a barrier method with hormonal contraceptives. Based on a dedicated clinical pharmacology study, no clinically relevant drug-drug interaction was observed when filgotinib was combined with ethinylestradiol and levonorgestrel. Therefore, there is no need for women of childbearing potential to supplement hormonal contraception with a condom as per the Clinical Trials Facilitation and Coordination Group guidance.

Applicable sections: [Appendix 5](#)

Rationale: Based on the results from the clinical testicular safety studies, the potential risk of impaired spermatogenesis has been removed from the IB. Hence, the requirement to discuss the potential risk of infertility for male subjects has been removed from the informed consent process.

Applicable sections: [9.1.3](#)

Rationale: 

Applicable sections: Protocol Synopsis, [3.8](#), [6.6](#), [6.8](#), [6.11](#), [Appendix 2](#)

Rationale: The Sponsor's medical leader has been updated due to transfer of responsibilities.

Applicable sections: cover page

Rationale: Communication references between the medical monitor and medical leader have been removed from the protocol because these details are provided in the Medical Monitoring Plan.

Applicable sections: [3.5](#), [7.6](#)

Rationale: Adverse events of interest have been updated to align with the latest version of the IB.

Applicable sections: [7.1.3](#)

Rationale: The sponsor's logo has been updated on the cover page.

Applicable sections: cover page

Rationale: Minor actualizations have been made to align with the most recent IB.

Applicable sections: [1.2.1](#), [1.4](#)

Amendment 7 (21-Jan-2022)
The overall reason for this amendment: The aim of this amendment is to include the option for the sponsor to terminate the study when filgotinib becomes commercially available. Including this option will reduce subject burden as subjects will be allowed to continue their treatment with the reimbursed product once they complete the study and will no longer have to attend study visits and undergo/complete study assessments. Further, the frequency of visits will be reduced to 6-monthly (every 24 weeks). Six-monthly evaluations are considered sufficient in stable subjects from a safety perspective and will reduce subject burden. In addition, minor administrative corrections were made.
The changes made to the clinical study protocol GS-US-417-0304 (GLPG0634-CL-304) Amendment 6, 11-Jun-2021, are listed below, reflecting a brief rationale of each change and the applicable sections.
Rationale: When filgotinib is commercially available, the continued participation in an interventional study could only increase subject burden from a disease management perspective. The subjects will be discontinued from the study following commercial availability of filgotinib to ensure continuous access to filgotinib therapy. Applicable sections: Protocol Synopsis, 3.4 , 6.8 (original section numbering: 6.9)
Rationale: The reduced frequency of onsite visits is aimed to reduce subject burden in terms of both travel/site attendance and assessments required. In terms of safety data collection, prompt reporting and follow-up of any potential intermittent safety event is emphasized and continued on an ongoing basis. Further, for evaluating sustained remission/low disease activity, the EULAR task force (Smolen et al., 2020) recommends disease activity assessment every 6 months. Applicable sections: Protocol Synopsis, 6.6 (original section numbering; section deleted), 6.6 (original section numbering: 6.7), 6.7 (original section number: 6.8), 6.8 (original section numbering: 6.9), 6.10.1 (original section numbering: 6.11.1), 6.10.5 (original section numbering: 6.11.5), Appendix 2
Rationale: The visit window for the 24-weekly and 48-weekly visits was extended from 5 to 10 days to allow more flexibility from a subject and site perspective. Applicable sections: Appendix 2
Rationale: The introduction was updated with the most up to date information. Applicable sections: 1.1 , 1.2.1 , 1.2.2.3
Rationale: It was further clarified that upon implementation of protocol amendment 4, the study design changed to open-label. Applicable sections: 3.3 , 5.1 , 5.1.1 , 5.2
Rationale: It was clarified that the “no” box on the ICF is not included in all regions. Applicable sections: 3.8.2
Rationale: It was clarified that the dose of corticosteroid injected should not exceed the equivalent dose of triamcinolone 40 mg suspension per joint . Applicable sections: 5.3 (original section numbering: 5.2)
Rationale: It was clarified that commercially available JAK inhibitors are prohibited concomitant medications. Applicable sections: 5.4
Rationale: The EULAR recommendation to administer the COVID-19 vaccine to rheumatic patients was added. This additional flexibility was added to accommodate other guidelines. Applicable sections: 5.5

Rationale: An additional condition was added for the local destruction of drug supplies. This can only occur if the study monitor has performed a drug accountability during an on-site monitoring visit and the sponsor provided approval for destruction. Applicable sections: 5.6.1, 9.1.7
Rationale: For additional flexibility, it was clarified that TB testing every 48 weeks after Day -1 is at the discretion of the investigator rather than the PI. Applicable sections: Protocol Synopsis, 6.2, 6.7 (original section numbering: 6.8)
Rationale: It was clarified that at the end of the study/upon early discontinuation, any remaining study drug as well as empty study drug containers will be returned to the investigator and an accountability check performed. Applicable sections: 6.8
Rationale: A protocol history page and summary of changes overview were added. Applicable sections: Clinical Study Protocol History, Summary of Changes
Rationale: A statement on the use of electronic signatures was added. Applicable sections: Signature Page

COVID-19: Coronavirus Disease 2019; EULAR: European League Against Rheumatism; ICF: informed consent form; JAK: Janus kinase; PI: principal investigator; TB: tuberculosis

An overview of the changes introduced in previous amendments can be found in the separate protocol amendment summary of changes document for each amendment.

PROTOCOL SYNOPSIS

Alfasigma S.p.A.
Via Ragazzi del '99 n. 5
40133 Bologna
Italy

Study Title: A Multicenter, Open-label, Long Term Extension Study to Assess the Safety and Efficacy of Filgotinib in Subjects with Rheumatoid Arthritis

IND Number: 115,510

EudraCT Number: 2016-003630-25

EU Trial Number: 2024-513919-27-00

Clinical Trials.gov Identifier: NCT03025308

Study Centers Planned: Approximately 450 centers worldwide
Study centers that participated in GS-US-417-0301, GS-US-417-0302, or GS-US-417-0303

Objectives: The primary objective of this study is as follows:

- To evaluate the long-term safety and tolerability of filgotinib in subjects who have completed one of the parent studies of filgotinib in Rheumatoid Arthritis (RA).

The secondary objectives of this study are as follows:

- To evaluate the long-term efficacy of filgotinib in subjects with RA.

The exploratory objectives of this study are:

- To evaluate the long-term effects of filgotinib on subject-reported outcomes, such as disability, fatigue, and quality of life.

Study Design: This study was originally designed and initiated as a dose-blinded, long term extension (LTE) study of safety and efficacy of filgotinib in subjects with RA. Subjects were enrolled in the study after having completed one of the 3 parent RA studies (GS-US-417-0301, GS-US-417-0302, or GS-US-417-0303). The study design changed to open-label following implementation of protocol amendment 4.

The subject's first dose of LTE study drug defines Day 1 of participation on the LTE, and should not occur sooner than the day after the final visit for the parent protocol. The Day -1 visit for this study will be performed at either the last visit for the parent protocol (Week 52 visit for GS-US-417-0301 and GS-US-417-303, Week 24 visit for GS-US-417-0302) or within 4 weeks after the final study visit for the parent protocol.

The subject may be consented and eligibility confirmed on Day -1 (the same day as the last visit for the parent protocol), with study drug dispensed to start on Day 1 of the LTE study.

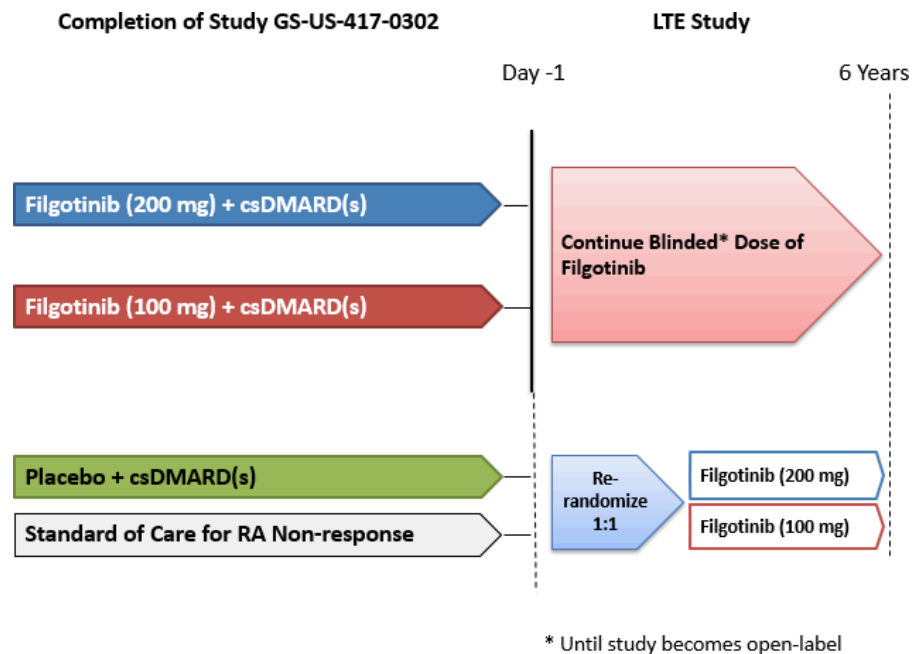
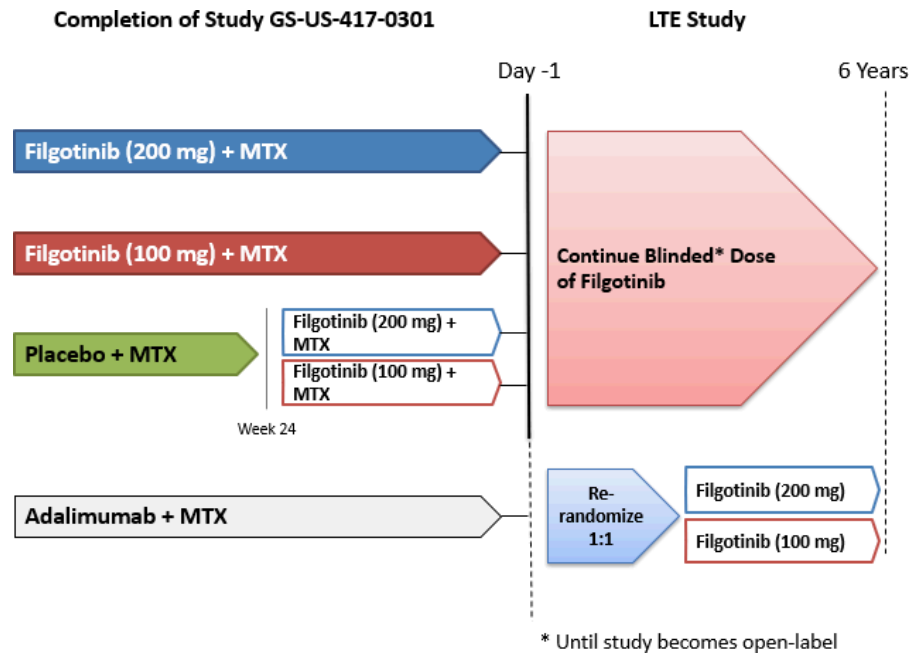
Eligibility for participation in the study will be confirmed on completion of the parent protocol. Subjects who wish to enroll in the extension study will review and sign the study ICF prior to any procedures or tests being performed.

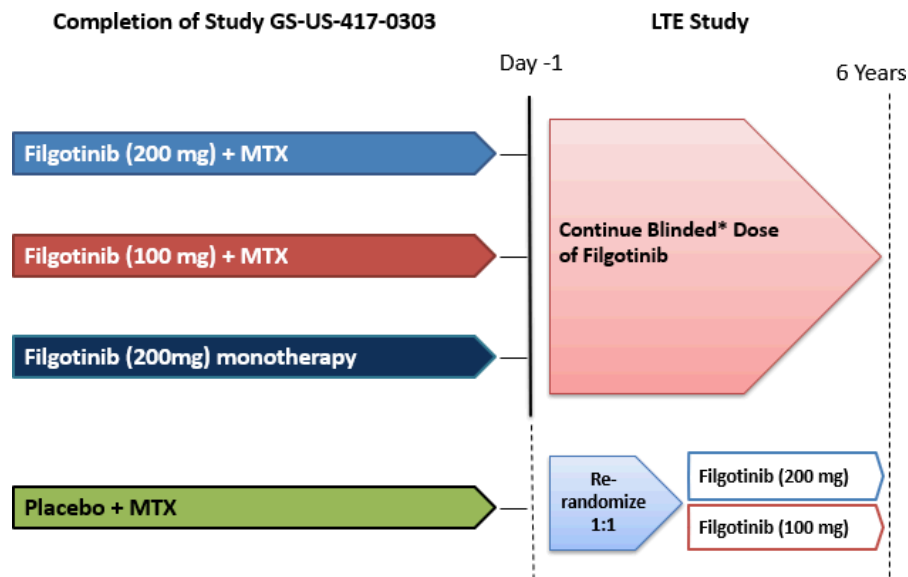
NOTE: Tuberculosis (TB) screening results will not be available at rollover – see Section 3.5.1 for required procedures relating to indeterminate or positive TB test results.

After eligibility for the study had been confirmed, the subject was assigned to one of the two filgotinib dosing arms in a blinded fashion:

- Subjects who were on blinded filgotinib at the final visit of the parent study continued on their same dose of filgotinib in a blinded fashion (100 mg or 200 mg QD) until study unblinding.
- Subjects who were receiving adalimumab (GS-US-417-0301), placebo (GS-US-417-0302), or methotrexate monotherapy (GS-US-417-0303) at their final visit of the parent study, were re-randomized on Day -1 of the LTE in a 1:1 ratio to either 100 mg or 200 mg filgotinib QD in a blinded fashion until study unblinding.
- Subjects from study GS-US-417-0302, who discontinued blinded study drug due to inadequate response of their RA, were eligible for the LTE, and were re-randomized on Day -1 of the LTE in a 1:1 ratio to either 100 mg or 200 mg filgotinib QD in a blinded fashion until study unblinding.
- Subjects from studies GS-US-417-0301 and GS-US-417-0303, who completed the studies after being transitioned to standard of care therapy, were not eligible for the LTE study.
- Subjects will be provided filgotinib for up to 6 years, until the sponsor terminates clinical development of filgotinib, or until filgotinib becomes commercially available; whichever comes first.

All subjects will remain blinded to their filgotinib daily dosing regimen until the study becomes open-label.





* Until study becomes open-label

All subjects may continue their stable dose of permitted csDMARD(s) as indicated in the parent protocol, with the exception of subjects from study GS-US-417-0303, who will discontinue their study drug doses of weekly MTX/PTM. These subjects may resume/start MTX and/or other csDMARDs (per investigator judgment) after at least 4 weeks of their first dose of study drugs in the LTE.

All subjects who are re-randomized on Day -1 of the LTE will be stratified by geographic region and parent study.

Number of Subjects Planned:	Approximately 2800 subjects
Target Population:	Subjects who have completed GS-US-417-0301, GS-US-417-0302, or GS-US-417-0303.
Duration of Treatment:	Up to 6 years, until the sponsor terminates clinical development of filgotinib, or until filgotinib becomes commercially available; whichever comes first.

Diagnosis and Main Eligibility Criteria: For a complete list of study inclusion and exclusion criteria, please refer to Sections 4.2 and 4.3.

Key Inclusion Criteria

- 1) Male or female subjects who may benefit from filgotinib as judged by the investigator AND who completed a Gilead sponsored filgotinib parent study for RA as outlined below:
 - a) Subjects who completed GS-US-417-0301, GS-US-417-0302, or GS-US-417-0303 on study drugOR
 - b) Subjects who completed GS-US-417-0302 on standard of care therapy due to RA non-responder status
- 2) Females of childbearing potential must have a negative pregnancy test prior to first dose of study drug in the LTE
- 3) Criterion modified per amendment 8.
 - 3.1) Female subjects of childbearing potential who engage in heterosexual intercourse must agree to protocol-approved methods of contraception

Key Exclusion Criteria

- 1) Diagnosis of an autoimmune or inflammatory joint disease other than RA, which would put the subject at risk by participating in the study or would interfere with study assessments/data interpretation, per judgment of the investigator
- 2) Known hypersensitivity to the study drug or its excipients
- 3) Any medical condition (including, but not limited to, cardiac or pulmonary disease, alcohol or drug abuse) which would put the subject at risk by participating in the study or would interfere with study assessments/data interpretation, per judgment of the investigator

Study Procedures/
Frequency: Participating subjects will visit the clinical study center at Day -1 (defined as the day of the subject's last visit in the parent study or any day up to 4 weeks after the last visit in the parent study), Weeks 2, 6, and every 24 weeks thereafter (every 12 weeks until protocol amendment 7 implementation); up to 6 years, until the sponsor terminates clinical development of filgotinib, or until filgotinib becomes commercially available, whichever comes first.

Subjects who tested negative on the parent protocol and have never been previously treated for TB will be retested at Day -1 and every 48 weeks thereafter per investigator discretion, while in the study. Refer to Section 3.5.1 for additional details.

Females of child-bearing potential will be tested for pregnancy via serum testing at Baseline, but as results may not be available prior to dosing, they must have a negative urine pregnancy test on Day - 1, prior to study drug administration, **and every 4 weeks thereafter while on the study.**

For urine pregnancy testing dates that do not coincide with study visits, urine pregnancy test kits will be provided to the subject and the site will contact the subject every 4 weeks to obtain and record the results of the home urine pregnancy test. Subjects may also return to the study site to perform the monthly urine pregnancy tests, if they prefer.

On study drug assessments will include: adverse events (AEs), concomitant medications, review of study medication compliance through drug accountability, SJC66, TJC68, Patient Reported Outcomes (including Subject's Global Assessment, Subject's Pain Assessment, HAQ-DI, Functional Assessment of Chronic Illness Therapy-Fatigue [FACIT-Fatigue], Short-Form Health Survey [SF36], [REDACTED]

[REDACTED] Physician's Global Assessment, physical examination, weight, vital signs, serum CRP, blood and urine sampling for safety laboratory tests and [REDACTED] (at selected visits), and urine pregnancy tests (females of child bearing potential only).

[REDACTED]

Post dosing follow-up assessments include AEs, concomitant medications, physical examination, weight, vital signs, blood and urine sampling for safety laboratory tests, and urine pregnancy tests (females of child bearing potential only).

Test Product, Dose, and Mode of Administration:	200 mg filgotinib orally once daily (QD) 100 mg filgotinib orally once daily (QD)
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Reference Therapy, Dose, and Mode of Administration:	Not applicable
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Permitted Background Therapy	Commercially available csDMARD(s) are permitted (but not required) as described in protocol and are to be administered according to the local product label. Subjects on commercially available MTX should also be prescribed folic acid (or equivalent), dosed as per judgment of investigator/local standard of care.
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**Criteria for
Evaluation:**

Safety:	Safety will be assessed by the reporting of AEs, clinical laboratory tests, physical examination, and vital signs.
Efficacy:	Efficacy will be evaluated by ACR-N in each arm. Exploratory Endpoints will include subject achievement of ACR20/50/70 and EULAR responses.
Pharmacokinetics:	Not applicable

Statistical Methods: Safety data will be listed by subject and summarized by treatment. Adverse events will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA). The severity will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE).

Number and Percentage of subjects of treatment-emergent AEs (TEAEs) will be summarized by treatment, system organ class and preferred term. TEAEs will also be summarized by relationship to study drug and severity. In addition, TEAEs leading to premature discontinuation of study drug will be summarized and listed.

Listings of individual subject laboratory results will be provided. Selected laboratory data will be summarized by treatment at scheduled visits and for the corresponding change from baseline. The incidence of treatment-emergent laboratory abnormalities will be summarized by treatment.

The primary analysis set for safety and efficacy is the Safety Analysis Set, which includes all enrolled subjects who received at least 1 dose of study drug.

The proportion of subjects who achieve ACR20/50/70 over time, ACR-N and EULAR responses over time, changes from baseline in DAS28 (CRP), HAQ-DI, CDAI, SDAI, SF-36, FACIT-Fatigue, [REDACTED] will be summarized over time from Day -1 through the end of treatment by treatment group. Differences across treatment groups will be summarized and treatment comparisons may be performed.

This study will be conducted in accordance with the guidelines of Good Clinical Practice (GCP) including archiving of essential documents.

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

Ab	Antibody
ACR X	American College of Rheumatology X% improvement
AE	adverse event
AEIs	adverse events of interest
ALC	absolute lymphocyte count
ALT	alanine aminotransferase
ANA	anti-nuclear antibody
aPTT	activated partial thromboplastin time
ATP	adenosine triphosphate
AST	aspartate aminotransferase
AUC _{0-τ}	area under the plasma drug concentration-time curve of a dosing interval
bDMARD(s)	Biologic disease modifying antirheumatic drug(s)
b.i.d.	bis in die; twice daily
C _τ	trough plasma concentration (just before the next dosing ie predose sample)
CCP	cyclic citrullinated peptide
CDAI	Clinical Disease Activity Index
csDMARD(s)	Conventional synthetic (cs) disease modifying antirheumatic drug(s)
CES	Carboxylesterases
CIA	collagen-induced arthritis
C _{max}	maximum observed plasma concentration
CMV	Cytomegalovirus
CNS	central nervous system
COVID-19	Coronavirus Disease 2019
CrCl	creatinine clearance
CRO	Contract Research Organization
CRP	C-reactive protein
CVEAC	Cardiovascular Safety Endpoint Adjudication Committee
CYP	Cytochrome P450
DAS28	Disease Activity Score based on 28 joints
DBP	diastolic blood pressure
DMARD(s)	diseasemodifying antirheumatic drug(s)
DMC	Data monitoring committee
dsDNA	double stranded deoxyribonucleic acid
DSS	dextran sulphate sodium
EDC	electronic data capture
ECG	Electrocardiogram
eCRF	electronic case report form
ET	early termination
EU	European Union
EULAR	European League Against Rheumatism

FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy-Fatigue
FAS	Full Analysis Set
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GGT	gamma glutamyl transferase
GI	gastrointestinal
GLPG	Galapagos
HAQ-DI	Health Assessment Questionnaire – Disability Index
HCV	hepatitis C virus
HCG	human chorionic gonadotropin
HCQ	Hydroxychloroquine
HDL	high density lipoprotein
hERG	human etheragogo related gene
HIV	human immunodeficiency virus
HR	heart rate
IC ₅₀	half maximal inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
IMP	investigational medicinal product
IRB	Independent Review Board
ITT	intent-to-treat
IWRS	Interactive web response system
JAK	janus kinase
LCMS/MS	liquid chromatography mass spectrometry
LDL	low density lipoprotein
LH	luteinizing hormone
LTE	Long Term Extension
MACE	major adverse cardiovascular event
MCV	mean corpuscular volume
MTX	Methotrexate
MTX-IR	inadequate response to Methotrexate
NSAIDs	nonsteroidal anti-inflammatory drugs
NYHA	New York Heart Association
OATs	organic anion transporters
PK	Pharmacokinetics
PP	per-protocol

PT	prothrombin time
PTM	Placebo to match
QD	quaque die; once daily
RA	rheumatoid arthritis
RF	rheumatoid factor
SAE	serious adverse event
SAP	Statistical Analysis Plan
SBP	systolic blood pressure
s.c.	Subcutaneous
SD	standard deviation
SDAI	Simplified Disease Activity Index
SF-36	short-form health survey
SI	international system of units
SJC66	swollen joint count based on 66 joints
SOC	Symptom Organ Class
TB	Tuberculosis
TEAEs	Treatment emergent adverse events
TJC68	tender joint count based on 68 joints
$t_{\max}$	the time of occurrence of maximum observed plasma concentration
TNF α	tumor necrosis factor alpha
UC	ulcerative colitis
UGTs	uridine diphosphate glucuronosyltransferases
ULN	upper limit of normal
US	United States

[REDACTED]
vs. Versus

WBC white blood cell
[REDACTED]

DEFINITION OF TERMS

QTcF

QT interval corrected for HR according to Fridericia's formula:

$QTcF = QT / (RR)^{1/3}$, where $RR = 60/HR$

RR = RR interval in seconds

HR = heart rate in beats per minute

Cockcroft-Gault
Formula (Creatinine
Clearance)

Cockcroft-Gault $CrCl = [(140 - \text{age}) \times (\text{Wt in kg}) \times (0.85 \text{ if female})] / (72 \times Cr)$

Wt= Weight in Kilograms

Cr= Creatinine in mg/dL

1. INTRODUCTION

1.1. Background

Rheumatoid arthritis (RA) is a chronic, systemic inflammatory disease that affects approximately 1.3 million adults in the United States (US) (Helmick et al., 2008). Rheumatoid arthritis manifests principally as an attack on peripheral joints and may lead to marked destruction and deformity of joints, with considerable disability and impact on quality of life. It is characterized by the production of autoantibodies, synovial inflammation with formation of pannus tissue, and erosion of underlying cartilage and bone. Although people of any age can be affected, the onset of RA is most frequent between the ages of 40 and 50 years, and women are affected 3 times more often than men. While the cause of RA is still not completely understood, aberrant B-cell activation, T-cell co-stimulation, osteoclast differentiation, and cytokine release have all been implicated in its pathogenesis.

Treatment of RA is dependent on severity, the patient's co-morbidities and initial response to therapy. Methotrexate (MTX) is a conventional, synthetic disease modifying anti-rheumatic drug (csDMARD) and continues to be the cornerstone of RA therapy (Singh et al., 2012). Patients with an inadequate response to csDMARD(s) are often treated with biologic therapies such as tumor necrosis factor inhibitors (TNFi) as an initial second line therapy. However, approximately 28% to 58% of RA patients with inadequate response to MTX fail TNFi as reviewed in (Redlich et al., 2003). In this setting, treatment guidelines recommend either switching to another TNFi, alternate biologic, or to a small molecule drug (Singh et al., 2012). Despite significant advances in disease management in recent years, there remains a need for new treatments since not all patients respond adequately to current therapies, have co-morbidities and some patients experience toxicities and/or intolerance that limit the use of approved therapies.

In November 2012, tofacitinib (Xeljanz®) became the first Janus kinase (JAK) inhibitor to receive Food and Drug Administration (FDA) approval for the treatment of adult patients with RA. Tofacitinib is a small molecule, has strong binding affinity for JAK1 and JAK3, and weaker affinity for JAK2. The extensive pre-clinical and 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. Baricitinib (Olmiant®; JAK 1/2 inhibitor), peficitinib (Smyraf®; since 2019), and upadacitinib (Rinvoq®; JAK 1 inhibitor) (since 2019) have been approved in various markets for the treatment of RA. Filgotinib has been granted marketing authorization in the European Union (EU), Japan, Taiwan, and Great Britain for treatment of adult patients with moderate to severe active RA who have had an inadequate response with, lost response to, or were intolerant to one or more disease modifying anti-rheumatic drugs (DMARDs).

While the pan JAK inhibitor tofacitinib has shown an early onset of action and long-term efficacy in RA as monotherapy and in combination with background conventional csDMARDs therapy, dose levels were limited by side effects potentially mediated by its effect on JAK 2 and JAK 3. This highlights the need for more selective and targeted therapies with improved immunomodulatory and hematologic effects.

JAK1 is thought to be an integral part of RA pathogenesis due its role in transmitting inflammatory cytokine signaling. Hence, targeted inhibition of JAK1 has great potential for the treatment of RA with an improved safety and side effect profile.

1.2. Filgotinib

1.2.1. General Information

Janus kinases are intracellular cytoplasmic tyrosine kinases (TYKs) that transduce cytokine signaling from membrane receptors through signal transducer and activator of transcription (STAT) to the nucleus of cells. JAK inhibitors block the signaling of various cytokines, growth factors, and hormones, including the pro-inflammatory cytokine interleukin (IL)-6.

Four different types of JAKs are known, JAK1, JAK2, JAK3, and TYK2 which co-interact with different sets of membrane receptors. Inhibition of JAKs is a promising therapeutic option for a range of inflammatory conditions.

Filgotinib (GS-6034, formerly GLPG0634) is a preferential inhibitor of JAK1. Filgotinib is approved for treatment of moderate to severe active RA and moderate to severe active ulcerative colitis (UC) in >30 countries worldwide.

In humans, filgotinib is metabolized to form one major active metabolite, GS-829845 [REDACTED]. Though the potency of this metabolite is lower than the parent molecule, the overall exposure and peak plasma concentration in humans is higher than seen in all tested animal species. 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.

For further information on filgotinib, refer to the current investigator's brochure (IB).

1.2.2. Nonclinical Pharmacology, Absorption, Distribution, Metabolism, and Excretion (ADME) and Toxicology

Filgotinib and its metabolite, GS-829845 have been extensively characterized in nonclinical studies. This program includes cellular assays demonstrating potency and selectivity of the compound against JAK1; efficacy studies in rats and mice; repeat dose toxicity studies (up to 26 weeks in the rat and 39 weeks in the dog), *in vitro* and *in vivo* safety pharmacology and genetic toxicology studies, and reproductive toxicology studies in rats and rabbits. Additional toxicology studies conducted include phototoxicity studies and dose-range finding studies in support of a definitive rat juvenile toxicity study and a 6 month carcinogenicity study in transgenic (TgrasH2) mice. A 2 year rat oral carcinogenicity study is ongoing.

1.2.2.1. Primary and Secondary Pharmacology

Filgotinib is an adenosine triphosphate (ATP)-competitive inhibitor of JAK1. It is highly selective for inhibition of JAK1 over 451 other kinases evaluated *in vitro*. In cellular assays, it inhibits JAK/STAT-driven processes with half maximal inhibitory concentration (IC₅₀) values from 179 nM onwards. In human whole blood, JAK1 is inhibited by filgotinib with an IC₅₀ of

629 nM and exhibits approximately 30-fold selectivity over JAK2. Filgotinib demonstrated significant efficacy in the rat collagen-induced arthritis (CIA) model as well as in the mouse dextran sulphate sodium (DSS)-induced colitis model.

Metabolite GS-829845 exhibits a similar JAK1 selectivity profile but is approximately 10 to 20-fold less potent than the parent filgotinib in *in vitro* assays. GS-829845 was as effective as filgotinib in the rat CIA model, but at doses that required a 10-fold higher exposure.

1.2.2.2. 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 exposure in RA subjects given filgotinib 200 mg QD. Filgotinib and GS-829845 had no relevant effects on cardiovascular parameters (human ether-a-gogo related gene [hERG] and dog telemetry studies), apart from a slight non-adverse increase in heart rate and arterial pressure with GS-829845 at exposures 7-fold that of the C_{max} in subjects with RA treated with 200 mg q.d. filgotinib. There were no relevant effects on electrocardiogram (ECG) and QT intervals, which was further confirmed by a negative Thorough-QT study in healthy adults.

1.2.2.3. Nonclinical ADME

Filgotinib demonstrates 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 generally dose proportional without gender differences. No accumulation occurs with repeated dosing. The mean terminal half-life after oral administration is 4 and 5 hours (h) in rats and dogs, respectively.

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

Excretion is nearly complete within 24 h (rat) and 48 h (dog) post-dosing. In the rat, fecal and urinary excretion accounted for 40% and 53% of the administered dose, respectively, with a bile secretion of about 15%. In the dog, fecal excretion was the primary route of excretion, accounting for 59% of the administered dose, with urinary excretion accounting for 25%.

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 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.

Administration of multiple doses of filgotinib had no clinically relevant effect on exposure of pravastatin, rosuvastatin, or atorvastatin, which are different organic anion transporting polypeptide substrates.

1.2.2.4. 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 resulted in an estimated mean clinical AUC of 2.80 $\mu\text{g}\cdot\text{h}/\text{mL}$, 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 toxicology 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 embryoletality and teratogenicity in rats and rabbits at exposures similar to the human exposure at 200 mg QD 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.

1.2.3. Clinical Trials of Filgotinib

Comprehensive data from the Phase 1 and 2 programs are available to support development into Phase 3. All relevant information from the nonclinical and clinical development program is included 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 1-1). 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 1-1. 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)***

ACR=American College of Rheumatology; ITT=Intent-to-treat; NRI=non-responder imputation; W=week

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

Source: GLPG0634-CL-203

At both Weeks 12 and 24 the mean decrease in DAS28 (CRP) ([Appendix 9](#)) was statistically significantly greater across all filgotinib dose groups compared with placebo. A dose-response was observed. No statistically significant difference was apparent between the once and twice daily regimens. At both Weeks 12 and 24, the mean decrease in Simplified Diagnostic Activity Index (SDAI) and Clinical Diagnostic 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 subject of these subjects with ≥ 1 serious TEAE, who received filgotinib 100 mg bid twice daily with concurrent MTX, died during the second 12 weeks of the treatment 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 QD 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 ($\geq 10\%$) 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 treatment 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). 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 remained 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 testosterone 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 QD compared to placebo at Week 12.

As shown in [Table 1-2](#) 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 1-2. 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)

ITT=Intent-to-treat; NRI=non-responder imputation; W=week

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

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. 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 at Week 12.

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 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.

Throughout the 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 QD 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 for efficacy endpoints and safety.

1.3. Rationale for This Study

Over the last decade, changes in RA treatment strategies, accompanied by advances in drug development and the addition of targeted biological therapies, have greatly improved the outcomes for subjects with RA. Despite these developments, therapeutic challenges remain. The current conventional and biologic DMARDs may be ineffective or produce only partial responses in some subjects and may be associated with significant safety and tolerability concerns. There is a medical need for simple, orally administered therapies with novel and targeted mechanisms of action that can effectively improve the disease course while being safe and well-tolerated. This need is especially pronounced for subjects that have had an inadequate response or are intolerant to bDMARDs, as they may have limited options remaining for further treatment. This LTE study is offered so that subjects who have completed one of the three parent studies for this protocol can be provided ongoing access to a drug that may provide therapeutic benefit for their chronic RA.

Filgotinib is an orally administered, small molecule inhibitor of JAK1 an intracellular tyrosine kinase that is dysregulated in subjects with inflammatory disorders including RA. Filgotinib has demonstrated clinical activity and a favorable safety and tolerability profile in Phase 2 studies in subjects with moderately to severely active RA.

1.3.1. Rationale for Study Design

GS-US-417-0304 (Study ID GLPG0634-CL-304) started as a Phase 3 randomized, double-blind, long term extension (LTE) study designed to evaluate the long-term safety, efficacy and durability of response of filgotinib in subjects with RA as single therapy or in combination with csDMARD(s). The study design changed to open-label upon implementation of protocol amendment 4.

As an LTE study, the study will begin after the subject's completion of the end of study treatment visit at Week 52 (GS-US-417-0301 and GS-US-417-0303), or Week 24 (GS-US-417-0302). All subjects entering the LTE were dosed in a double-blind fashion until implementation of protocol amendment 4 and study unblinding. The study's primary goal 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 100 mg or 200 mg dose 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, quality of life, treatment satisfaction and health care utilization. The efficacy assessments will be the same as for the previous Phase 3 studies, with the exception of imaging outcomes.

1.3.2. Rationale for the Outcome Measures

Safety and tolerability will be assessed by the evaluation of adverse events (AEs), selected clinical laboratory parameters, vital signs, and physical examinations, all of which are standard safety evaluations in clinical research studies.

The ACR20, ACR50, and ACR70 responses and the DAS28 (CRP) are considered reliable measures of response to treatment and disease activity, respectively, in subjects with RA. Evaluation of continuous outcome measures of DAS28 and ACR-N enables the demonstration of improvement and magnitude of benefit. The EULAR response criteria classify subjects as non-, moderate-, or good-responders depending on the extent of change and the level of disease activity reached. These response criteria are useful when describing clinically meaningful therapeutic results. The Clinical Disease Activity Index (CDAI) and the Simplified Disease Activity Index (SDAI) have been widely used in clinical studies to demonstrate the impact of a study drug on controlling disease activity.

Assessing quality of life (measured by the Functional Assessment of Chronic Illness Therapy [FACIT-Fatigue], 36-item short form health survey [SF-36], [REDACTED] at Day -1 and during the course of study treatment provides insight into the effects on modifying disease course and impact on daily life. Assessing the change in economic impact [REDACTED] RA over the course of the study provides insight into the subject's ability to work and other daily activities as well as the impact on the burden of healthcare resources.

1.3.3. Rationale for the Choice of Dose and Dosing Interval

All enrolled subjects will take daily filgotinib during the LTE at either 200 mg QD or 100 mg QD, depending on their dosing arm assignment at the end of their respective parent study.

The 100 mg and 200 mg QD dose regimens are being studied in the respective parent studies based on the safety and efficacy data from the Phase 2 studies in RA. The observed plateau in the pSTAT1 response at the 200 mg dose indicates that doses above 200 mg are unlikely to add additional benefit. Inclusion of two doses in the LTE will enable establishment of an appropriate nominal dose for the treatment of RA and determine the regimen with the most favorable risk: benefit profile in these populations on a long-term basis.

Safety data collected across the four Phase 2 clinical studies showed no dose-dependent trends in the incidence of AEs or SAEs, including infections, or laboratory abnormalities with the exception of numerical increase in select gastrointestinal AEs (eg, nausea, vomiting, abdominal pain, and upper abdominal pain). This numerical increase was observed in the 200 mg total daily dose arm as compared to the 100 mg total daily dose arm. However, the overall frequency was low and clinical relevance is unknown. Filgotinib, administered at a dose of 100 mg or 200 mg QD was found to be safe and well tolerated. The safety profile was consistent with that observed for an immunomodulatory compound administered to subjects with RA.

1.4. Risk/Benefit Assessment for the Study

The safety profile for filgotinib has been informed by results from nonclinical and clinical studies evaluating a wide range of doses. More information about the known and expected benefits, risks, and reasonably anticipated adverse events (AEs) may be found in the investigator's brochure (IB). An independent data monitoring committee (DMC) is appointed to monitor the study until the study is unblinded and will provide an additional level of risk mitigation.

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 resulted in an estimated mean clinical AUC of 2.80 $\mu\text{g}\cdot\text{h/mL}$, which represents an exposure margin of 2.3, 1.8, and 3.4-fold when considering the mean AUC in male dogs at the NOEL in the 26 week and 39 week chronic toxicity studies, and the 39 week targeted exposure toxicity study, respectively.

Decreased lymphocytes have been observed in nonclinical studies and lymphopenia is an identified adverse drug reaction of filgotinib.

Filgotinib has shown an increased risk of embryofetal malformations at exposures similar to human doses; the use of highly effective contraception in the female subject population is utilized to mitigate this risk.

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

For additional information about the risks of filgotinib, reference is made to the IB.

1.5. Compliance

This study will be conducted in compliance with this protocol, Good Clinical Practice (GCP), and all applicable regulatory requirements.

2. OBJECTIVES

The primary objective of this study is:

- To evaluate the long-term safety and tolerability of filgotinib in subjects who have completed one of the parent studies of filgotinib in RA.

The secondary objective of this study is:

- To evaluate the long-term efficacy of filgotinib in subjects with RA.

The exploratory objectives of this study are:

- To evaluate the long-term effects of filgotinib on subject-reported outcomes, such as disability, fatigue, and quality of life.

3. STUDY DESIGN

3.1. Endpoints

The primary endpoint is:

- Safety, evaluated through AEs, clinical laboratory tests, and vital signs.

Secondary endpoint:

- ACR-N over time in each arm

Exploratory endpoints:

- Achievement of ACR20/50/70
- EULAR responses; ACR/EULAR remission

- Evolution of CDAI, SDAI, and DAS28(CRP) over time
- Evolution of patient reported outcomes over time

3.2. Study Design

This study was originally designed and initiated as a double-blind, LTE study in adult male and female subjects with RA who have completed one of the parent filgotinib RA studies (GS-US-417-0301, GS-US-417-0302, or GS-US-417-0303). The study design changed to open-label following implementation of protocol amendment 4. This study is designed to evaluate the safety, tolerability and efficacy of filgotinib in RA and its effect on patient-reported outcomes, including work productivity, fatigue, and quality of life.

After signing the informed consent for the LTE, subjects will be evaluated for eligibility. Subjects who are qualified for the LTE will receive daily filgotinib as per the following:

All subjects who were assigned to an active filgotinib arm at the time of their parent study completion will be maintained on their blinded filgotinib dose (100 mg or 200 mg QD). Subjects who received adalimumab (GS-US-417-0301), placebo (GS-US-417-0302), or methotrexate monotherapy at their final visit (GS-US-417-0303) will be re-randomized at LTE entry in a 1:1 ratio to either 100 mg or 200 mg filgotinib QD in a blinded fashion. The assigned filgotinib daily dose will remain the same but will be unblinded once the study becomes open-label.

Subjects from studies GS-US-417-0301 and GS-US-417-0303, who completed the study on standard of care therapy, are not eligible. Subjects from study GS-US-417-0302, who discontinued study drug due to nonresponse of their RA but completed all study visits, are eligible and will be re-randomized at LTE entry in a 1:1 ratio to either 100 mg or 200 mg filgotinib QD in a blinded fashion until the study becomes open-label (dose will remain the same but will be unblinded). Subjects who discontinued study drug in GS-US-417-0302 due to an AE unrelated to study drug, but who completed all study visits, are eligible to enroll at the judgment of the investigator. In these cases it is necessary for the investigator to confirm eligibility with the medical monitor.

All subjects should continue to be maintained on their parent protocol approved background therapy (csDMARD(s)), where applicable, except for subjects from the GS-US-417-0303 study, who will discontinue MTX/PTM study tablets upon entering the LTE. Subjects from GS-US-417-0303 may resume/start MTX and/or other csDMARDs (as permitted in this protocol) after at least 4 weeks of their first dose of study drugs in the LTE; background csDMARD therapy for all subjects during the LTE will be managed by the primary investigator/clinician and should be adjusted as needed for safety and disease control.

All subjects who require re-randomization will be stratified by geographic region and parent study protocol. For dosing schema, see [Appendix 11](#).

3.2.1. Dose Adjustments during the LTE

Based on clinical judgment, the investigator may request a study drug dose adjustment via IWRS.

When dose reduction has been requested, subjects on 200 mg QD of filgotinib will have the dose reduced to 100 mg QD. Dose reductions will not be allowed for subjects on 100 mg QD of filgotinib.

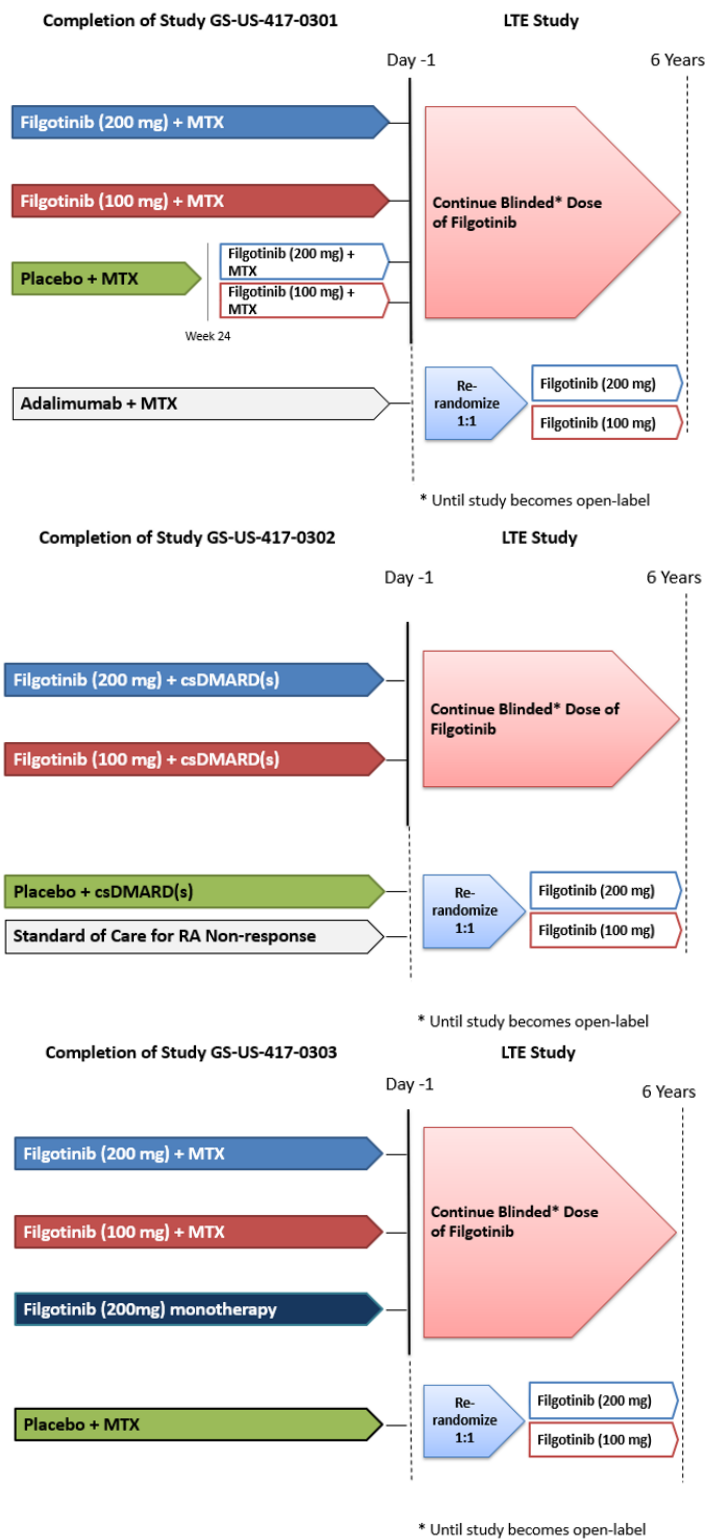
Elderly patients (65 years of age and above) with well-controlled disease should use the lowest effective dose of filgotinib. While choosing the lowest effective dose, individual benefit-risk based on previous safety events and recorded disease response need to be carefully evaluated by the investigator.

Subjects on 200 mg QD of filgotinib with moderate renal impairment should have the dose reduced to 100 mg QD of filgotinib as specified in Section 3.5.

In case of insufficient disease control, a dose escalation can be allowed to 200 mg QD of filgotinib. This is also applicable for elderly subjects (65 years and above) on 100 mg QD with insufficient disease control who may be escalated to filgotinib 200 mg QD. There will be no dose increase allowed in a subject after a study drug reduction due to safety reasons.

If the subject continues to experience side effects that are related to study drug based on the opinion of the investigator, the subject should be discontinued from study drug. The assessments planned to be performed at each visit are detailed in the study procedures table ([Appendix 2](#)). A diagram of the study design is provided below.

Figure 3-1. Study Design



3.3. Study Treatments

Subjects completing the parent study on filgotinib will be maintained at their assigned dose: subjects completing the parent study on non-filgotinib study drug or on standard of care, will be re-randomized in a 1:1 ratio to filgotinib 200 mg QD, or filgotinib 100 mg QD, in a blinded fashion.

Background medications for RA are permitted to be continued in the LTE, with the exception of the weekly MTX/PTM study drug in GS-US-417-0303, which will be discontinued at the end of the parent study. These subjects may resume/start MTX and/or other csDMARDs (per investigator judgment) after at least 4 weeks of their first dose of study drug in the LTE.

- Blinded study treatment:

Filgotinib 200 mg group: filgotinib 200 mg QD + PTM filgotinib 100 mg QD

Filgotinib 100 mg group: filgotinib 100 mg QD + PTM filgotinib 200 mg QD

- Open-label study treatment:

Filgotinib 200 mg group: filgotinib 200 mg QD

Filgotinib 100 mg group: filgotinib 100 mg QD

The study design changed to open-label upon implementation of protocol amendment 4. Elderly patients (65 years of age and above) with well-controlled disease should use the lowest effective dose of filgotinib.

3.4. Duration of Treatment

Subjects will be provided filgotinib for up to 6 years, until the sponsor terminates clinical development of filgotinib, or until filgotinib becomes commercially available; whichever comes first. The duration of the treatment for any subject in this study is expected to last for several years (from Entry visit to End of Treatment/ Early Termination Visit [ET]).

When filgotinib becomes commercially available in a country, the sponsor will evaluate the situation in the country and decide if the study will terminate in that country. The sponsor will inform the sites accordingly. Should the sponsor decide to terminate the study in a country where filgotinib becomes commercially available, subjects will be contacted to plan their End of Treatment Visit as soon as possible. When the End of Treatment Visit is performed, subjects will be considered as having completed the treatment part of the study. In addition, subjects will be requested to attend a Post Treatment Week 4 Visit approximately 4 weeks after the End of Treatment Visit.

3.5. Criteria for Interruption or Discontinuation of Study Treatment

3.5.1. Study Drug Interruption

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 interrupt study drug dosing and be evaluated for active TB. Subjects who are diagnosed with latent TB should initiate an adequate course of prophylaxis as per local standard of care; appropriate, ongoing, prophylactic treatment for latent TB must be initiated prior to the continuation of study medication. Subjects may resume study drug only after investigator's consultation with the medical monitor. Subjects with indeterminate QuantiFERON® test results should interrupt study drug dosing and repeat the QuantiFERON® test once via the central lab. If the repeat result is also indeterminate, the result will be considered positive for the purposes of this study and subjects should be evaluated for active TB. QuantiFERON® tests with indeterminate results can be repeated only once. A positive initial test cannot be followed by a repeat test.
- For subjects with confirmed absolute lymphocyte count (ALC) less than 500 cells/mm³, retest within 3 to 7 days, filgotinib should be interrupted until grade returns to ≤ Grade 2 (more than 500 cells/mm³). If ALC does not return to ≤ Grade 2 within 4 weeks or returns to less than 500 cells/mm³ following re-challenge with filgotinib, then filgotinib should be permanently discontinued and the subject managed according to local practice.
- For subjects with absolute neutrophil counts <1000 cells/mm³ (international system of units [SI]: <1.0 x 10⁹ cells/L); an unscheduled visit should occur to retest within 3-7 days after establishing, treating, and resolving any possible underlying condition. The study drug should be interrupted until the retest result is available. If the abnormal neutrophil count has been confirmed by a retest, the study drug will be interrupted until the value returns to ≥1000 cells/mm³ (SI: ≥1.0 x 10⁹ cells/L). If the neutrophil abnormality does not return to ≥1000 cells/mm³ within 4 weeks or recurs following a re-challenge with study drug and is

considered related to study drug, then study drug should be permanently discontinued and the subject should be managed according to local clinical practice.

- After a confirmed laboratory change representing moderate renal impairment (estimated creatinine clearance [CrCl] ≥ 35 mL/min and < 60 mL/min per Cockcroft-Gault formula) at any time during the study for subjects on filgotinib 200 mg QD, the following actions should be taken by the investigator and documented:
 - Establish possible underlying condition and initiate appropriate action to resolve.
 - Retest CrCl within 8 weeks.
 - Carefully consider individual benefit/risk of continuation of filgotinib in relation to the observation.
 - If continuation of filgotinib is considered appropriate, reduce the dose of filgotinib to 100 mg QD (dose re-escalation to 200 mg is not allowed if CrCl < 60 mL/min).
 - If continuation of filgotinib is not considered appropriate, interrupt treatment until retest confirms CrCl ≥ 60 mL/min.
 - The investigator/designee should assess individual subject benefit/risk with regards to re-initiation of treatment after repeat or prolonged interruptions, or if re-initiation is not considered appropriate. The medical monitor should be consulted prior to study drug re-initiation when medically feasible.

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.

3.5.2. Study Drug Discontinuation

Study medication should be permanently discontinued in the following instances:

- Any opportunistic infection
- Any subject with active TB should be discontinued from the study.
- 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
- Any serious thromboembolic event

- 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
- Uncontrolled RA disease activity at any time (per judgment of investigator) that requires protocol prohibited therapy
- Subject request to discontinue for any reason
- Subject noncompliance
- Pregnancy during the study (Section 7.7.2.1 and Appendix 5)
- Discontinuation of the study at the request of the sponsor, 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:
 - ALC: For subjects with confirmed ALC less than 500 cells/mm³, retest within 3 to 7 days, filgotinib should be interrupted until grade returns to ≤ Grade 2 (more than 500 cells/mm³). If ALC does not return to ≤ Grade 2 within 4 weeks or returns to less than 500 cells/mm³ following re-challenge with filgotinib, then filgotinib should be permanently discontinued and the subject managed according to local practice.
 - Absolute neutrophil count: For subjects with absolute neutrophil counts <1000 cells/mm³ (international system of units [SI]: <1.0 x 10⁹ cells/L); an unscheduled visit should occur to retest within 3-7 days after establishing, treating, and resolving any possible underlying condition. The study drug should be interrupted until the retest result is available. If the abnormal neutrophil count has been confirmed by a retest, the study drug will be interrupted until the value returns to ≥1000 cells/mm³ (SI: ≥1.0 x 10⁹ cells/L). If the neutrophil abnormality does not return to ≥1000 cells/mm³ within 4 weeks or recurs following a re-challenge with study drug and is considered related to study drug, then study drug should be permanently discontinued and the subject should be managed according to local clinical practice.
 - 2 sequential platelet counts <75,000 platelets/mm³ (SI: <75.0×10⁹ cells/L)
 - 2 sequential AST or ALT elevations >3×ULN and ≥1 total bilirubin value >2×ULN or accompanied by symptoms consistent with hepatic injury.¹

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

- 2 sequential AST or ALT elevations $>5 \times \text{ULN}$
- 2 sequential values for estimated CrCl <35 mL/min based on the Cockcroft Gault formula.

After becoming aware of any of the above-described abnormal laboratory changes occurring at any one time, an unscheduled visit should occur to re-test. Re-testing should occur within 3 to 7 days (except for creatinine which should be retested 7 to 14 days later).

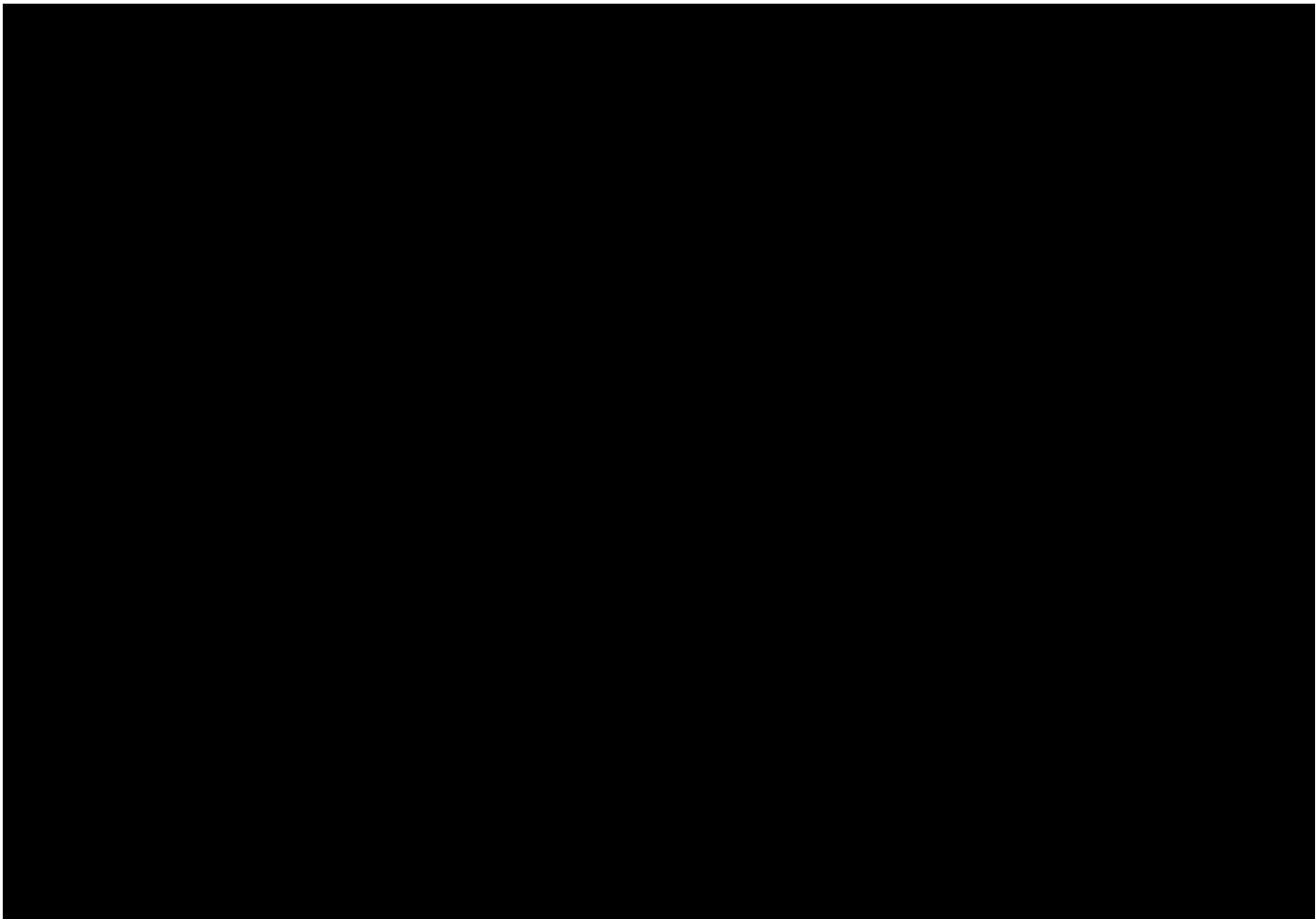
Subjects withdrawing from the study should complete ET and Post Treatment Week 4 visits. Subjects are free to withdraw from the study at any time without providing reason(s) for withdrawal and without prejudice to further treatment. The reason(s) for withdrawal will be documented in the electronic case report form (eCRF).

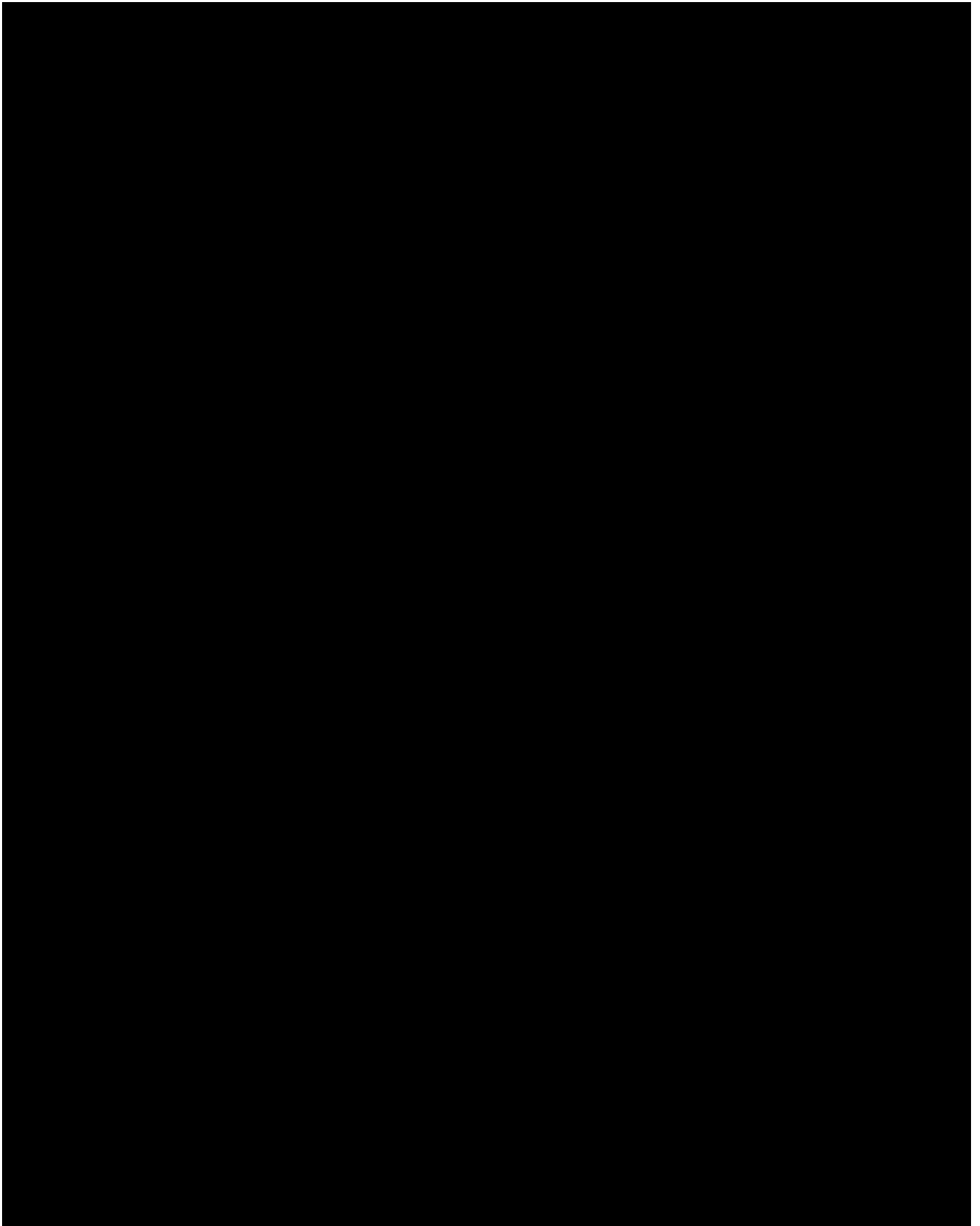
3.6. End of Study

End of Study is defined as when the last subject has completed their last study visit or until study closure, eg, for the reasons indicated in Section 3.4.

3.7. Post Study Care

The long term care of subjects will remain the responsibility of their primary treating physician.





4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

Subjects who have completed the parent filgotinib RA studies and provide written informed consent will be enrolled and maintained on their original blinded dose of filgotinib administered during the parent study, or re-randomized to one of two dosing groups if they were not on filgotinib during their parent study participation. The subject's filgotinib daily dosing will not be impacted by unblinding of the study.

4.2. Inclusion Criteria

Subjects must meet all of the following to be eligible for participation in this study.

- 1) Able and willing to sign the informed consent as approved by the IRB/IEC. Written consent must be provided before initiating any Day -1 evaluations for this study. Subjects must have read and understood the ICF, must fully understand the requirements of the study, and must be willing to comply with all study visits and assessments; subjects who cannot read or understand the ICF may not be enrolled by a guardian or any other individual.
- 2) Male or female subjects who may benefit from filgotinib as judged by the investigator AND who completed a Gilead sponsored filgotinib parent study for RA as outlined below:
 - a) Subjects who completed GS-US-417-0301, GS-US-417-0302, or GS-US-417-0303 on study drug
 - OR
 - b) Subjects who completed GS-US-417-0302 on standard of care therapy due to RA non-responder status
- 3) Females of childbearing potential must have a negative pregnancy test at Day -1 and must agree to continued monthly pregnancy testing during the study
- 4) Lactating female subjects must agree to discontinue nursing at Day -1 for the duration of the study
- 5) Criterion modified per amendment 8.
 - 5.1) Female subjects of childbearing potential who engage in heterosexual intercourse must agree to use protocol specified method(s) of contraception as described in [Appendix 5](#), during the study and through 35 days after their last dose of study drug.
- 6) Subjects receiving protocol permitted RA medications should be on a stable dose (defined as no change in prescription) within 7 days or 5 half-lives (whichever is longer) prior to the first administration of LTE study drug on Day 1, as much as possible.

Note: Subjects from parent study GS-US-417-0303 will discontinue MTX/PTM capsules at Day -1 of transfer to the LTE and may be evaluated for resumption of MTX and/or start of other csDMARDs after 4 weeks of study drug dosing. The decision to resume MTX and/or other csDMARDs (and the dose to be administered, if any) will be determined by the investigator.

- 7) Subjects, who meet study drug interruption criteria (as outlined in Section 3.5.1) at Day -1, are eligible to enter into the LTE but should not start study drug until deemed medically appropriate, as outlined in Section 3.5.1.

4.3. Exclusion Criteria

Subjects who meet *any* of the following are not to be enrolled in this study.

- 1) An autoimmune or inflammatory joint disease other than RA, which would put the subject at risk by participating in the study or would interfere with study assessments/data interpretation, per judgment of the investigator; (Sjogren's syndrome or stable thyroiditis is permitted).
- 2) Known hypersensitivity to the study drug, its metabolites or formulation excipients.
- 3) Any medical condition (including, but not limited to, cardiac or pulmonary disease, alcohol or drug abuse) which would put the subject at risk by participating in the study or would interfere with study assessments/data interpretation, per judgment of the investigator;
- 4) Administration of a live/ attenuated vaccine within 30 days prior to Day -1
- 5) Currently on any therapy for chronic infection (such as pneumocystis, cytomegalovirus, herpes zoster, and atypical mycobacteria)
- 6) History of disseminated/complicated herpes zoster infection (multi-dermatomal involvement, ophthalmic zoster, central nervous system involvement or postherpetic neuralgia)
- 7) Any condition or circumstances which in the opinion of the investigator or Sponsor may make a subject unlikely or unable to complete the study or comply with study procedures and requirements
- 8) Use of prohibited medication as outlined in Section 5.4
- 9) Subjects who meet discontinuation criteria as outlined in Section 3.5.2

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Randomization, Blinding and Treatment Codes

An Interactive Web Response System (IWRS) will be used to manage subject randomization and treatment assignments. It is the responsibility of the investigator to ensure that the subject is

eligible for the study prior to enrollment. Randomization scheme for each parent study's rollover to the LTE is outlined in [Appendix 11](#).

The study design changed to open-label upon implementation of protocol amendment 4.

5.1.1. Procedures for Breaking Treatment Codes (until the study becomes open-label)

In the event of a medical emergency where breaking the blind is required to provide medical care to the subject, the investigator may obtain the individual subject treatment assignment directly from the IWRS system. The sponsor recommends but does not require that the investigator contact the medical monitor before breaking the blind. Dose assignments should remain blinded unless that knowledge is necessary to determine emergency medical care for the subject. The rationale for unblinding must be clearly explained in source documentation and on electronic case report form (eCRF), along with the date on which the treatment assignment was unblinded. The investigator is requested to contact the medical monitor promptly in case of any treatment unblinding.

The sponsor may independently unblind cases for expedited reporting of suspected unexpected serious adverse reactions (SUSARs) to Regulatory Authorities.

The study design changed to open-label upon implementation of protocol amendment 4.

5.2. Description and Handling of Filgotinib and PTM Filgotinib

Once protocol amendment 4 was implemented and the study was unblinded, subjects were no longer required to take PTM filgotinib tablets and these were no longer provided.

5.2.1. Formulation of Filgotinib and PTM Filgotinib

Filgotinib is provided as 100 mg and 200 mg strength tablets. Filgotinib tablets, 100 mg and 200 mg, are beige, debossed with "GSI" on one side and "100" or "200" on the other, capsule-shaped, biconvex, film-coated tablets for clinical use. Each tablet contains the equivalent of 100 mg or 200 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.

Placebo to match filgotinib tablets, 100 mg and 200 mg, are identical in appearance to the respective active tablets. Placebo to match filgotinib tablets contain the following inactive ingredients: microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate, macrogol/PEG 3350, polyvinyl alcohol, talc, titanium dioxide, iron oxide yellow, and iron oxide red. For the purpose of this LTE study, PTM will only be utilized for the maintenance of the parent study's treatment assignment blind and not as a comparator treatment to active filgotinib. Once protocol amendment 4 was implemented and the study was unblinded, subjects were no longer required to take PTM filgotinib tablets and these were no longer provided.

5.2.2. Packaging and Labeling

Filgotinib tablets, 100 mg and 200 mg (and PTM filgotinib tablets, 100 mg and 200 mg during blinded study treatment) are packaged in white, high density polyethylene (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 and aluminum-faced liner.

Sufficient quantities of filgotinib tablets, 100 mg and 200 mg, (and PTM filgotinib tablets during blinded study treatment) to complete the entire study will be shipped to the investigator or qualified designee by the sponsor (or its designee).

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

5.2.3. Storage and Handling

Filgotinib tablets (and PTM filgotinib tablets during blinded study treatment) 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 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 they are 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.

5.2.4. Dosage and Administration

Filgotinib tablets, 100 mg and 200 mg (or PTM filgotinib 100 mg and 200 mg tablets during blinded study treatment) will be administered once daily with or without food. Each subject should be given instructions to maintain approximately the same daily time of administration to ensure similar dosing interval is maintained between study drug doses.

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.

5.3. Prior and Concomitant Medications

All continuing concomitant medication from the parent study of participation is to be documented in the eCRF. Concomitant therapies taken for treatment of pre-existing conditions

can continue during the study provided they are in accordance with the prohibited medications criteria (see Section 5.4). It is preferred that these medications be continued without variation of dose or regimen during the study, as much as possible. Any biologic agent (eg, denosumab) that is planned to be started or continued during the study requires written approval by the medical monitor. Any changes to a subject's concomitant medication since completing the parent study should be confirmed as non-prohibitory and documented in the eCRF.

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.

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 include:

- Corticosteroids are permitted, but are not to exceed 20 mg oral prednisone (or equivalent) per day. The dose of the oral steroid can and should be reduced or tapered off during this LTE study based on the investigator's judgment; doses may also be increased during the LTE, but should not exceed 20 mg oral prednisone (or equivalent) per day.

The total daily dose of corticosteroids (oral, parenteral, inhaled or other) that exceeds 20 mg oral prednisone (or equivalent) per day for short duration for the treatment of an AE is allowed. The AE and medications administered should be documented in the eCRF.

- NSAIDs are permitted, and should be kept at a stable dose and regimen, as much as possible; NSAID doses (oral and/or topical) should be held starting 12 hours before a study visit until all scheduled assessments have taken place, as much as possible
- Analgesics are permitted, including opioids and other non-NSAID based therapies, and should be kept at a stable dose and regimen, as much as possible; analgesic doses should be held starting 12 hours before a study visit until after all scheduled assessments have taken place, as much as possible.
- Subjects may receive a maximum of 3 intra-articular injections of corticosteroid every 12 months while participating in this LTE study. The dose of corticosteroid injected should not exceed the equivalent dose of triamcinolone 40 mg suspension per joint. 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.
- Subjects may receive a maximum of 1 (or 1 treatment regimen consisting of series of 3-5 weekly injections per local standard) intra-articular injection of hyaluronic acid (or its derivatives) every 12 months while participating in this long-term extension study. For the analysis of the TJC68 and SJC66, these joints will be considered "not assessable" for 6 months from the time of the last intra-articular injection.

Permitted csDMARD(s) during the LTE study are as follows:

- a) MTX is permitted as oral or parenteral medication: Subjects on MTX should receive folic acid (≥ 5 mg/week or as per local clinical practice), which should be confirmed at study visits and continued throughout the study as long as MTX is administered. Doses of MTX > 25 mg/week are not permitted.
- b) Oral hydroxychloroquine ≤ 400 mg/day or chloroquine ≤ 250 mg/day
- c) Oral sulfasalazine ≤ 3 g/day
- d) Oral leflunomide ≤ 20 mg/day

NOTE: leflunomide is not permitted to be used in combination with MTX.

- Dose adjustments of the above medications for management of toxicity or for changes in RA disease activity are allowed and should be documented, along with documentation of the AE (as applicable) which led to the change in the medication. New starts or discontinuation of these medications are also allowed, as long as the parameters above are maintained.

Female subjects of childbearing potential must agree to use highly effective birth-control methods as outlined in [Appendix 5](#). 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 followed.

Hormone replacement therapy, thyroid replacement and other chronic therapies (such as those for controlled diabetes or hypertension) are permitted during the study, and should be kept at a stable dose and regimen, as much as possible.

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

5.4. Prohibited Medications

Prohibited concomitant medications while on study drugs include:

- Oral or injectable gold
- Azathioprine
- D penicillamine, minocycline
- Cyclosporine
- Any cytotoxic agent, including chlorambucil, cyclophosphamide, nitrogen mustard, and other alkylating agents
- Potent P-gp inducers (eg, rifampin, phenytoin, carbamazepine, and St. John's Wort)

- bDMARDs
- Other JAK inhibitors or advanced small molecule immunomodulators

5.5. Vaccine Guidelines

- Live or attenuated vaccines (including, but not limited to varicella and inhaled flu vaccine) are prohibited throughout the study, and for 12 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.
- The interruption or continuation of filgotinib around the period of approved non-live Coronavirus Disease 2019 (COVID-19) vaccine administration is at the investigator's discretion, based on disease activity, concomitant medications, concurrent conditions and local applicable guidelines.

5.6. Accountability for Study Drugs

The investigator is responsible for ensuring adequate accountability of all used and unused study drugs. This includes acknowledgment of receipt of each shipment of study drugs (quantity and condition). All used and unused study drugs dispensed to subjects must be returned to the site.

Filgotinib accountability records will be provided to each study site to:

- Record the date received and quantity of study drugs
- Record the date, subject number, subject initials, the study drug number dispensed
- Record the date, quantity of used and unused study drugs returned, along with the initials of the person recording the information.

- Dispensing records will include the initials of the person dispensing the study drug or supplies.

5.6.1. Investigational Medicinal Product Return or Disposal

At study initiation, the monitor will evaluate the site's standard operating procedure for investigational medicinal product disposal/destruction in order to ensure that it complies with the sponsor's requirements. Study drug may be returned to the assigned depot or destroyed at the site upon sponsor approval on an ongoing basis during the study if appropriate. At the end of the study, following final drug inventory reconciliation by the monitor, the study site will dispose of and/or destroy all unused investigational medicinal product supplies, including empty containers, according to these procedures. If the site cannot meet the sponsor's requirements for disposal, arrangements will be made between the site and the sponsor or its representative for destruction or return of unused investigational medicinal product supplies.

All drug supplies and associated documentation will be periodically reviewed and verified by the study monitor over the course of the study.

For additional information about study drug accountability and return, refer to Section [9.1.7](#).

6. STUDY PROCEDURES

The study procedures to be conducted are presented in tabular form in [Appendix 2](#) and described in the text that follows. Additional information is provided in the study procedures manual and [Appendix 10](#).

The investigator must document any deviation from protocol procedures and notify the sponsor or contract research organization (CRO).

The study assessments as described below will be performed at the time points specified in the Study Procedures Table ([Appendix 2](#)). Visits are to be scheduled within a window as specified in the Study Procedures Table and in such a way that the total study duration from Day -1 to last dosing does not exceed 6 years, as much as possible.

6.1. Subject Enrollment and Treatment Assignment

After completion of the parent study's end of treatment visit, subjects who sign the informed consent will have the same subject ID, as on the parent study, assigned by IWRS.

It is the responsibility of the investigator to ensure that each subject is eligible for the study before randomization. A subject will be considered enrolled once randomized.

6.2. Day -1 Assessments

In cases where there is no gap between the last visit of the parent study and the first visit of the LTE study, the Entry Visit (Visit 1) will take place on Day -1 relative to the start of the study medication and the following will be performed:

- Obtain written Informed Consent
- Review of Inclusion/Exclusion Criteria

Entry Visit data will include those data collected at the last parent study visit. Subjects should have had a complete physical examination, concomitant medications assessment, 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, [REDACTED] and SF-36 questionnaire. Data on demographics, baseline characteristics, and medical history will be reviewed from the Screening visit of the parent protocol. Additional assessments to be performed at the Day -1 visit are:

Subjects who tested negative on the parent protocol and who have never been previously treated for latent TB will be retested at Day -1 of the study, using the QuantiFERON®-TB central lab test (+/- chest X-rays, per local standard of care). Annual/every 48 week QuantiFERON® TB central lab test is not required however, can be performed per investigator discretion. Result(s) are to be reviewed and documented by the site when the data are available.

Subjects with newly positive (converted) QuantiFERON® [or equivalent] TB test should interrupt study drug dosing and be evaluated for active TB. Subjects who are diagnosed with latent TB should initiate an adequate course of prophylaxis as per local standard of care; appropriate, ongoing, prophylactic treatment for latent TB must be initiated prior to the continuation of study medication. Subjects may resume study drug only after investigator's consultation with the medical monitor. Subjects with indeterminate QuantiFERON® test results should interrupt study drug dosing and repeat the QuantiFERON® test once via the central lab. If the repeat result is also indeterminate, the result will be considered positive for the purposes of this study and subjects should be evaluated for active TB. QuantiFERON® tests with indeterminate results can be repeated only once. A positive initial test cannot be followed by a repeat test.

- Study Drug Dispensation, adherence and contraception counseling.
- Study Drug Administration (*To be completed by the subject at home the day following the Day-1 visit*); *the first dose of study drug corresponds to LTE Day 1.*
- Any ongoing or unresolved AEs and concomitant medications from the preceding parent study will be documented in the medical history and concomitant medication pages of the eCRF, respectively.

The entry Visit (Visit 1, Day -1) can take place any time up to 4 weeks after the last visit of the parent study. In cases where there is a gap between the parent studies and the LTE study, all Day-1 assessments need to be completed, NOTE: If the HAQ-DI with pain VAS, physician global, patient global, SJC66/TJC68, SF-36, [REDACTED] FACIT, [REDACTED] and [REDACTED] were assessed less than 14 days prior to Day -1, data from the previous parent study visit can be utilized).

Patient's Global Assessment, health assessment questionnaire – disability index (HAQ-DI), FACIT fatigue scale, [REDACTED] and SF-36 questionnaire are recommended to be

completed by the subject before the completion of any other study procedures. Invasive study procedures such as blood draws should be done at the end of a study visit, as much as possible.

6.3. Randomization

Subjects who do not complete the parent study on filgotinib, will be re-randomized 1:1 to filgotinib 100 mg or 200 mg QD, according to a pre-specified randomization scheme prepared by an independent statistician, using a computerized IWRS system. Randomization will be stratified by geographic region and parent study.

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

6.4. Week 2 and 6 Assessments

The following assessments will be completed at the Week 2 and 6 study visits. All assessments are summarized in the Study Procedures Table ([Appendix 2](#)).

Subject's Global Assessment and HAQ-DI and Pain Scale are recommended to be completed by the subject before any other study procedures. Invasive study procedures such as blood draws should be done at the end of a study visit, as much as possible.

- HAQ-DI with Pain Scale
- Subject's Global Assessment
- Symptom Directed Physical Exam
- Weight
- Vital Signs
- SJC66/TJC68
- Physician's Global Assessment
- Obtain blood samples for:
 - Hematology and Serum Chemistry
 - Serum CRP
- Urine pregnancy test, if applicable
- Study Drug Dispensation
- Review of Concomitant Medication
- Assessment of Adverse Events

6.5. Assessments to be Completed Every 4 Weeks Post Day -1

Urine pregnancy tests for women of childbearing potential (as defined per protocol).

During the periods where study visits are >4 weeks apart, women should continue to have pregnancy tests every 4 weeks, using urine pregnancy test kits that will be provided to them. The site will contact the subject every 4 weeks to obtain results of these pregnancy tests and will record the information in the source documents and CRF. Subjects may also return to the study site to perform the monthly urine pregnancy tests, if they prefer.

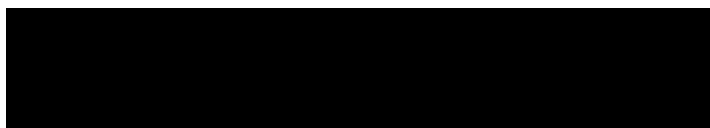
Subjects are to be instructed that for any positive urine pregnancy test, they should stop taking study drugs immediately and present to the site for a serum pregnancy test.

6.6. Assessments to be completed every 24 Weeks Post Day -1

The following assessments will be completed every 24 weeks (or as specified). Assessments are summarized in the Study Procedures Table ([Appendix 2](#)).

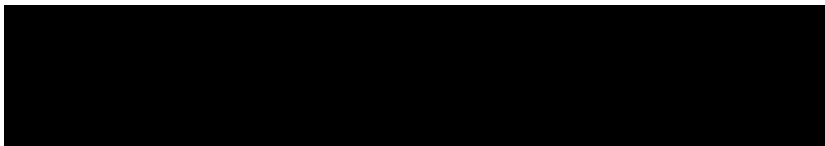
Subject's Global Assessment, HAQ-DI and Pain Scale, FACIT-Fatigue, and SF-36 are recommended to be completed by the subject before any other study procedures. Invasive study procedures such as blood draws should be done at the end of a study visit as much as possible.

- Subject Global Assessment
- HAQ-DI with Pain Scale
- FACIT-Fatigue, SF-36, [REDACTED]



- Physician's global assessment
- Review of Concomitant Medication
- Assessment of Adverse Events
- Study drug dispensation
- Vital signs
- Symptom-Directed Physical Examination
- Weight
- SJC66/TJC68
- Obtain blood samples for:

- Hematology and Serum Chemistry
- Lipid profile (fasting)
- Serum CRP



- Viral monitoring:
 - Viral monitoring for HBV for subjects that screened positive on the parent study for HBV exposure and/or
 - Viral monitoring for HCV for subjects that screened positive on the parent study for HCV exposure



- Urinalysis
- Urine pregnancy test

6.7. Assessments to be completed every 48 Weeks Post Day -1, in addition to the 24 Week Assessments

- TB testing per investigator discretion
 - Assessment of TB exposure risks
- Full Physical Examination with Weight

6.8. End of Treatment/Early Termination

When filgotinib becomes commercially available, subjects will be contacted to plan their End of Treatment Visit as soon as possible. When the End of Treatment Visit is performed, the subjects will be considered as having completed the treatment part of the study. In addition, subjects will be requested to attend a Post Treatment Week 4 Visit approximately 4 weeks after the End of Treatment Visit.

If a subject discontinues the study early (for example, as a result of an AE), every attempt should be made to perform the Early Termination (ET) visit and post-dosing Week 4 follow up visit (see Section 3.5, Criteria for Discontinuation of Study Treatment). The post-dosing Week 4 follow up does not need to be performed for any subject who discontinues study drug >4 weeks prior to



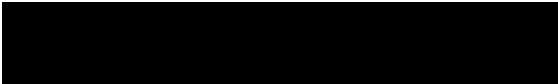
their most recent visit. Following completion of the ET visit and post-dosing Week 4 follow up, subject participation in the study is considered completed and no additional study visits are to be performed. However, AE and SAE reporting/follow up post study completion should be performed as stipulated in Section 7.3.

Subject's Global Assessment, HAQ-DI and Pain Scale, FACIT-Fatigue, and SF-36 are recommended to be completed by the subject before any other study procedures. Invasive study procedures such as blood draws should be done at the end of a study visit, as much as possible.

The following assessments should be completed at the End of Treatment and ET Visit:

- Any remaining study drug as well as empty study drug containers will be returned to the investigator and an accountability check performed.
- HAQ-DI with Pain Scale
- Subject Global Assessment
- FACIT-Fatigue, SF-36, [REDACTED]

- Complete Physical Examination
- Weight
- Vital signs
- Perform SJC66/TJC68
- Physician's Global Assessment
- Obtain Blood Samples For:
 - Hematology and Serum chemistry
 - Lipid profile (fasting)
 - Serum CRP

- 
- Urinalysis
 - Serum Pregnancy Test
 - Assessment of Adverse Events
 - Review of Concomitant Medications

6.9. Post-Treatment Week 4 Follow-up Assessments

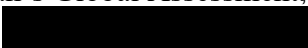
The following procedures will be completed 4 weeks after the subject's last dose of study drug.

Subjects who discontinue study drug >4 weeks prior to their last study visit do not need a post-dosing Week 4 follow up.

- Symptom Directed Physical examination
- Weight
- Vital signs
- Assessment of Adverse Events
- Review of Concomitant Medication
- Obtain blood samples for:
 - Hematology and Serum Chemistry
 - Serum CRP
- Urinalysis (including urine pregnancy test, if applicable)

6.10. Study Assessments

6.10.1. Efficacy

- Efficacy assessments will be carried out at Day -1 and at a frequency of every 24 weeks thereafter (every 12 weeks until protocol amendment 7 implementation) until the end of subject's study participation. Entry Visit data will be those collected at the last visit from the subject's parent study. Only subjects who have a gap of more than 14 days between the last study assessment and the Day -1 assessments should repeat the HAQ-DI with pain scale, Physician's Global Assessment, Subject's Global Assessment, SJC66/TJC68, SF-36, FACIT, 

Assessments of RA will include the derived ACR (ACR20, 50, 70) over time as well as ACR-N and EULAR response criteria over time, DAS28 (CRP), CDAI, and SDAI as well as the individual components of the ACR response criteria [TJC68, SJC66, HAQ-DI, Physician's Global assessment, Subject's Global Assessment, Subject's Assessment of Arthritis Pain and CRP]).

6.10.1.1. Evaluation of Disease Activity: Tender and Swollen Joint Counts

Assessment of tender and swollen joints will take place at the time points indicated in the study procedures table ([Appendix 2](#)).

Each of 68 joints will be evaluated for tenderness and each of 66 joints will be evaluated for swelling ([Appendix 7](#)).

An independent joint assessor with adequate training and experience in performing joint assessments will be designated at each study site to perform all joint assessments, and should be blinded to the other study assessments performed on that day. The joint assessor should preferably be a rheumatologist; however, if a rheumatologist is not available, it should be a health care provider with experience in performing joint assessments. The subject's assessor should remain the same throughout, as much as possible. The designated joint assessor is to identify an appropriate back up assessor to provide coverage if the designated joint assessor is absent.

6.10.1.2. Subject's Global Assessment of Disease Activity

The Subject's Global assessment of Disease Activity will be performed at the time points indicated in the study procedures table ([Appendix 2](#)). The Subject's Global assessment of Disease Activity should be completed before any other study procedures.

The Subject's Global Assessment of Disease Activity will be recorded on a 0-100 mm visual analog scale (VAS), with 0 indicating "no arthritis" and 100 indicating "severe arthritis".

6.10.1.3. Physician's Global Assessment of Disease Activity

The Physician's Global assessment of Disease Activity will be performed at the time points indicated in the study procedures table ([Appendix 2](#)).

The Physician's Global Assessment of Disease Activity will be recorded on a 0-100 mm VAS, with 0 indicating "no disease activity" and 100 indicating "maximum disease activity". The evaluating physician and the subject should complete the global assessments independently of each other.

6.10.1.4. Serum CRP

The subject's serum CRP will be measured at the time points indicated in the study procedures table ([Appendix 2](#)).

6.10.1.5. Health Assessment Questionnaire – Disability Index and Pain Scale

The functional status of the subject will be assessed using the HAQ-DI at the time points indicated in the study procedures table ([Appendix 2](#)) and should be completed before any other study procedures. The HAQ-DI is a 20-question instrument that 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 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.

As part of the HAQ-DI, subjects will be asked to assess their average pain during the last week on a 0-100 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.

6.10.1.6. FACIT Fatigue Scale

The FACIT-Fatigue (version 4) will be completed at the time points indicated in the study procedures table ([Appendix 2](#)) and should be completed before any other study procedures where local language QOL questionnaires are available. The FACIT-Fatigue 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. Higher scores indicate a better quality of life.

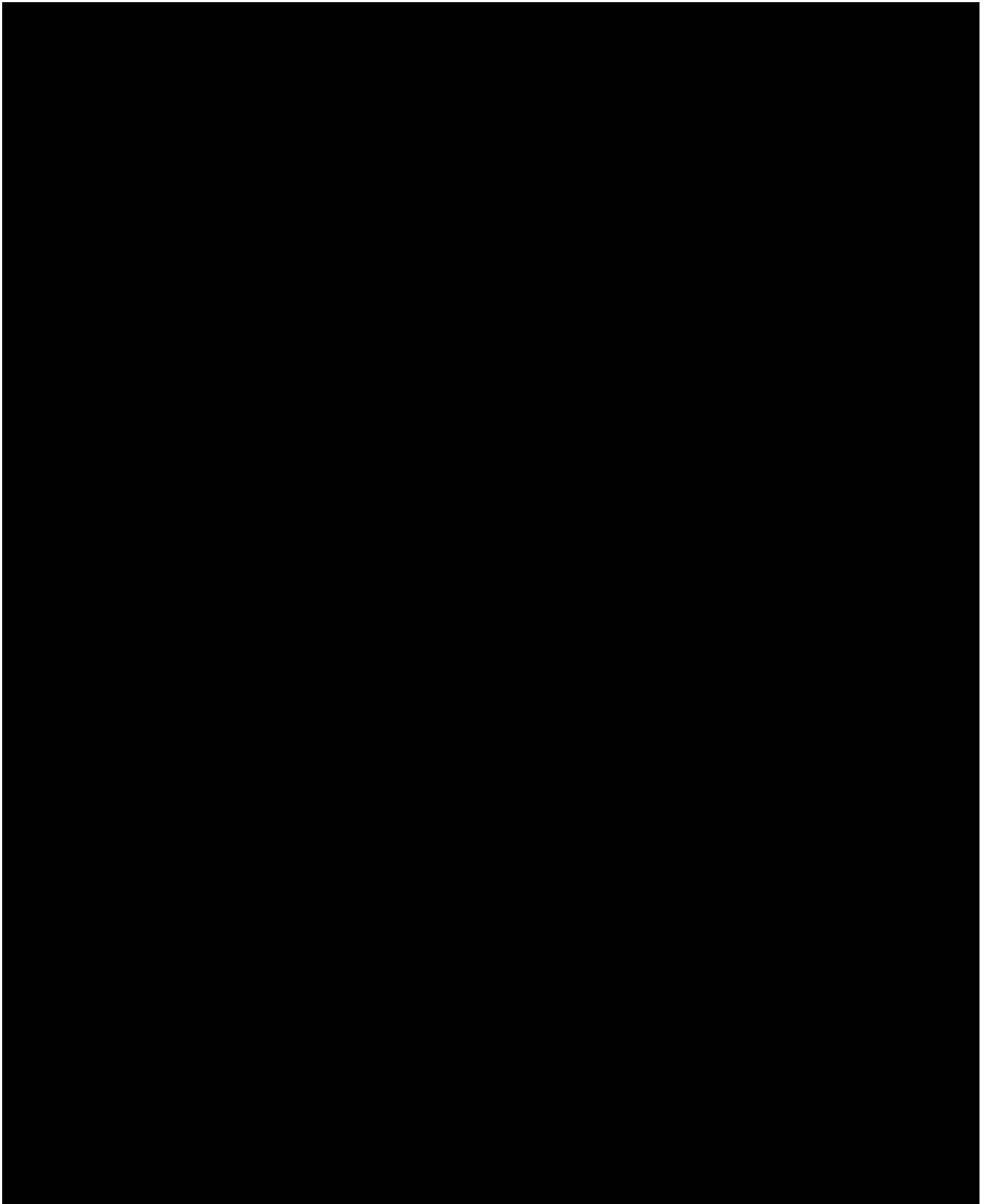
6.10.1.7. 36-Item Short-form Health Survey

The SF-36 (version 2) will be completed at the time points indicated in the study procedures table ([Appendix 2](#)) and should be completed before any other study procedures.

The SF-36 is a health related quality of life instrument consisting of 36 questions belonging to 8 domains in 2 components and covers a 4-week recall period:

- Physical Well-Being: 4 Domains: Physical Functioning (10 Items), Role Physical (4 Items), Bodily Pain (2 Items), And General Health Perceptions (5 Items)
- Mental Well-Being: 4 Domains: Vitality (4 Items), Social Functioning (2 Items), Role Emotional (3 Items), And Mental Health (5 Items)

The remaining item (health transition) is not part of the above domains but is kept separately. 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. The SF-36 is not disease specific and has been validated in numerous health states.



6.10.2. Safety and Tolerability

Adverse events (AEs), physical examinations, vital signs, and laboratory assessments (standard hematology, serum/plasma chemistry, and urinalysis) will be collected.

6.10.3. Clinical Laboratory Evaluations

The hematology and serum chemistry laboratory analyses will be performed at a central laboratory. Reference ranges will be supplied by the central laboratory and will be used by the investigator to assess the laboratory data for clinical significance and pathological changes.

Blood samples will be collected by venipuncture (or optional indwelling catheter for pharmacokinetic sampling days) in the arm at the time points indicated in the study procedures table ([Appendix 2](#)). In addition, urine samples for the clinical laboratory assessments will be collected. Subjects only need to be fasted at days were lipid profiling is scheduled.

Please refer to [Appendix 6](#) for table of Clinical laboratory tests.

The laboratory values outside the normal range will be flagged and clinical relevance will be assessed by the investigator. More frequent sampling as well as additional tests may be performed as deemed necessary by the investigator as indicated.

Note that in the case where clinically significant laboratory test results are a potential reason for discontinuation from the study drug and withdrawal from the study, retesting of the affected parameter(s) should be prompt (within 3 to 7 days) after the investigator has consulted with the medical monitor. A decision regarding subject discontinuation should be made after the results from the retest are available (see Section [3.5](#) for additional information).

The details of sample handling and shipment instructions will be provided in a separate laboratory manual.

6.10.4. Vital Signs

Vital signs will be measured at the time points indicated in the study procedures table ([Appendix 2](#)).

Vital signs should be taken after the subject has been resting for 5 min and will include heart rate, respiratory rate, SBP, DBP, and body temperature.

6.10.5. Physical Examination

A physical examination should be performed at the time points indicated in the study procedures table ([Appendix 2](#)).

Any changes from Baseline (Day -1) will be recorded.

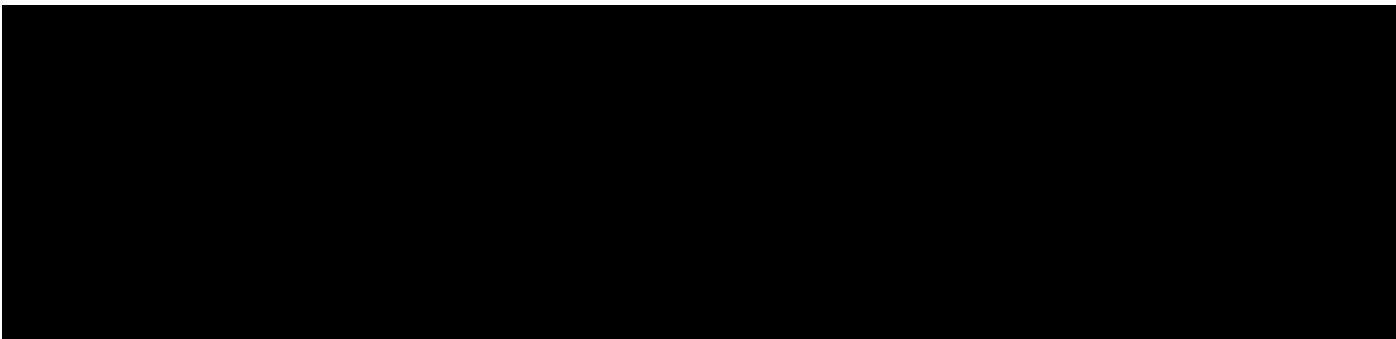
At Day -1, a complete physical exam will be performed, if not completed at the final treatment visit of the subject's parent study. For visits occurring thereafter, (ie, at Weeks 2, 6, and every 24 weeks after Day -1 [every 12 weeks until protocol amendment 7 implementation] until last visit or ET), symptom-directed physical examinations should be performed. Weight is measured at all clinical visits where a complete or directed physical exam is performed.

6.10.6. Other Safety Assessments

6.10.6.1. 12-lead Electrocardiogram

A resting 12-lead ECG will be performed at the Day -1 visit as indicated in the study procedures table ([Appendix 2](#)).

The ECG should be obtained after the subject has been resting in the supine position for ≥ 5 min and will include heart rate (HR), PR interval, QRS, uncorrected QT, morphology, and rhythm analysis. QT interval corrected for HR according to Fridericia (QTcF) will be derived during the statistical analysis. ECGs will be interpreted by the investigator or qualified designee for clinical significance and results will be entered into the eCRF.



7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

7.1. Definitions of Adverse Events, Adverse Reactions, and Serious Adverse Events

7.1.1. Adverse Events

An adverse event (AE) is any untoward medical occurrence in a clinical study subject administered a medicinal product, which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. AEs may also include pre- or post-treatment complications that occur as a result of protocol specified procedures, lack of efficacy, overdose, drug abuse/misuse reports, or occupational exposure. Preexisting events that increase in severity or change in nature during or as a consequence of participation in the clinical study will also be considered AEs.

An AE does not include the following:

- Medical or surgical procedures such as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an adverse event and must be reported.
- Pre-existing diseases, conditions, or laboratory abnormalities present or detected before the Day -1 visit that do not worsen
- Situations where an untoward medical occurrence has not occurred (ie, hospitalization for elective surgery, social and/or convenience admissions)
- Overdose without clinical sequelae (see Section 7.7)
- Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed and not related to a protocol-associated procedure is not an AE. It is considered to be pre-existing and should be documented on the medical history CRF.

7.1.2. Serious Adverse Events

A **serious adverse event** (SAE) is defined as an event that, at any dose, results in the following:

- Death
- Life-threatening (Note: The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.)
- In-patient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity

- A congenital anomaly/birth defect
- A medically important event or reaction: such events 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 constituting SAEs. Medical and scientific judgment must be exercised to determine whether such an event is a reportable under expedited reporting rules. Examples of medically important events include intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; and development of drug dependency or drug abuse. For the avoidance of doubt, infections resulting from contaminated medicinal product will be considered a medically important event and subject to expedited reporting requirements.

7.1.3. Adverse Events of Interest (AEIs)

AEIs in this study include but are not limited to serious and opportunistic infections, herpes zoster/shingles, thromboembolism, major adverse cardiovascular events (MACE), gastrointestinal perforation, and malignancy. Additional information for AEIs may be collected through eCRF/electronic data capture (EDC) and/or through direct site communication.

7.1.4. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Laboratory abnormalities without clinical significance are not to be recorded as AEs or SAEs. However, laboratory abnormalities (eg, clinical chemistry, hematology, and urinalysis) that require medical or surgical intervention or lead to IMP interruption, modification, or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (eg, electrocardiogram, x-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE or SAE as described in Sections 7.1.1 and 7.1.2. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (eg, anemia), not the laboratory result (ie, decreased hemoglobin).

For specific information on handling of clinical laboratory abnormalities in this study, please refer to Section 7.5 and Section 3.5.2.

7.2. Assessment of Adverse Events and Serious Adverse Events

The investigator or qualified subinvestigator is responsible for assessing AEs and SAEs for causality and severity, and for final review and confirmation of accuracy of event information and assessments.

7.2.1. Assessment of Causality for Study Drugs and Procedures

The investigator or qualified subinvestigator is responsible for assessing the relationship to study drug therapy using clinical judgment and the following considerations:

- **No:** Evidence exists that the adverse event has an etiology other than the study drug. For SAEs, an alternative causality must be provided (eg, pre-existing condition, underlying disease, intercurrent illness, or concomitant medication).
- **Yes:** There is reasonable possibility that the event may have been caused by the investigational medicinal product.

It should be emphasized that ineffective treatment should not be considered as causally related in the context of adverse event reporting.

The relationship to study procedures (eg, invasive procedures such as venipuncture or biopsy) should be assessed using the following considerations:

- **No:** Evidence exists that the adverse event has an etiology other than the study procedure.
- **Yes:** The adverse event occurred as a result of protocol procedures, (eg, venipuncture).

7.2.2. Assessment of Severity

The severity of AEs will be graded using the modified CTCAE, version 4.03. For each episode, the highest grade attained should be reported. Laboratory abnormalities without clinical significance should not be recorded as AEs or SAEs (see Section 7.5).

If a CTCAE criterion does not exist, the investigator should use the grade or adjectives: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening) or Grade 5 (fatal) to describe the maximum intensity of the adverse event. For purposes of consistency with the CTCAE, these intensity grades are defined in Table 7-1 and Appendix 4.

Table 7-1. Grading of Adverse Event Severity

Grade	Adjective	Description
Grade 1	Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate	Local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL
Grade 3	Severe	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
Grade 4	Life-threatening	Urgent intervention indicated
Grade 5	Death	Death related AE

* Activities of Daily Living (ADL) Instrumental ADL refer to opening preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

** Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

7.3. Investigator Requirements and Instructions for Reporting Adverse Events and Serious Adverse Events to the Sponsor

Requirements for collection prior to study drug initiation:

After informed consent, but prior to initiation of study medication, the following types of events should be reported on the case report form (CRF/eCRF): all SAEs and adverse events related to protocol-mandated procedures.

Adverse Events

Following initiation of study medication, collect all AEs, regardless of cause or relationship, until 30-days after last administration of study drug must be reported to the CRF/eCRF database as instructed.

All AEs should be followed up until resolution or until the adverse event is stable, if possible. The sponsor may request that certain AEs be followed beyond the protocol defined follow up period.

Serious Adverse Events

All SAEs, regardless of cause or relationship, that occurs after the subject first consents to participate in the study (ie, signing the informed consent) and throughout the duration of the study, including the protocol-required post treatment follow-up period, must be reported in the CRF/eCRF database and the sponsor, as instructed. This also includes any SAEs resulting from protocol-associated procedures performed after informed consent is signed.

Any SAEs and deaths that occur after the post treatment follow-up visit but within 30-days of the last dose of study drug, regardless of causality, should also be reported.

Investigators are not obligated to actively seek SAEs after the protocol defined follow up period however, if the investigator learns of any SAEs that occur after study participation has concluded and the event is deemed relevant to the use of study drug, he/she should promptly document and report the event to the sponsor.

All AEs and SAEs will be recorded in the CRF/eCRF database within the timelines outlined in the CRF/eCRF completion guideline.

Electronic Serious Adverse Event (eSAE) Reporting Process

- Site personnel record all SAE data in the eCRF database and from there transmit the SAE information to the sponsor within 24 hours of the investigator's knowledge of the event. Detailed instructions can be found in the eCRF completion guidelines.
- If for any reason it is not possible to record the SAE information electronically, ie, the eCRF database is not functioning, record the SAE on the paper serious adverse event reporting form and submit within 24 hours as described below.

E-mail:



- As soon as it is possible to do so, any SAE reported via paper must be transcribed into the eCRF database according to instructions in the eCRF completion guidelines.
- If an SAE has been reported via a paper form because the eCRF database has been locked, no further action is necessary.
- All AEs and SAEs will be recorded in the eCRF database within the timelines outlined in the eCRF completion guideline.
- For fatal or life-threatening events, copies of hospital case reports, autopsy reports, and other documents are also to be submitted by e-mail or fax when requested and applicable. Transmission of such documents should occur without personal subject identification, maintaining the traceability of a document to the subject identifiers.
- Additional information may be requested to ensure the timely completion of accurate safety reports.
- Any medications necessary for treatment of the SAE must be recorded onto the concomitant medication section of the subject's CRF/eCRF and the event description section of the SAE form.

7.4. Sponsor Reporting Requirements

Depending on relevant local legislation or regulations, including the applicable US FDA Code of Federal Regulations, the EU Clinical Trial Regulation No 536/2014 and relevant updates, and other country-specific legislation or regulations, the sponsor may be required to expedite to worldwide regulatory agencies reports of SAEs, serious adverse drug reactions (SADRs), or suspected unexpected serious adverse reactions (SUSARs). In accordance with the EU Clinical Trial Regulation No 536/2014, the sponsor or a specified designee will notify worldwide regulatory agencies and the relevant IEC in concerned Member States of applicable SUSARs as outlined in current regulations.

Assessment of expectedness for SAEs will be determined by the sponsor or designee using reference safety information specified in the IB or relevant local label as applicable.

All investigators will receive a safety letter notifying them of relevant SUSAR reports associated with any study drug. The investigator should notify the IRB or IEC of SUSAR reports as soon as is practical, where this is required by local regulatory agencies, and in accordance with the local institutional policy.

7.5. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Adverse events will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA). Severity should be recorded and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03, which can be found at:

https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

For AEs associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality.

All clinical and clinically significant laboratory toxicities will be managed according to uniform guidelines detailed in [Appendix 3](#) and as outlined below.

7.5.1. Grades 1 and 2 Laboratory Abnormality or Clinical Event

Refer to Section [3.5.1](#) and [3.5.2](#), if not outlined in that section then continue study drug at the discretion of the investigator.

7.5.2. Grade 3 Laboratory Abnormality or Clinical Event

Refer to Section [3.5.1](#) and [3.5.2](#), if not outlined in that section then:

- For Grade 3 clinically significant laboratory abnormality or clinical event, investigational medicinal product may be continued if the event is considered to be unrelated to investigational medicinal product.
- For a Grade 3 clinical event, or clinically significant laboratory abnormality confirmed by repeat testing, that is considered to be related to investigational medicinal product, investigational medicinal product should be withheld until the toxicity returns to $\leq$ Grade 2.

If a laboratory abnormality recurs to $\geq$ Grade 3 following re-challenge with investigational medicinal product and is considered related to investigational medicinal product, then investigational medicinal product should be permanently discontinued and the subject managed according to local clinical practice. Recurrence of laboratory abnormalities considered unrelated to investigational medicinal product may not require permanent discontinuation.

7.5.3. Grade 4 Laboratory Abnormality or Clinical Event

Refer to Section [3.5.1](#) and [3.5.2](#), if not outlined in that section then:

- For a Grade 4 clinical event or clinically significant Grade 4 laboratory abnormality confirmed by repeat testing that is considered related to investigational medicinal product, investigational medicinal product should be permanently discontinued and the subject managed according to local practice. The subject should be followed as clinically indicated until the laboratory abnormality returns to baseline or is otherwise explained, whichever occurs first. A clinically significant Grade 4 laboratory abnormality that is not confirmed by repeat testing should be managed according to the algorithm for the new toxicity grade.
- Investigational medicinal product may be continued without dose interruption for a clinically non-significant Grade 4 laboratory abnormality (eg, Grade 4 CK after strenuous exercise or triglyceride elevation that is nonfasting or that can be medically managed) or a clinical event considered unrelated to investigational medicinal product.

7.6. Toxicity Management

Treatment-emergent toxicities will be noted by the investigator and brought to the attention of the medical monitor, who will have a discussion with the investigator and decide the appropriate course of action. Whether or not considered treatment-related, all subjects experiencing AEs must be monitored periodically until symptoms subside, any abnormal laboratory values have resolved or returned to Day -1 levels or they are considered irreversible, or until there is a satisfactory explanation for the changes observed.

Grade 3 or 4 clinically significant laboratory abnormalities should be managed as outlined in [Appendix 3](#).

Any questions regarding toxicity management should be directed to the medical monitor.

7.6.1. Thromboembolic Events

Subjects experiencing a thromboembolic event should be evaluated for the overall risk of recurrent thromboembolism and referred to a specialist for further testing as appropriate (including but not limited to evaluation for an underlying inherited hypercoagulable state).

7.7. Special Situations Reports

7.7.1. Definitions of Special Situations

Special situation reports include all reports of medication error, abuse, misuse, overdose, reports of adverse events associated with product complaints, occupational exposure with an AE, pregnancy reports regardless of an associated AE and AE in an infant following exposure from breastfeeding.

Medication error is any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the health care provider, subject, or consumer.

Abuse is defined as persistent or sporadic intentional excessive use of a medicinal product by a subject.

Misuse is defined as any intentional and inappropriate use of a medicinal product that is not in accordance with the protocol instructions or the local prescribing information.

An overdose is defined as an accidental or intentional administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose as per protocol or in the product labelling (as it applies to the daily dose of the subject in question). In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the subject has taken the excess dose(s). Overdose cannot be established when the subject cannot account for the discrepancy except in cases in which the investigator has reason to suspect that the subject has taken the additional dose(s).

Product complaint is defined as complaints arising from potential deviations in the manufacture, packaging, or distribution of the medicinal product.

Occupational exposure is defined as exposure to a medicinal product as a result of one's professional or non-professional occupation.

7.7.2. Instructions for Reporting Special Situations

7.7.2.1. Instructions for Reporting Pregnancies

The investigator should report pregnancies in female study subjects that are identified after initiation of study medication and throughout the study, including the post study drug follow-up period, to [REDACTED] using the pregnancy report form within 24 hours of becoming aware of the pregnancy.

Refer to [Appendix 5](#) and the CRF/eCRF completion guidelines for full instructions on the mechanism of pregnancy reporting.

The pregnancy itself is not considered an AE nor is an induced elective abortion to terminate a pregnancy without medical reasons.

In case of an onset of SAE or an unfavorable outcome occurs (abortion, abnormalities in the fetus, early termination of pregnancy) a SAE form also must be filled-in by the investigator and immediately sent to the sponsor.

Any premature termination of pregnancy (eg, a spontaneous abortion, an induced therapeutic abortion due to complications or other medical reasons) must be reported within 24 hours as an SAE. The underlying medical reason for this procedure should be recorded as the AE term.

A spontaneous abortion is always considered to be an SAE and will be reported as described in Sections [7.1.1](#) and [7.1.2](#). Furthermore, any SAE occurring as an adverse pregnancy outcome post study must be reported to [REDACTED]

The subject should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome should be reported to [REDACTED] using the pregnancy outcome report form. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to [REDACTED]

Refer to [Appendix 5](#) for Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements.

7.7.2.2. Reporting Other Special Situations

All other special situation reports must be reported on the special situations report form and forwarded to [REDACTED] within 24 hours of the investigator becoming aware of the situation. These reports must consist of situations that involve study drug, but do not apply to concomitant medications.

Special situations involving concomitant medications do not need to be reported on the special situations report form; however, for special situations that result in AEs due to a concomitant medication, the AE should be reported on the AE form.

Any inappropriate use of concomitant medications prohibited by this protocol should not be reported as “misuse,” but may be more appropriately documented as a protocol deviation.

Refer to the CRF/eCRF completion guidelines for full instructions on the mechanism of special situations reporting.

All clinical sequelae in relation to these special situation reports will be reported as AEs or SAEs at the same time using the AE CRF/eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management, and outcome will be reported, when available.

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Objectives and Endpoints

8.1.1. Analysis Objectives

The primary objective of this study is:

- To evaluate the long-term safety and tolerability of filgotinib in subjects who have completed one of the parent studies of filgotinib in RA.

The secondary objective of this study is:

- To evaluate the long-term efficacy of filgotinib in subjects with RA.

The exploratory objectives of this study are:

- To evaluate the long-term effects of filgotinib on subject-reported outcomes, such as disability, fatigue, and quality of life.

8.1.2. Primary Endpoint

The primary endpoint is:

Safety, evaluated through AEs, clinical laboratory tests, and vital signs.

8.1.3. Secondary Endpoints

The secondary endpoints are:

- ACR-N over time in each arm

8.1.4. Exploratory Endpoints

- Achievement of ACR20/50/70
- EULAR responses; ACR/EULAR remission
- Evolution of CDAI, SDAI, and DAS28(CRP) over time
- Evolution of patient reported outcomes over time
- Absolute value and change from baseline in SF-36, FACIT-Fatigue, and [REDACTED] overtime from Day -1 through the end of treatment
- Absolute value and change from baseline in [REDACTED] over time from Day -1 through the end of treatment

8.2. Analysis Conventions

8.2.1. Analysis Sets

8.2.1.1. Safety/Efficacy

The primary analysis set for safety and efficacy is the Safety Analysis Set, which includes all enrolled subjects who received at least 1 dose of study drug.

8.3. Data Handling Conventions

Values for missing safety laboratory data will not be imputed. If no baseline laboratory value is available, the baseline value will be assumed to be normal (ie, no grade [Grade 0]) for the summary of graded laboratory abnormalities. If safety laboratory results for a subject are missing

for any reason at a time point, the subject will be excluded from the calculation of summary statistics for that time point.

Laboratory data that are continuous in nature but are less than the lower limit of quantitation or above the upper limit of quantitation will be imputed to the value of the lower or upper limit minus or plus one significant digit, respectively (eg, if the result of a continuous laboratory test is < 20, a value of 19 will be assigned; if the result of a continuous laboratory test is < 20.0, a value of 19.9 will be assigned).

8.4. Demographic Data and Baseline Characteristics

Demographic and Baseline characteristics will be summarized by treatment group using standard descriptive statistics including sample size, mean, SD, median, Q1, Q3, minimum, and maximum for continuous variables and numbers and percentages of subjects for categorical variables.

Demographic data will include sex, race, ethnicity, and age.

Baseline characteristics include DAS28 (CRP), HAQ-DI, SDAI, CDAI, and other variables of interest.

8.5. Efficacy Analysis

For secondary and exploratory endpoints listed under Section 8.1 summary statistics will be provided by treatment group. Differences across treatment groups will be summarized and treatment comparisons may be performed. Details on efficacy analyses will be described in the SAP.

8.6. Safety Analysis

Safety will be evaluated by assessment of clinical laboratory tests, physical examinations, vital signs measurements at various time points during the study, and by the documentation of AEs.

All safety data collected on or after the first dose of study drug administration up to 30 days after the last dose of study drug will be summarized. All data collected during the course of the study will be included in data listings.

8.7. Extent of Exposure

A subject's extent of exposure to study drug will be generated from the study drug administration page of the eCRF. Exposure data will be summarized by treatment group.

Duration of exposure to study drug will be expressed as the number of weeks between the first and last dose of the study drug, inclusive, regardless of temporary interruptions in study drug administration and summarized by treatment group.

8.8. Adverse Events

Clinical and laboratory adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). System Organ Class (SOC), High-Level Group Term (HLGT), High-Level Term (HLT), Preferred Term (PT), and Lower-Level Term (LLT) will be attached to the clinical database.

Treatment-Emergent Adverse Events (TEAEs) are:

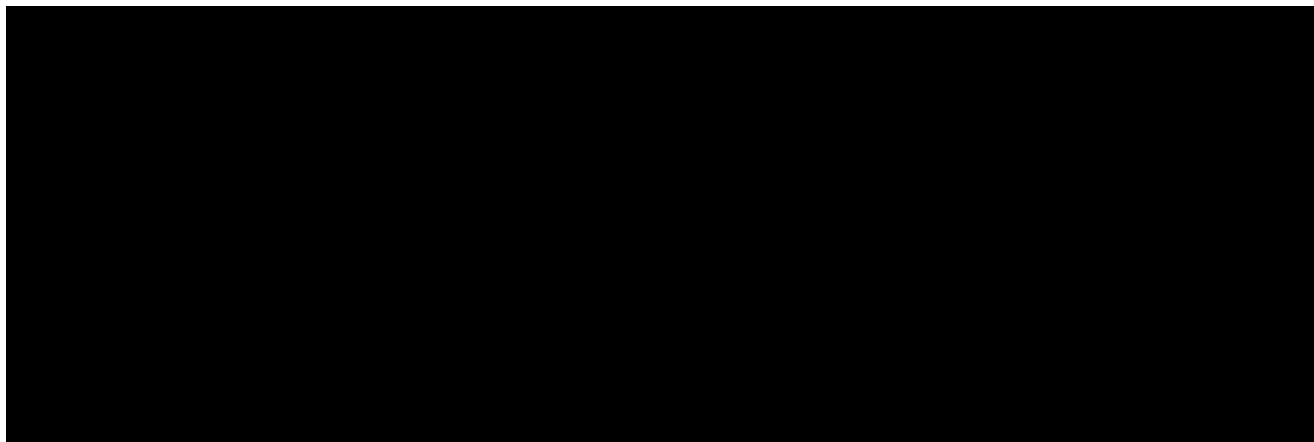
- Any AEs with an onset date of on or after the study drug start date and no later than 30 days after permanent discontinuation of study drug or
- Any AEs leading to premature discontinuation of study drug.

Summaries (number and percentage of subjects) of TEAEs by SOC and PT will be provided by treatment group. TEAEs will also be summarized by relationship to study drug and severity. In addition, TEAEs leading to premature discontinuation of study drug will be summarized and listed.

8.9. Laboratory Evaluations

Selected laboratory data will be summarized (n, mean, SD, median, Q1, Q3, minimum, and maximum) by treatment group and study visit along with corresponding change from Baseline. The incidence of treatment-emergent graded laboratory abnormalities will be summarized similarly.

Graded laboratory abnormalities will be defined using CTCAE 4.03 grading scale. Exposure-response analysis may be performed.



8.11. Sample Size

No formal hypothesis testing is planned for this study and sample size calculation is not conducted. All subjects who have completed or met protocol specified discontinuation criteria in a prior filgotinib treatment study in RA may enroll in this long-term extension study.

8.12. Data Monitoring Committee

An external multidisciplinary DMC will review the progress of the study, perform interim reviews of safety data and provide recommendations to the sponsor whether the nature, frequency and severity of adverse effects warrant the early termination of the study, whether the study should continue as planned, or should continue with modifications. The committee is established for each of the parent protocols (GS-US-417-0301, GS-US-417-0302, GS-US-417-0303) and will continue to review safety data for this LTE study until the study is unblinded.

The DMC's specific activities are defined by the parent studies' mutually agreed charters, including the DMC's membership, conduct and meeting schedule. While the DMC will be asked to advise the sponsor regarding future conduct of the study, including possible early study termination, the sponsor retains final decision-making authority on all aspects of the study.

8.13. Cardiovascular Safety Endpoint Adjudication Committee (CVEAC)

An independent adjudication committee governed by a charter will be set up to perform adjudication of potential MACE and thromboembolic events reported during the study. The adjudication of these events will be performed in a blinded fashion (until the study remains blinded to dose) for the purposes of data analysis and not for monitoring of subject safety.

Additional information regarding the logistics of adjudication will be described in the charter.

8.14. Analysis Schedule

Interim analyses may be performed for regulatory submission purposes. The pre-specified interim analysis was performed when all randomized subjects had completed their Week 24 visit in parent studies (or prematurely discontinued from the parent studies prior to Week 24). Additional interim analyses may be performed after all randomized subjects have completed their Week 52 visit in parent studies (or prematurely discontinued from the parent studies prior to Week 52).

The final analysis for primary and secondary objectives will be performed upon study completion, which is defined in Section 3.4.

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki, International Council for Harmonisation (ICH) guidelines, or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study subject. These standards are consistent with the EU Clinical Trial Regulation No 536/2014 and the Medicines for Human Use (Clinical Trials) Regulations 2004

(S.I. 2004/1031) and Amendment Regulations 2006 (S.I. 2006/1928) and European Data Protection Regulation (GDPR 676/2016).

The investigator will ensure adherence to the basic principles of Good Clinical Practice, as outlined in 21 CFR 312, subpart D, “Responsibilities of Sponsors and Investigators,” 21 CFR, part 50, 1998, and 21 CFR, part 56, 1998.

The investigator and all applicable subinvestigators will comply with 21 CFR, Part 54, 1998, providing documentation of their financial interest or arrangements with the sponsor, or proprietary interests in the investigational drug under study. This documentation must be provided prior to the investigator’s (and any subinvestigator’s) participation in the study. The investigator and subinvestigator agree to notify the sponsor of any change in reportable interests during the study and for 1 year following completion of the study. Study completion is defined as the date when the last subject completes the protocol-defined activities.

9.1.2. Institutional Review Board (IRB)/Independent Ethics Committee (IEC) Review and Approval

The investigator (or sponsor as appropriate according to local regulations) will submit this protocol, informed consent form, and any accompanying material to be provided to the subject (such as advertisements, subject information sheets, or descriptions of the study used to obtain informed consent) to an IRB/IEC. The investigator will not begin any study subject activities until approval from the IRB/IEC has been documented and provided as a letter to the investigator.

Before implementation, the investigator will submit to and receive documented approval from the IRB/IEC any modifications made to the protocol or any accompanying material to be provided to the subject after initial IRB/IEC approval, with the exception of those necessary to reduce immediate risk to study subjects.

9.1.3. 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 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.

9.1.4. Confidentiality

The investigator must assure that subjects’ anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only subject initials, date of birth, another unique identifier (as allowed by local law) and an identification code will be recorded on any form or biological sample submitted to the Sponsor, IRB/IEC, or laboratory. Laboratory specimens must be labeled in such a way as to protect subject identity while allowing the results to be recorded to the proper subject. Refer to specific laboratory instructions. NOTE: The

investigator must keep a subject log showing codes, names, and addresses for all subjects screened and for all subjects enrolled in the trial. Subject data will be processed in accordance with all applicable regulations.

The investigator agrees that all information received from the sponsor, including but not limited to the investigator brochure, this protocol, CRF/eCRF, the study drug, and any other study information, remain the sole and exclusive property of the sponsor during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from the sponsor. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

9.1.5. Study Files and Retention of Records

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following two categories: (1) investigator's study file, and (2) subject clinical source documents.

The investigator's study file will contain the protocol/amendments, CRF and query forms, IRB/IEC and governmental approval with correspondence, informed consent, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

The required source data should include sequential notes containing at least the following information for each subject:

- Subject identification (name, date of birth, gender);
- Documentation that subject meets eligibility criteria, ie, history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria);
- Documentation of the reason(s) a consented subject is not enrolled;
- Participation in study (including study number);
- Study discussed and date of informed consent;
- Dates of all visits;
- Documentation that protocol specific procedures were performed;
- Results of efficacy parameters, as required by the protocol;
- Start and end date (including dose regimen) of study drug, including dates of dispensing and return;
- Record of all adverse events and other safety parameters (start and end date, and including causality and severity);

- Concomitant medication (including start and end date, dose if relevant; dose changes);
- Date of study completion and reason for early discontinuation, if it occurs.

All clinical study documents must be retained by the investigator until at least 2 years or according to local laws, whichever is longer, after the last approval of a marketing application in an ICH region (ie, United States, Europe, or Japan) and until there are no pending or planned marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if specified by regulatory requirements, by local regulations, or by an agreement with the sponsor. The investigator must notify the sponsor before destroying any clinical study records.

Should the investigator wish to assign the study records to another party or move them to another location, the sponsor must be notified in advance.

If the investigator cannot provide for this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and the sponsor to store these records securely away from the site so that they can be returned sealed to the investigator in case of an inspection. When source documents are required for the continued care of the subject, appropriate copies should be made for storage away from the site.

9.1.6. Case Report Forms

For each subject consented, an eCRF casebook will be completed by an authorized study staff member whose training for this function is completed in EDC. The eCRF casebook will only capture the data required per the protocol schedule of events and procedures. The Inclusion/Exclusion Criteria and Enrollment eCRFs should be completed only after all data related to eligibility have been received. Subsequent to data entry, a study monitor will perform source data verification within the EDC system. System-generated or manual queries will be issued to the investigative site staff as data discrepancies are identified by the monitor or the data management staff, who routinely review the data for completeness, correctness, and consistency. The site coordinator is responsible for responding to the queries in a timely manner, within the system, either by confirming the data as correct or updating the original entry, and providing the reason for the update (eg, data entry error). Original entries as well as any changes to data fields will be stored in the audit trail of the system. Prior to any interim time points or database lock (as instructed by the sponsor), the investigator will use his/her log in credentials to confirm that the forms have been reviewed, and that the entries accurately reflect the information in the source documents. At the conclusion of the trial, the sponsor will provide the site with a read-only archive copy of the data entered by that site. This archive must be stored in accordance with the records retention requirements outlined in Section [9.1.5](#).

9.1.7. Investigational Medicinal Product Accountability and Return

Where possible, study drug should be destroyed at the site. At the start of the study, the study monitor will evaluate each study center's study drug disposal procedures and provide appropriate instruction for disposal or return of unused study drug supplies. If the site has an appropriate standard operating procedure (SOP) for drug destruction as determined by the sponsor, the site

may destroy used (empty or partially empty) and unused study drug supplies as long as performed in accordance with the site's SOP. This can occur only after the study monitor has performed drug accountability during an on-site monitoring visit and the sponsor provided approval for destruction.

A copy of the site's Study Drug Disposal SOP or written procedure (signed and dated by the PI or designee) will be obtained for the sponsor's site files. If the site does not have acceptable procedures in place, arrangements will be made between the site and the sponsor (or the sponsor's representative) for return of unused study drug supplies.

If study drug is destroyed on site, the investigator must maintain accurate records for all study drugs destroyed. Upon study completion, copies of the study drug accountability records must be filed at the site. Another copy will be returned to the sponsor.

The study monitor will review study drug supplies and associated records at periodic intervals.

9.1.8. Inspections

The investigator will make available all source documents and other records for this trial to the sponsor's appointed study monitors, to IRBs/IECs, or to regulatory authority or health authority inspectors.

9.1.9. Protocol Compliance

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by the sponsor. The investigator must submit all protocol modifications to the IRB/IEC in accordance with local requirements and receive documented IRB/IEC approval before modifications can be implemented. In case of substantial amendment to the protocol, an approval from the Competent Regulatory Authority will be sought before implementation.

9.2.2. Study Report and Publications

A clinical study report (CSR) will be prepared and provided to the regulatory agency(ies). The sponsor will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

Investigators in this study may communicate, orally present, or publish in scientific journals or other scholarly media only after the following conditions have been met:

the results of the study in their entirety have been publicly disclosed by or with the consent of the sponsor in an abstract, manuscript, or presentation form or the study has been completed at all study sites for at least 2 years

The investigator will submit to the sponsor any proposed publication or presentation along with the respective scientific journal or presentation forum at least 30 days before submission of the publication or presentation.

No such communication, presentation, or publication will include the sponsor's confidential information (see Section 9.1.4).

The investigator will comply with the sponsor's request to delete references to its confidential information (other than the study results) in any paper or presentation and agrees to withhold publication or presentation for an additional 60 days in order to obtain patent protection if deemed necessary.

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Payment Reporting

Investigators and their study staff may be asked to provide services performed under this protocol, ie attendance at Investigator's Meetings. If required under the applicable statutory and regulatory requirements, the sponsor will capture and disclose to Federal and State agencies any expenses paid or reimbursed for such services, including any clinical trial payments, meal, travel expenses or reimbursements, consulting fees, and any other transfer of value.

9.3.2. Access to Information for Monitoring

In accordance with regulations and guidelines, the study monitor must have direct access to the investigator's source documentation in order to verify the accuracy of the data recorded in the CRF/eCRF.

The monitor is responsible for routine review of the CRF/eCRF at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any subject records needed to verify the entries on the CRF/eCRF. The investigator agrees to cooperate with the monitor to ensure that any problems detected through any type of monitoring (central, on site) are resolved.

9.3.3. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or of the sponsor may conduct inspections or audits of the clinical study. If the investigator is notified of an inspection by a regulatory authority the investigator agrees to notify the medical monitor immediately. The investigator agrees to provide to representatives of a regulatory agency or the sponsor access to records, facilities, and personnel for the effective conduct of any inspection or audit.

9.3.4. Study Discontinuation

Both the sponsor and the investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures and notify the appropriate regulatory authority(ies), IRBs, and IECs. In terminating the study, the sponsor and the investigator will assure that adequate consideration is given to the protection of the subjects' interests.

10. REFERENCES

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11. APPENDICES

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STUDY ACKNOWLEDGEMENT

A Multicenter, Open-label, Long term Extension Study to Assess the Safety and Efficacy of
Filgotinib in Subjects with Rheumatoid Arthritis

GS-US-417-0304, Amendment 9, 10-June-2024

This protocol has been approved by Alfasigma S.p.A. An electronic signature for the sponsor is provided at the end of the document.

Name (Printed)
Author

Signature

Date

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 Alfasigma S.p.A. 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

Appendix 2.Study Procedures Table

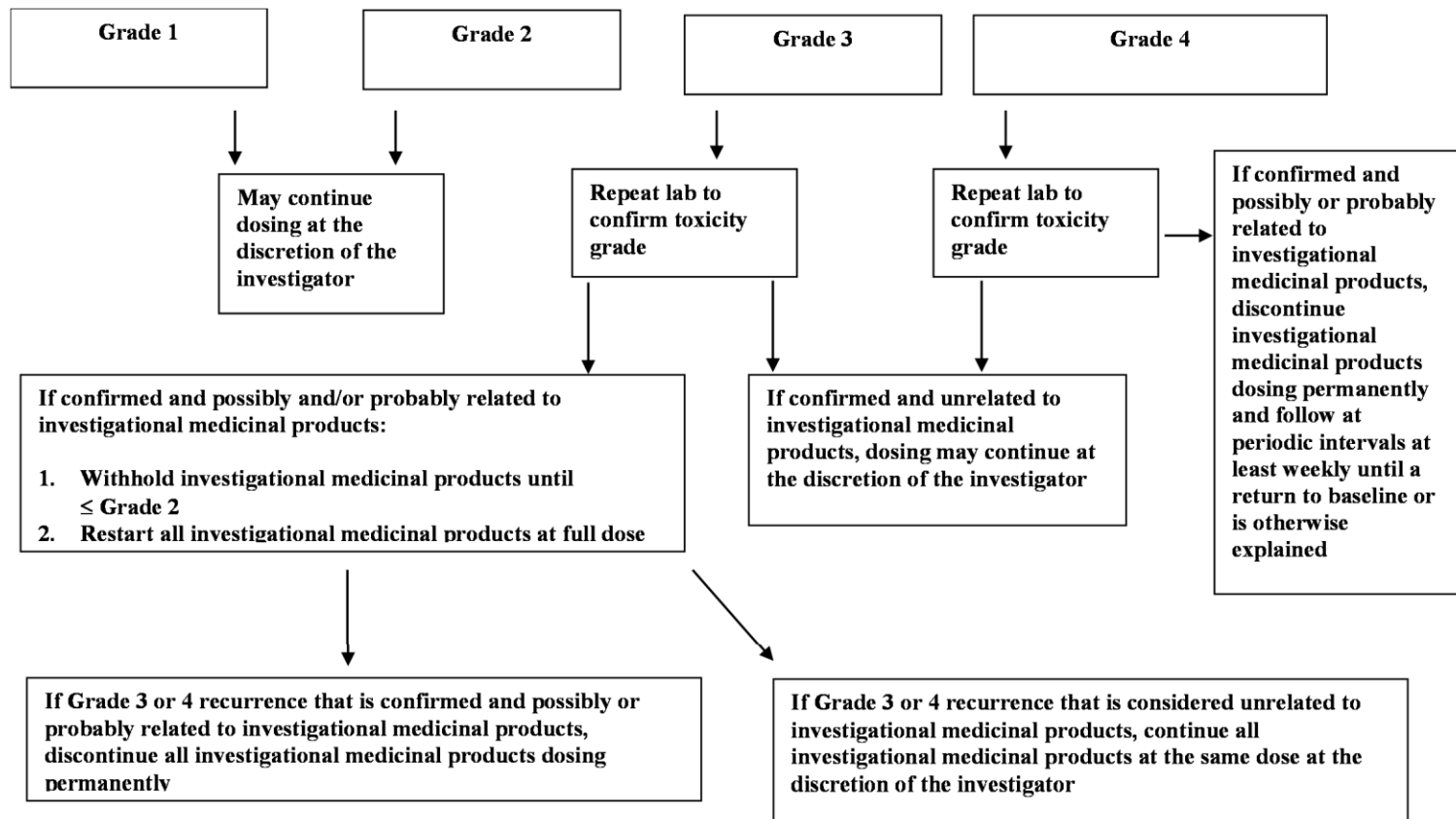
EVENT			Post Day -1 Assessments						
Study days (D)/Weeks (W)		D -1 (+28 days) ¹	W 2 (+/- 3 days)	W 6 (+/- 3 days)	Q4 Weeks (+/- 5 days)	Q24 Weeks (+/- 10 Days)	Q48 Weeks (+/- 10 days), in addition to the 24 Week assessments	End of Treatment / Early Termination (+/-5 days)	Post- Treatment Week 4 (± 5 days)
Baseline Assessment	Informed Consent	X							
	Inclusion/Exclusion Criteria	X							
	RA Diagnosis And Prior Treatment, Medical History ²	X							
	TB Screening ³	X					X ³		
Patient Questionnaires ⁴	Subject’s Global Assessment	X	X	X		X		X	
	HAQ-DI And Pain Scale	X	X	X		X		X	
	FACIT-FATIGUE, SF-36 Questionnaire, ██████████ ██████	X				X		X	
	Physician’s Global Assessment	X	X	X		X		X	
Clinical Assessments	Complete Physical Exam With Weight	X					X	X	
	Vital Signs	X	X	X		X		X	X
	Symptom Directed Physical Examination, Including Weight		X	X		X		X	X
	12-Lead ECG	X							
	SJC 66/TJC 68	X	X	X		X		X	

EVENT		Post Day -1 Assessments							
Study days (D)/Weeks (W)		D-1 (+28 days) ¹	W 2 (+/- 3 days)	W 6 (+/- 3 days)	Q4 Weeks (+/- 5 days)	Q24 Weeks (+/- 10 Days)	Q48 Weeks (+/- 10 days), in addition to the 24 Week assessments	End of Treatment / Early Termination (+/-5 days)	Post- Treatment Week 4 (± 5 days)
Laboratory Assessments ⁵	Hematology And Chemistry	X	X	X		X		X	X
	Urinalysis	X				X		X	X
	Lipid Profile (Fasting) ⁶	X				X		X	
	Viral Monitoring For Hepatitis B and/or Hepatitis C ¹³	X				X ⁷		X	
	Pregnancy Test (urine)	X			X ⁸	X			X
	Pregnancy Test (serum)	X						X	
	Serum CRP	X	X	X		X		X	X
Randomization/Reassignment ⁹		X							
Study Drug Dispensation ¹⁰		X	X	X		X			
Concomitant medications		Throughout the study							
AE assessment ¹¹		Throughout the study							

1. The Day -1 visit for this study (to have subject consented and eligibility confirmed) will be performed at either the last visit for the parent protocol (Week 52 for GS-US-417-0301 and GS-US-417-0303 or Week 24 for GS-US-417-0302) or on any day within 4 weeks of the final study visit for the parent protocol. Procedures that are performed as part of the last study visit on the parent study will be considered to be performed for Day -1 and need not be repeated unless otherwise indicated. Refer to Section 6.2.
2. Medical/Surgical History recall will be concentrated for any changes to subject's history since documentation in the parent study.
3. Refer to Section 6.2. Annual/every 48 weeks TB testing is optional (PI discretion).
4. Patient Reported Outcome measures should be completed prior to invasive assessments and diagnostic procedures, as much as possible.
5. Any AEs or tests showing abnormal results will be repeated as deemed appropriate by the investigator until the abnormality is resolved, returns to baseline, or is otherwise explained. Refer to list provided in Laboratory assessment table (Appendix 6).
6. Fasting is defined as 8 hours without food or drink (except water), prior to laboratory draw.
7. To be completed for subjects who tested positive for HBV or HCV exposure, with negative viral load.

8. To be completed at subject's home and confirmed via site contact with subject for confirmation of negative result. Test to be performed on urine sample only. Subjects may return to the study site for any of the monthly urine pregnancy tests, if they prefer.
9. To be completed in accordance with [Appendix 11](#). Randomization/Treatment Scheme. Subject assignment will remain blinded until the study becomes open-label.
10. Dosing will begin at Day 1 which the subject will perform outside of the clinic. Screening for the LTE should occur only after all prior filgotinib study procedures have been completed and dosing should not take place until confirmation that the subject is eligible to participate in this study. Dosing will occur daily. Doses should be taken at home.
11. Ongoing AEs from previous filgotinib studies should be recorded as medical history. Collection of AEs and SAEs related to protocol-mandated procedures will begin once informed consent is signed and will continue through the Post Treatment Week 4 Follow-Up Visit.
[REDACTED]
13. Only for subjects that screened positive on the parent protocol for HBV and/or HCV exposure, if not completed at the final study visit for the parent protocol. Refer to Section [6.6](#).
[REDACTED]

Appendix 3. Management of Clinical and Laboratory Adverse Events⁷



⁷ For study specific interruption and stopping criteria, please refer to Section 3.5. For all other Laboratory Abnormality or Clinical Events not specified in Section 3.5, management according to Appendix 3 and as outlined in Section 7.5.

Appendix 4. Common Terminology Criteria for Adverse Events (CTCAE) v4.03

CTCAE v4.03 can be accessed from the below link:

<http://www.hrc.govt.nz/sites/default/files/CTCAE%20manual%20-%20DMCC.pdf>

The only modification to the CTCAE criteria is the addition of a Grade 1 upper respiratory infection as follows:

CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	CTCAE v4.03 AE Term Definition
Upper respiratory infection	Mild symptoms; symptomatic relief (eg, cough suppressant, decongestant)	Moderate symptoms; oral intervention indicated (eg, antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by an infectious process involving the upper respiratory tract (nose, paranasal sinuses, pharynx, larynx, or trachea).

Appendix 5. Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements

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, permanently sterile or with medically documented ovarian failure.

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. Women of any age with amenorrhea ≥ 12 months may also be considered postmenopausal if their FSH level is in the postmenopausal range at Day -1 and they are not using hormonal contraception or hormonal replacement therapy. In addition, women of any age with amenorrhea ≥ 12 months during the course of the study may also be considered postmenopausal if their FSH level is in the postmenopausal range and in consultation with the medical monitor.

Permanent sterilization includes hysterectomy, bilateral oophorectomy, or bilateral salpingectomy in a female subject of any age.

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.

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 female subjects, hormonal contraceptives will be permitted as a form of contraception. 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, which should be reaffirmed throughout the subject's participation in the study and documented in the study records by the investigator. Women must have a negative serum pregnancy test at Day -1 and a negative urine pregnancy test on the Baseline/Day 1 visit prior to randomization. Pregnancy tests will be performed at monthly intervals thereafter. 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 Day -1 until 35 days following the last dose of study drug:

- 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)

These above-described methods are considered *preferred methods* of highly effective contraception in this protocol.

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 permitted for use in this protocol are as follows:

- Oral contraceptives (either combined estrogen/progestin or progesterone only)
- Injectable progesterone
- Implants of levonorgestrel
- Transdermal contraceptive patch
- Contraceptive vaginal ring

All female subjects must also refrain from egg donation and in vitro fertilization during study participation and for at least 35 days after the last study drug dose.

3) 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.

4) Procedures to be Followed in the Event of Pregnancy

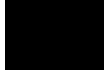
Subjects will be instructed to notify the investigator if they become pregnant at any time during the study, or if they become pregnant within 35 days of last study drug dose. Subjects who become pregnant or who suspect that they are pregnant during the study must report the information to the investigator and discontinue study drugs immediately.

Instructions for reporting pregnancy and pregnancy outcome are outlined in Section [7.7.2.1](#).

Pregnancy Testing

All females of childbearing potential will have urine pregnancy testing every 4 weeks during the study. If a positive urine pregnancy test is reported, the female subject should stop all study drugs and return to the clinic for a serum pregnancy test.

Appendix 6.Laboratory Assessment Table

Hematology	Chemistry	Urinalysis
Hematocrit Hemoglobin Platelet count Red blood cell (RBC) count Red blood cell indices White blood cell (WBC) count Differentials (absolute and percentage), including: Leukocytes Monocytes Neutrophils Eosinophils Basophils Mean corpuscular volume (MCV)	Alkaline phosphatase Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Gamma-glutamyl transpeptidase (GGT) Total bilirubin Direct and indirect bilirubin Total protein Albumin Bicarbonate Blood urea nitrogen (BUN) Calcium Chloride CPK Serum creatinine Glucose Phosphorus Magnesium Potassium Sodium Amylase Lipase <u>Lipid profile:</u> Triglycerides Cholesterol and its sub-fractions (high-density lipoprotein [HDL] and low-density lipoprotein [LDL])	Appearance Blood Color Glucose Specific gravity Nitrites Leukocyte esterase pH Protein Urobilinogen Reflex to microscopic urinalysis if dipstick result is abnormal.
Other		Pregnancy
C-reactive protein QuantiFERON®-TB  FSH (for women only)		<i>In females of childbearing potential:</i> Serum β -hCG (to be measured on Day -1 and repeated for any positive urine β -hCG) Urine β -hCG (all visits starting with Day -1) and every 4 weeks thereafter

Appendix 7. List of Joints to be Evaluated (66/68 Joint Count)

An overview of the joints to be assessed bilaterally is provided below:

- 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
- Hip⁸
- Knee
- Ankle
- Tarsus
- Metatarsophalangeal: first, second, third, fourth, fifth
- Proximal interphalangeal (toe): first, second, third, fourth, fifth

Replaced/missing (or otherwise not assessable) joints should be documented at Day -1 and omitted from further evaluation during the study.

⁸ Assessed for tenderness only

Appendix 8.American College of Rheumatology Response Evaluations / Preliminary Definition of Improvement in Rheumatoid Arthritis (Felson et al., 1995)

ACR 20 Required $\geq 20\%$ improvement in tender joint count, AND
 $\geq 20\%$ improvement in swollen joint count, AND
 $\geq 20\%$ improvement in at least 3 of the following 5 items:

- Subject pain assessment
- Subject global assessment of disease activity
- Physician global assessment of disease activity
- Subject assessment of physical function (HAQ-DI)
- Acute-phase reactant (CRP)

The following lists the disease activity measure followed by the method of assessment

Tender joint count

ACR tender joint count is an assessment of 68. The joint count should be done by scoring several different aspects of tenderness, as assessed by pressure and joint manipulation on physical examination. The information on various types of tenderness should then be collapsed into a single tender-versus-nontender dichotomy.

Swollen joint count

ACR swollen joint count is an assessment of 66. Joints are classified as either swollen or not swollen.

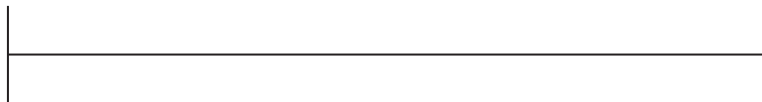
Subject's assessment of pain

The pain score from the HAQ-DI will be used to calculate ACR response.

Subject's global assessment of disease activity

A horizontal, visual analog scale will be used to provide the patient's overall assessment of how the arthritis is doing.

Place a mark on the line below to indicate how you assess your current rheumatoid arthritis disease activity:



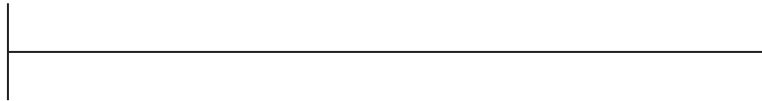
No arthritis

Severe arthritis

Physician's global assessment of disease activity

A horizontal visual analog scale will be used to measure the physician's assessment of the subject's current disease activity.

Place a mark on the line below to indicate RA disease activity (independent of the subject's self-assessment):

A horizontal line representing a visual analog scale, with short vertical lines at each end to indicate the range of activity.

No Disease Activity

Maximum Disease Activity

Subject's assessment of physical function

The HAQ-DI will be used to provide a subject's self-assessment of physical function.

Acute-phase reactant value

C-reactive protein level as measured at the central laboratory

Appendix 9. Disease Activity Score (DAS28) (Prevoo et al., 1995)

Assessments of RA in patients by the Disease Activity Score (modified to include the 28 joint counts according to Smolen* 1995) will be conducted at the measured timepoints. The DAS28 consists of a composite score of the following variables: tender joint count, swollen joint count, CRP, and patient global score. The following equation will be used to calculate the DAS28-CRP

- $$\text{DAS28-CRP} = 0.56 \sqrt{TJC28} + 0.28 \sqrt{SJC28} + 0.36 \ln(CRP + 1) + 0.014(\text{patients global VAS}) + 0.96$$
- TJC28 = number of joints tender out of 28
- SJC28 = number of joints swollen out of 28
- CRP = C-reactive protein
- Subject global VAS = patient global assessment as defined in [Appendix 8](#)

Appendix 10. Procedures and Specifications Complete Physical Examination

A complete physical examination should include source documentation of general appearance, and the following body systems: Head, neck and thyroid; eyes, ears, nose, throat, mouth and tongue; chest (excluding breasts); respiratory; cardiovascular; lymph nodes, abdomen; skin, hair, nails; musculoskeletal; neurological (must be performed at Day -1).

Blood Pressure

Assessment of vital signs will include measurement of resting blood pressure, pulse, respiratory rate, and temperature.

Blood pressure will be measured using the following standardized process:

- Subject should be resting for ≥ 5 minutes with feet flat on the floor and measurement arm supported so that the midpoint of the manometer cuff is at heart level;
- Use a mercury sphygmomanometer or automatic blood pressure device with an appropriately sized cuff with the bladder centered over the brachial artery;
- Measure and record the blood pressure to the nearest 2 mmHg mark on the manometer or to the nearest whole number on an automatic device.

12-Lead ECG

Subjects should be resting in a supine position for ≥ 5 minutes prior to making a recording.

The investigator (or qualified designee) should review the ECG traces recorded in real time for clinically significant abnormalities.

Appendix 11. Randomization Schemes

The following scheme represents subject re-randomization or maintenance of parent study filgotinib dose assignment, as applicable. The parent study dose and LTE dosing assignments will be maintained in a blinded fashion within the IWRS in accordance with these schemes utilized at the Day -1 Visit until the study becomes open-label.

GS-US-417-0301 Dosing Arms		
Week 1-23	Week 24-52	Roll over to LTE (double-blind)
adalimumab	Adalimumab	Re-randomized 1:1 to filgotinib 100 mg or 200 mg QD
filgotinib 100 mg QD	filgotinib 100 mg QD	Continue with filgotinib 100 mg QD
filgotinib 200 mg QD	filgotinib 200 mg QD	Continue with filgotinib 200 mg QD
Placebo	Re-randomized 1:1 to filgotinib 100 mg or 200 mg QD	Continue with assigned filgotinib 100 mg or 200 mg QD
RA non-responders	Standard of care	Not eligible

GS-US-417-0302 Dosing Arms		
Week 1-14	Week 15-24	Roll over to LTE (double-blind)
filgotinib 100 mg QD	filgotinib 100 mg QD	Continue with filgotinib 100 mg QD
filgotinib 200 mg QD	filgotinib 200 mg QD	Continue with filgotinib 200 mg QD
Placebo	Placebo	Re-randomized 1:1 to filgotinib 100 mg or 200 mg QD
RA non-responders	Standard of care	If judged by the investigator to potentially receive benefit from filgotinib, subjects are eligible to enter and will be re-randomized 1:1 to filgotinib 100 mg or 200 mg QD
Subjects who discontinued study drug in GS-US-417-0302 due to an AE unrelated to study drug, but who completed all study visits		If judged by the investigator to potentially receive benefit from filgotinib, eligible subjects will be re-randomized 1:1 to filgotinib 100 mg or 200 mg QD

GS-US-417-0303 Dosing Arms		
Week 1-24	Week 25-52	Roll over to LTE (double-blind)
MTX monotherapy	MTX monotherapy	Re-randomized 1:1 to filgotinib 100 mg or 200 mg QD
filgotinib 100 mg QD + MTX	filgotinib 100 mg QD and MTX	Continue with filgotinib 100 mg QD
filgotinib 200 mg + MTX	filgotinib 200 mg QD and MTX	Continue with filgotinib 200 mg QD
filgotinib 200 mg QD monotherapy	filgotinib 200 mg QD monotherapy	Continue with filgotinib 200 mg QD
RA non-responders	Standard of care	Not eligible

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Approval	Clinical Development 10-Jun-2024 08:59:35 GMT+0000
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