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CLINICAL STUDY PROTOCOL

Project Number:	GLPG0634		
Study Number:	GLPG0634-CL-341		
Study Title	A randomized, double-blind, controlled, multi-center study to evaluate the efficacy and safety of dose de-escalation of orally administered filgotinib in subjects with ulcerative colitis in clinical remission		
Short Study Title	A study evaluating the effect of filgotinib dose de-escalation in patients with ulcerative colitis in remission		
Development Phase:	3b		
Status	Final		
Protocol Version:	2.0	Date:	17-Mar-2023
Amendment:	1		
EudraCT No:	2022-000719-30	CT.gov No:	NCT05479058
IND No:	129647		
Sponsor:	Galapagos NV, Generaal De Wittelaan L11 A3, 2800 Mechelen, Belgium		
Medical Leader:	[redacted]		
General CSP			

Confidentiality Statement

EMERGENCY CONTACT INFORMATION

In case of a **serious adverse event (SAE)** (if it is not possible to record SAE information electronically), a special situation (see Section 11.1.6) or in case of **pregnancy** during the clinical study, the investigator must report this immediately, and under no circumstances later than 24 hours following the knowledge of the event as follows:

E-mail: [redacted]

or

[redacted] Medical Safety SAE Fax #: [redacted]

In case of medical questions during the course of the study, the investigator must contact the contract research organization (CRO) medical monitor or, if unavailable, his/her back-up (contact details are provided separately):

The following number is available for urgent medical contact:
24-Hour Answering Service for Urgent Medical Issues:

[redacted] Medical Monitoring Support Center (MMSC)

Phone: [redacted]

Fax: [redacted]

Sponsor back-up contact number[1]:

[redacted]

[1] This is the number of a contact center, which will refer the requester to the appropriate sponsor contact for the study.

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CLINICAL STUDY PROTOCOL HISTORY

Clinical Study Protocol (CSP)/Amendment #	Date	Main Rationale General/Country-Specific
CSP Version 1.0	04-Apr-2022	Initial CSP Version General
CSP Version 2.0 / Amendment 1	17-Mar-2023	The risk of venous thromboembolism has been added to the protocol to align with the Investigator's Brochure (IB) Edition 17, 15-Jul-2022. Study drug interruption criteria for lymphopenia, neutropenia, and moderate renal impairment were added, information about possible effects on spermatogenesis was updated, and contraceptive requirements for male subjects and reporting of pregnancies in their female partners were removed to align with the IB Edition 17, 15-Jul-2022. Clarifications from the Protocol Clarification Note dated 11-Jul-2022, regarding ulcerative colitis flare and biopsies, were incorporated. Clarifications were added regarding corticosteroids, food intake, End of Treatment visit, unblinding of subjects at the study primary analysis endpoint, and hepatitis B virus (HBV) surveillance. The eligibility criteria and screening assessments were updated, re-screening allowed, and the screening period was extended. The definitions of women of childbearing potential and postmenopausal female were changed. General

SUMMARY OF CHANGES

Amendment 1 (17-Mar-2023)

The overall reasons for this amendment:

a The risk of venous thromboembolism has been added to the benefit/risk section to align with the potential risks in the Investigator's Brochure (IB) Edition 17, 15-Jul-2022 and the specific discontinuation criterion in this clinical study protocol (CSP).

b To add a study drug interruption criterion regarding lymphopenia, neutropenia, and moderate renal impairment to align with the IB Edition 17, 15-Jul-2022.

c To update the information on possible effects on spermatogenesis to align with the IB Edition 17, 15-Jul-2022.

d To remove contraceptive requirements for male subjects and reporting of pregnancies in their female partners during this study to align with the IB Edition 17, 15-Jul-2022.

e To change the definitions of childbearing potential and postmenopausal female; follicle stimulating hormone (FSH) test at screening was added to confirm postmenopausal status if applicable.

f To clarify when an endoscopy (i.e. sigmoidoscopy) should be conducted to align with the Schedule of Activities, and to clarify that 2 biopsies should be collected during each sigmoidoscopy, including any non-scheduled endoscopy performed when a subject experiences flare.

g To extend the screening period to 28 days to allow the investigator time to complete all required assessments, and to introduce re-screening of subjects after screening failure to increase the chance for subjects to participate in this study.

h To add fecal calprotectin (FCP) as a screening test if the last observation was >6 months prior to screening or the most recent FCP value was >250 µg/g, to increase the chance for subjects to participate in this study.

i To clarify the tuberculosis (TB) assessments at screening.

j To clarify hepatitis B virus (HBV) eligibility requirements and surveillance during the study.

k To clarify that orally- and/or rectally-administered corticosteroids may be used during flare, but intravenous corticosteroids are not permitted during the study.

l To clarify that the investigational product (IP) may be taken both with and without food.

m To clarify that in countries where filgotinib becomes commercially available, the Week 48 visit can replace or occur on the same day as the End of Treatment (EoT) visit.

n To clarify unblinding of subjects at the study primary analysis time point and to add an unscheduled visit for IP dispensing, to ensure all subjects have sufficient IP to cover the period until the next 24-weekly visit.

In addition, minor updates and administrative corrections were made.

The changes made to the CSP GLPG0634-CL-341 (CAPYBARA) Version 1.0, 4-April-2022, are listed below, reflecting a brief rationale of each change and the applicable sections.

Change and Rationale: The risk of venous thromboembolism has been added to the benefit/risk section to align with the potential risks in the IB Edition 17, 15-Jul-2022 and the specific discontinuation criterion in this CSP. **Applicable section**: 5.5 Potential Risks and Benefits
Change and Rationale: A study drug interruption criterion for subjects with an absolute lymphocyte count <500 cells/mm^3 was added. The requirement to permanently discontinue a subject after 2 sequential neutrophil counts <750 neutrophils/mm^3 was removed and replaced with a study drug interruption criterion for absolute neutrophil counts <1000 neutrophils/mm^3. A study drug interruption criterion for confirmed moderate renal impairment was added. These changes were made to align with the IB Edition 17, 15-Jul-2022. **Applicable Section:** 5.4.1 Treatment Discontinuation
Change and Rationale: The information on possible effects on spermatogenesis was updated to align with the IB Edition 17, 15-Jul-2022. Based on the results from the clinical testicular safety studies, Galapagos NV has proposed to remove the potential risk of impaired spermatogenesis. **Applicable Section:** 5.5 Potential Risks and Benefits
Change and Rationale: The requirements for male subjects to use contraception and for pregnancies in their female partners to be reported during this study were removed in alignment with the IB Edition 17, 15-Jul-2022. The use of male contraception is not mentioned in the IB, as possible seminal transfer is not considered to lead to relevant systemic exposure in partners of childbearing potential. **Applicable Sections:** Protocol Synopsis 6.1 Inclusion Criteria 6.2 Exclusion Criteria 6.3.1.2 (section deleted) Male Subjects 6.3.1.4 Procedures to be Followed in the Event of Pregnancy 11.3.3 Pregnancy 12.7.2 Informed Consent

Change and Rationale: The definition of childbearing potential and postmenopausal female was changed to align with the sponsor's current standards, which are aligned with the Clinical Trials Facilitation Group's "Recommendations related to contraception and pregnancy testing in clinical trials". Assessment of follicle stimulating hormone (FSH) was added as a laboratory test at screening to confirm postmenopausal status in female subjects who may have become postmenopausal during the parent study. The contraception requirements for females were modified to remove the requirement for the use of a barrier method with hormonal contraceptives because in the dedicated clinical pharmacology study there was no effect on the pharmacokinetics of the combined oral contraceptive ethinyl estradiol and levonorgestrel when coadministered with filgotinib. **Applicable Sections:** 6.3.1.1.1 Definition of Childbearing Potential 6.3.1.1.2 Contraceptive Methods (females) 8.9 Schedule of Activities Appendix 3: Clinical Laboratory Assessments
Change and Rationale: It was clarified that 2 biopsies should be collected during each sigmoidoscopy, and that these biopsies should be carried out at Week 48 and every 48 weeks thereafter, and also at the time of suspected ulcerative colitis (UC) flare. **Applicable Sections:** 5.1 Clinical Study Design 8.3.1 Endoscopy and Biopsy Sample Collection 8.9.1 Regular Schedule of Activities
Change and Rationale: The screening period was extended to 28 days to allow the investigator time to complete all required assessments, and re-screening of subjects after screening failure was introduced to increase the chance for subjects to be able to participate in this study. **Applicable Sections:** Protocol Synopsis 5.1 Clinical Study Design 8.1 Timing of Assessments 8.1.3 (new section) Re-screening of Subjects 8.9.1 Regular Schedule of Activities
Change and Rationale: Fecal calprotectin (FCP) was added as a screening test if the last observation was >6 months prior to screening or the most recent value was >250 µg/g, to increase the chance for subjects to be able to participate in this study. **Applicable Sections:** Protocol Synopsis 5.1 Clinical Study Design 6.1 Inclusion Criteria 8.1 Timing of Assessments 8.9.1 Regular Schedule of Activities

Change and Rationale: Subjects who had a positive QuantiFERON® test or 2 indeterminate QuantiFERON® TB test results during any of the visits of the SELECTION-LTE but do not have active or latent tuberculosis (TB) at the time of screening, or had latent TB and underwent adequate treatment and continued in the SELECTION-LTE, and subjects who were previously treated for TB with a complete and adequate course of therapy as per local standard of care and as verified by the investigator, and do not need to have yearly QuantiFERON® tests, should be screened for signs and symptoms consistent with reactivation of TB and do not need to perform QuantiFERON® at the time of screening. Exclusion criterion 8 was modified to include screening for signs and symptoms of TB reactivation for subjects not requiring QuantiFERON® test. **Applicable Section:** Protocol Synopsis 6.2 Exclusion criteria 8.1 Timing of Activities 8.9.1 Regular Schedule of Activities
Change and Rationale: Exclusion criterion 9 for subjects with a history of malignancy was aligned with the eligibility of the parent UC studies by adding the specification that it applies to the last 5 years prior to or during participation in the UC parent studies. **Applicable Sections:** Protocol Synopsis 6.2 Exclusion criteria
Change and Rationale: Subjects with positive hepatitis B virus core antibodies (HBcAb) and hepatitis B virus (HBV) DNA below the lower limit of quantification (LLOQ) in a parent UC study require ongoing HBV DNA monitoring every 12 weeks during this study. These subjects may also require prophylactic treatment per investigator discretion in accordance with local guidelines and standard of care. Any subject who has HBV DNA ≥LLOQ will be discontinued. **Applicable Section:** **5.5. Potential Risks and Benefits** **8.9.1 Regular Schedule of Activities**
Change and Rationale: It was clarified that orally- and/or rectally-administered corticosteroids may be used during flare and should not exceed prednisone 30 mg/day equivalents (except for at least 12 weeks prior to screening and including baseline of the present study) and that intravenous corticosteroids are not permitted during the study. **Applicable Sections:** 5.1 Clinical Study Designs 6.3.2.1 Allowed Medications 6.3.2.2 Prohibited Medications
Change and Rationale: It was clarified that the IP may be taken both with and without food. **Applicable Section:** 6.3.3 Food and Beverage Restrictions 7.2 Dosage and Administration

Change and Rationale: It was clarified that in countries where filgotinib becomes commercially available, the Week 48 visit can replace or occur on the same day as the EoT visit. **Applicable Section:** Protocol Synopsis 5.1 Clinical Study Design 8.1.2 (new section) End of Treatment visit 8.9.1 Regular Schedule of Activities
Change and Rationale: It was clarified that all subjects should be invited for an unblinding visit no later than 4 weeks after study primary endpoint unblinding. If no regular visit is scheduled within this time frame, an unscheduled visit should be performed for IP dispensing to ensure the subject has sufficient IP to cover the period until the next 24-weekly visit. **Applicable Sections:** Protocol Synopsis 5.1 Clinical Study Design 8.1.4 (new section) Unblinding of subjects at the primary analysis time point
Change and Rationale: It was clarified that the secondary estimand for the primary endpoint would estimate the effect of decreasing the filgotinib dose from 200 mg q.d. to 100 mg q.d. versus remaining on 200 mg q.d. regardless of permanent treatment discontinuation as well as flare, or temporary treatment interruptions, in subjects who are in stable clinical remission at study entry. **Applicable Sections:** Protocol Synopsis 9.3.4.1.2 Secondary Efficacy Estimand 9.3.4.2.1 Analyses for Continuous Efficacy Data
Change and Rationale: The end of study definition for a country was modified because some subjects may not switch to commercially available filgotinib, but instead to local standard of care. **Applicable Sections:** Definition of terms Protocol Synopsis 5.1 Clinical Study Design
Change and Rationale: To align with the risk mitigation in Section 5.5, diagnosis of malignancy (except successfully treated non-melanoma skin cancer or cervical carcinoma in situ) was added to the conditions for permanent discontinuation of study treatment. **Applicable Sections:** 5.4.1.1 Permanent Treatment Discontinuation 5.5 Potential Risks and Benefits

Change and Rationale: The Schedule of Activities after re-escalation was corrected to add vital signs, weight and urine pregnancy test assessments.

Applicable Sections:

8.9.2 Schedule of Activities After Re-escalation

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviations

ADL	Activities of Daily Living
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
[redacted]	[redacted]
CES	carboxylesterase
CI	confidence interval
[redacted]	[redacted]
CrCl	creatinine clearance
CRF	case report form
CRO	contract research organization
CRP	C-reactive protein
CSP	clinical study protocol
CTCAE	Common Terminology Criteria for Adverse Events
CVEAC	Cardiovascular Safety Endpoint Adjudication Committee
DVT	deep venous thrombosis
EBS	endoscopy/bleeding/stool
ECG	electrocardiogram
ED	early discontinuation
e-Diary	electronic diary
EoS	End of Study
EoT	End of Treatment
[redacted]	[redacted]
ES	endoscopic score
EU	European Union
FAS	full analysis set
FCP	fecal calprotectin
GCP	Good Clinical Practice
HBV	hepatitis B virus
HCV	hepatitis C virus
HDL	high-density lipoprotein

[redacted]	[redacted]
IB	investigator's brochure
IBDQ	Inflammatory Bowel Disease Questionnaire
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IL	interleukin
INR	international normalized ratio
IP	investigational product
IRB	Institutional Review Board
JAK	Janus Kinase
LDL	low-density lipoprotein
LLOQ	lower limit of quantitation
LOCF	last observation carried forward
LTE	long-term extension
MCS	Mayo Clinical Score
mMCS	modified Mayo Clinical Score
PE	pulmonary embolism
PEG	polyethylene glycol
PGA	Physician's Global Assessment
[redacted]	[redacted]
pMCS	partial Mayo Clinical Score
PRO2	patient-reported outcome based on 2 items
PT	prothrombin time
PTM	placebo-to-match
PTT	partial thromboplastin time
Q1	first quartile
Q3	third quartile
q.d.	once daily (quaque die)
RBC	red blood cell
RTSM	randomization and trial supply management
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD	standard deviation

SE	standard error
[redacted]	[redacted]
SI	international system of units
SOC	System Organ Class
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
TEAE	treatment-emergent adverse event
[redacted]	[redacted]
TMF	trial master file
TNF	tumor necrosis factor
UC	ulcerative colitis
UK	United Kingdom
ULN	upper limit of normal
US	United States
WBC	white blood cell
WOCBP	women of childbearing potential
[redacted]	[redacted]

Definition of Terms

baseline assessment	last available assessment prior to the first intake of investigational product (IP) in the present study
clinical study	a clinical study as described in this protocol refers to a clinical trial in which subjects are assigned to treatment with an IP to discover or verify its clinical efficacy, safety, pharmacological, or other pharmacodynamic effects
Cockroft-Gault formula	estimate of creatinine clearance (CrCl) using serum creatinine level: CrCl (male) = ([140-age] × weight in kg)/(serum creatinine × 72) CrCl (female) = CrCl (male) × 0.85
end of the study in a particular country	the end of the study may differ between the countries and depends on the commercial availability of filgotinib in that country: – in countries where filgotinib becomes commercially available: date when the last subject in that country has completed the safety follow-up visit – in countries where filgotinib is not commercially available: date when the last subject in that country completes 216 weeks in the study
global end of the study	date of the last visit for the last subject in the last country (i.e. last subject last visit)
endoscopic score (ES)-confirmed ulcerative colitis (UC) flare	a flare defined as an increase in rectal bleeding subscore by at least 1 point AND an increase in stool frequency subscore by at least 2 points AND an increase in endoscopic subscore by at least 1 point
[redacted]	[redacted]
Mayo Clinical Score (MCS)	composed of subscores from endoscopic findings, rectal bleeding, stool frequency, and Physician's Global Assessment (PGA)
modified Mayo Clinical Score (mMCS)	composed of subscores from rectal bleeding, stool frequency, and endoscopic findings

mMCS remission	mMCS score ≤2, with endoscopic subscore of ≤1, stool frequency subscore of ≤1, and a rectal bleeding subscore of 0
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
PRO2 flare	a flare defined as a PRO2 (patient-reported outcome based on 2 items) score worsening of at least 2 points and an absolute PRO2 score of at least 3, with stool frequency subscore ≥2, and rectal bleeding subscore ≥1
re-escalation	the term re-escalation is used to describe the switch to open-label 200 mg filgotinib once daily (q.d.) after ES-confirmed UC flare regardless of the blinded treatment received before the switch, i.e. from blinded 100 mg q.d. to open-label 200 mg q.d. (real re-escalation) or from blinded 200 mg to open-label 200 mg q.d. (dummy re-escalation)
stable pMCS clinical remission	defined as pMCS remission on at least 2 consecutive quarterly visits in the SELECTION-LTE study prior to screening of the present study
study start	date when the first informed consent form is signed (i.e. first subject first visit)

1. CLINICAL STUDY PROTOCOL SYNOPSIS

Title of Study

A randomized, double-blind, controlled, multi-center study to evaluate the efficacy and safety of dose de-escalation of orally administered filgotinib in subjects with ulcerative colitis in clinical remission

Short Title of Study

A study evaluating the effect of filgotinib dose de-escalation in patients with ulcerative colitis in remission

Phase of Development: Phase 3b

Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the efficacy of filgotinib in subjects in stable clinical remission on 200 mg filgotinib once daily (q.d.) for whom the dose was decreased to 100 mg q.d. compared to subjects remaining on 200 mg q.d.	– Proportion of subjects in corticosteroid-free[1] clinical remission based on modified Mayo Clinical Score (mMCS)[2] at Week 48.
Secondary	
To evaluate the effect of dose de-escalation of filgotinib on time to flare.	– Time to PRO2 flare[3]. – Time to endoscopic score (ES)-confirmed ulcerative colitis (UC) flare.
To evaluate the effect of dose de-escalation of filgotinib on disease-specific biomarkers and Inflammatory Bowel Disease Questionnaire (IBDQ).	– Change from baseline in C-reactive protein (CRP) and fecal calprotectin (FCP) up to Week 48. – Change from baseline in IBDQ at Week 48.
To evaluate the safety and tolerability of filgotinib.	– Frequency and severity of treatment-emergent adverse events (TEAEs), treatment-emergent serious AEs (SAEs), and TEAEs leading to treatment discontinuation.

Planned Number of Subjects

Approximately 80 subjects are planned to be randomized.

[1] Free of corticosteroids for at least 12 weeks.
[2] mMCS of ≤2 points, with endoscopic subscore of ≤1, stool frequency subscore of ≤1, and a rectal bleeding subscore of 0.
[3] Defined as a PRO2 (patient-reported outcome based on 2 items) score worsening of at least 2 points and an absolute PRO2 score of at least 3, with stool frequency subscore ≥2 and rectal bleeding subscore ≥1.

Study Design

This study is a Phase 3b, randomized, double-blind, controlled, multi-center study to evaluate the efficacy and safety of dose de-escalation of orally administered filgotinib in subjects with UC in corticosteroid-free clinical remission.

Approximately 80 subjects, who are in clinical remission on 200 mg filgotinib q.d. for at least 2 consecutive quarterly visits in the ongoing SELECTION-LTE study (GLPG0634-CL-307), are planned to be rolled over and randomized (1:1) to receive either 100 mg or 200 mg filgotinib q.d. Subjects will be stratified according to ES (0 or 1) at baseline to ensure treatment balance in each stratum. The study will consist of the following study periods:

- screening period: maximum of 28 days with at least 2 screening visits;
- treatment period:
  - During the blinded treatment period, study visits will be on Day 1 (randomization to blinded treatment), at Week 4, Week 12, and then every 12 weeks. Subjects will receive blinded treatment until the primary analysis time point (i.e. after the last subject completed their Week 48 postbaseline visit or has completed their Week 12 post re-escalation visit, or after the last follow-up of subjects discontinuing prior to Week 48, whichever comes last), with the exception of subjects with ES-confirmed UC flare who will be switched to open-label 200 mg filgotinib q.d. (as explained below).
  - After unblinding at the study primary analysis time point, subjects will receive unblinded treatment and the frequency of study visits will be reduced to every 24 weeks, as detailed in the protocol.
- follow-up: 4 weeks after last dose (End of Study [EoS] visit).

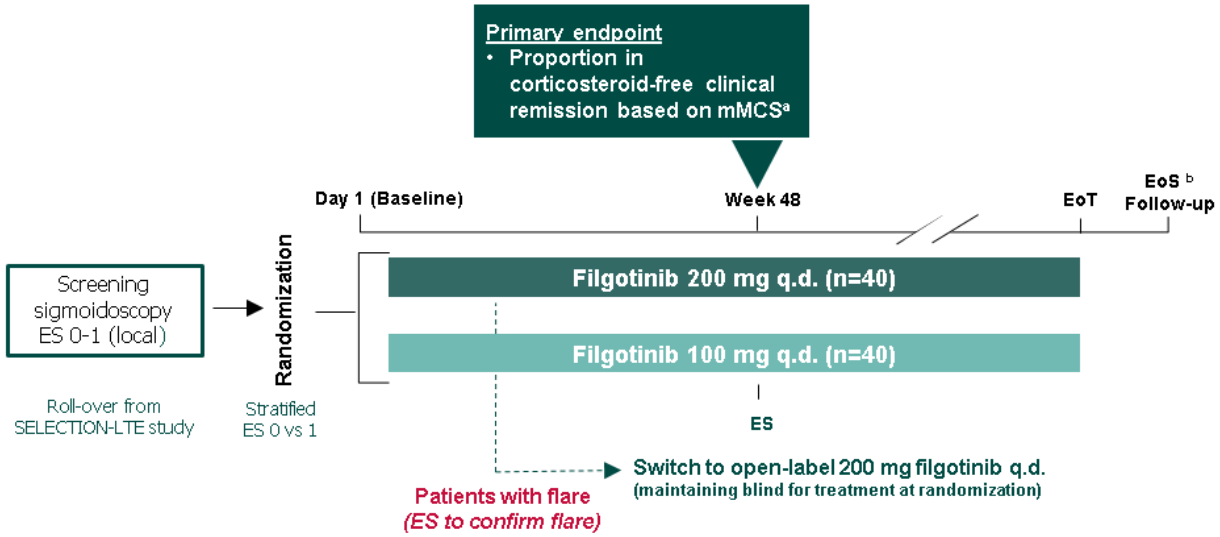
Subjects who experience an ES-confirmed UC flare during treatment will be "re-escalated"[1] to open-label 200 mg filgotinib q.d. for at least 12 weeks, while maintaining the blind for the treatment at randomization. An ES-confirmed UC flare should be reported as an adverse event. In case of further worsening of symptoms after Week 2 following re-escalation and/or no improvement in partial Mayo Clinical Score (pMCS) is detected at Week 4, addition of corticosteroid treatment (i.e. orally- and/or rectally-administered corticosteroids) can be considered with a maximum dose of 30 mg q.d. prednisone equivalent.

If the subject does not respond to re-escalation therapy within a timeframe of maximum 12 weeks, the subject will be permanently discontinued from the treatment and invited to remain in the study up to Week 48.

If subject improvement is sufficient in the opinion of the investigator, the subject may continue on open-label 200 mg filgotinib q.d. until the end of the study.

After unblinding at the study primary analysis time point, subjects will receive unblinded treatment q.d. until the end of the study.

A schematic diagram of clinical study design, procedures, and stages is provided below.



EoT: End of Treatment; EoS: End of Study; ES: endoscopic score; mMCS: modified Mayo Clinical Score; n: number of subjects in the treatment group; q.d.: once daily.
[a] mMCS of ≤2 points, with endoscopic subscore of ≤1, stool frequency subscore of ≤1, and rectal bleeding subscore of 0.
[b] EoS: when the last subject has completed the safety follow-up visit in that country (i.e. after completing minimum 48 weeks of treatment and the safety follow-up visit) OR (in countries where filgotinib is not commercially available) when the last subject completes 216 weeks in the study.

Study Duration

Each subject will be in the study for a minimum of approximately 56 weeks (screening period 28 days + 48 weeks of treatment + 4 weeks follow-up) in countries where filgotinib will become commercially available, and for a maximum duration of 216 weeks (approximately 4 years) in case filgotinib will not become commercially available. In case of re-escalation, the subject will remain in the study at least until the next regular scheduled visit after the 12 weeks post re-escalation visit, or until the end of the study in that country, whichever is longer.

In countries where filgotinib becomes commercially available, the study will be terminated for the subjects who have already completed at least 48 weeks of treatment. Subjects will then be requested to attend the End of Treatment (EoT) visit as soon as possible. For the subjects who have not yet completed the Week 48 visit when filgotinib becomes commercially available, the Week 48 visit can replace or occur on the same day as the EoT visit. When the EoT visit is performed, the subjects will be considered as having completed the treatment part of the study and can start taking commercial filgotinib or local standard of care the next day. In addition, subjects will be requested to attend a follow-up visit 4 weeks after the EoT visit. The study will be terminated in that country when the last subject in that country has completed the safety follow-up visit.

[1] The term re-escalation is used to describe the switch to open-label 200 mg filgotinib q.d. after ES-confirmed UC flare regardless of the blinded treatment received before the switch, i.e. from blinded 100 mg q.d. to open-label 200 mg q.d. (real re-escalation) or from blinded 200 mg to open-label 200 mg q.d. (dummy re-escalation).

Main Criteria for Inclusion and Exclusion

Main Inclusion Criteria

– Criterion modified per amendment 1.
Subjects must be participating in the SELECTION-LTE study, currently on 200 mg filgotinib q.d. and fulfill the following conditions:
  - pMCS remission[1] over a period of at least 2 consecutive quarterly visits in the SELECTION-LTE study prior to screening of the present study;
  - free of corticosteroids for at least 12 weeks prior to and including baseline;
  - FCP <=250 µg/g at last observation within 6 months prior to screening or FCP <=250 µg/g during the screening of the present study.
  - sigmoidoscopy ES of 0 or 1 (local score) at screening.

– Willing to refrain from live attenuated vaccines during the study and for 12 weeks after the last dose of filgotinib in the study.
– Female subjects of childbearing potential must have a negative highly sensitive (serum beta human chorionic gonadotropin) pregnancy test during screening and must agree to continued monthly urine dipstick pregnancy testing during filgotinib treatment
– Criterion modified per amendment 1.
Female subjects of childbearing potential must agree to use highly effective contraception measures as defined in the protocol.

Main Exclusion Criteria

– Any chronic medical condition (including but not limited to, cardiac or pulmonary disease, alcohol, or drug abuse) that, in the opinion of the investigator or sponsor, would make the subject unsuitable for the study or would prevent compliance with the study protocol.
– Subject has a known hypersensitivity to filgotinib ingredients or history of a significant allergic reaction to filgotinib ingredients as determined by the investigator.
– Female subject who is pregnant or breastfeeding, or intending to become pregnant or breastfeed, and/or plans to undergo egg donation or egg harvesting for the purpose of current or future fertilization, during the study and until the end of the study.
– Subject is unable or unwilling to comply with restrictions regarding prior and concomitant medication as described in the protocol.Criterion modified per amendment 1.
Subject has a positive QuantiFERON® tuberculosis (TB) test at screening or has 2 indeterminate QuantiFERON® TB test results that require IP treatment interruption, or subject has sign and symptoms of TB reactivation at screening.
– Criterion modified per amendment 1.
History of malignancy during or in the last 5 years prior to participation in the UC parent studies, except for subjects who have been successfully treated for nonmelanoma skin cancer or cervical carcinoma in situ.
– Subject meets discontinuation criteria of the SELECTION-LTE study.

[1]pMCS of ≤2 points, with Physician's Global Assessment (PGA) ≤1, stool frequency subscore ≤1,and rectal bleeding subscore = 0.

Treatment and Treatment Schedule

Subjects will be randomized to receive either 100 mg or 200 mg filgotinib q.d.

In case of ES-confirmed UC flare during treatment, subjects will be re-escalated to open-label 200 mg filgotinib q.d. for at least 12 weeks, while maintaining the blind for the treatment at randomization. If the subject does not respond to re-escalation therapy within a timeframe of maximum 12 weeks, the subject will be permanently discontinued from the treatment. If subject improvement is sufficient in the opinion of the investigator, the subject may continue on open-label 200 mg filgotinib q.d. until the end of the study.

Investigational Product, Dosage, and Mode of Administration

Filgotinib is available as 200 mg and 100 mg strength tablets. Filgotinib tablets, 200 mg and 100 mg are beige, debossed with "GSI" on one side and "200" or "100" on the other, capsule-shaped, biconvex, film-coated tablets for clinical use. Each tablet contains the equivalent of 200 mg or 100 mg filgotinib free base in the form of filgotinib maleate. In addition to the active ingredient, filgotinib tablets contain the following inactive ingredients: microcrystalline cellulose, lactose monohydrate, fumaric acid, pregelatinized starch, silicon dioxide, magnesium stearate, macrogol/polyethylene glycol (PEG) 3350, polyvinyl alcohol, talc, titanium dioxide, iron oxide yellow, and iron oxide red.

Placebo-to-match (PTM) 200 mg and 100 mg filgotinib tablets are identical in appearance to the respective active filgotinib tablets. PTM 200 mg and 100 mg 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.

The IP needs to be taken q.d. at approximately the same time. Subjects will be asked to swallow the IP with a glass of water.

<u>Blinded treatment up to the primary analysis time point</u>

Doses of 100 mg or 200 mg filgotinib, as a combination of 2 tablets (filgotinib and PTM) for blinding purposes, will be taken q.d. orally.

Subjects will be provided with medication kits containing 2 bottles with blinded IP, either:

– 100 mg filgotinib tablets in bottle 1 and PTM 200 mg filgotinib tablets in bottle 2;
– 200 mg filgotinib tablets in bottle 1 and PTM 100 mg filgotinib tablets in bottle 2.

If on Day 1, the subject has already taken the IP as assigned in the SELECTION-LTE study, the first dose as assigned in this study should be taken on Day 2. Starting from Day 2, subjects will be instructed to take 1 tablet from each bottle q.d. (i.e. a total of 2 tablets).

Re-escalation

Subjects who are re-escalated to open-label 200 mg filgotinib q.d. will be provided with bottles containing unblinded IP (200 mg filgotinib tablets in 1 bottle). If the subject has already taken IP on the re-escalation baseline day, the first adjusted dose should be taken on re-escalation Day 2. Subjects will be instructed to take 1 tablet q.d.

After unblinding at the primary analysis time point

For continued q.d. treatment after unblinding until the end of the study, subjects will be provided with unblinded IP, either:

– 1 bottle with 100 mg filgotinib tablets;
– 1 bottle with 200 mg filgotinib tablets.

Subjects will be instructed to take 1 tablet q.d.

Statistical Analysis

Interim analysis

The data collected from this study will be analyzed at 2 time points. An unblinded interim analysis of the clinical study data will be performed by the sponsor on cleaned and locked data, when the last subject completed their Week 48 postbaseline visit or has completed their Week 12 post re-escalation visit (if baseline of re-escalation is within the first 48 weeks of the study), or after the last follow-up of subjects discontinuing prior to Week 48, whichever comes last. This analysis will be the primary analysis. The analyses will be conducted on efficacy data up to Week 48 and safety data up to the data cut-off date, to be able to evaluate the primary, secondary, and exploratory efficacy endpoints, and safety. The subjects and the clinical study team will be unblinded at the time of the Week 48 analysis.

The final analysis will be performed after the global end of the study (i.e. date of the last visit for the last subject in the last country) and the database is cleaned and locked. At the final analysis, all available efficacy and safety data will be summarized using descriptive statistics.

Efficacy analysis

No hypothesis testing will be performed. The de-escalation effect will be described using standard descriptive statistics, but also with model-based estimates for the differences with 95% confidence intervals (CIs) as appropriate.

Primary endpoint

The primary efficacy estimand for the primary endpoint targets to estimate the effect of decreasing the filgotinib dose from 200 mg q.d. to 100 mg q.d. versus remaining on 200 mg q.d. on corticosteroid-free mMCS remission without ES-confirmed flare or discontinuation of treatment at Week 48, regardless of treatment interruptions, in subjects who are in stable clinical remission at study entry. The effect size will be estimated using the Mantel-Hanszel method and expressed as a difference in proportions.

The secondary estimand for the primary endpoint targets to estimate the effect of decreasing the filgotinib dose from 200 mg q.d. to 100 mg q.d. versus remaining on 200 mg q.d. on corticosteroid-free mMCS remission at Week 48, regardless of flare, permanent treatment discontinuation, or temporary treatment interruptions, in subjects who are in stable clinical remission at study entry. The effect size will be estimated using the Mantel-Hanszel method and expressed as a difference in proportions.

Secondary endpoints

Estimands for the secondary efficacy endpoints are described in the protocol.

Safety analysis

Safety data will be summarized descriptively by treatment group according to the filgotinib dosing regimen actually received at randomization.

For the primary safety analysis, any data collected after ES-confirmed UC flare will not be included in the analyses.

For the secondary safety analysis, data will be included regardless of flare.

Additionally, safety data may be analyzed in the subgroup of subjects who are initially assigned to 100 mg filgotinib q.d. and are re-escalated later to 200 mg q.d. in the safety analysis set.

2. INTRODUCTION

2.1. Clinical Study Rationale

Ulcerative colitis (UC) is a chronic, idiopathic, inflammatory disease that affects the colon and is most prevalent in adults between the ages of 30 and 40 years. It is characterized by relapsing and remitting mucosal inflammation extending from the rectum to the proximal segments of the colon.

The etiology of the disease is believed to involve immune, genetic, environmental, and microbial factors. Discoordinated activity of both the innate and adaptive immune response in combination with defects of the epithelial barrier and dysbiosis lead to an inflammatory cascade resulting in bloody diarrhea, rectal urgency and tenesmus, and in its later stages an increased risk for colorectal cancer. Further UC extraintestinal symptoms include ocular lesions, skin lesions, arthritis, and primary cholangitis.

Historically, UC has been managed with anti-inflammatory drugs and general immunosupressants. In the last 2 decades, approaches have become more targeted using biologics acting on tumor necrosis factor (TNF) alpha, and more recently anti-integrin and anti-interleukin (IL)-12/IL-23 antibodies.

However, while biologics have provided substantial improvements in patient therapy, about 30% of patients do not respond to biologics and a further 30 to 50% will stop responding during therapy.

A new approach to UC therapy involves orally bioavailable small-molecules inhibiting signal transduction pathways involved in UC pathogenesis, such as Janus Kinase (JAK) inhibitors. Filgotinib is a preferential JAK1 inhibitor approved for the treatment of rheumatoid arthritis and UC in the European Union (EU), United Kingdom (UK), and Japan.

While clinical data indicate that response to 200 mg filgotinib once daily (q.d.) is more rapid and pronounced compared to 100 mg filgotinib q.d. in subjects with moderate to severely active UC, maintenance of clinical remission may be achieved at a lower dose.

This study will explore the possibility of dosing flexibility in subjects who are in clinical remission on 200 mg filgotinib q.d. in the SELECTION-LTE (GLPG0634-CL-307) study.

For more details refer to the latest version of the investigator's brochure (IB) and its relevant updates/addenda.

This clinical study will be conducted in compliance with this clinical study protocol (CSP), the current International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use – Good Clinical Practice (ICH-GCP) Guideline E6, and applicable local ethical and legal requirements (see also Section 12).

2.2. Background - Nonclinical Studies

For nonclinical pharmacology, PK, and toxicology data of filgotinib, refer to the IB (Section 1, Company Core Data Sheet).

2.3. Background - Clinical Studies

The efficacy and safety of 200 mg and 100 mg filgotinib q.d. in 1351 subjects with moderately to severely active UC were evaluated in a randomized, double-blind, placebo-controlled combined Phase 2b/3 study over a duration of 58 weeks (SELECTION, GS-US-418-3898). The study combined 2 consecutive substudies: an induction study assessing subject response at Week 10 and a maintenance study continuing until Week 58. Subjects who achieved either endoscopy/bleeding/stool (EBS) remission or Mayo Clinical Score (MCS) response at Week 10 of the induction study were re-randomized into the maintenance study.

A significant number of subjects receiving 200 mg filgotinib q.d. achieved clinical remission at the end of the induction study compared to placebo. At Week 58 and the end of the maintenance study, significance was achieved by both the 200 mg q.d. and the 100 mg q.d. cohort.

A long-term extension (LTE) study (SELECTION-LTE, GS-US-418-3899, GLPG0634-CL-307) is ongoing in 1161 subjects who have completed the SELECTION study. Subjects who did not achieve EBS remission or MCS response as well as subjects who met the prespecified definition of disease worsening during the SELECTION study were given the option to receive open-label 200 mg filgotinib in the SELECTION-LTE study.

Filgotinib 100 mg and 200 mg q.d. were generally well tolerated in both studies. In an integrated safety analysis based on results of the SELECTION study and interim results of the SELECTION-LTE study, including 1253 subjects, no significant differences between treatment groups in occurrence of adverse events (Aes), serious Aes (SAEs), or Aes leading to study discontinuation could be found. Rates of serious infections, herpes zoster, opportunistic infections, venous thrombosis, pulmonary embolism, malignancies, and gastrointestinal perforation were low and comparable across treatment groups. Overall, 3 deaths were reported; none of the Aes leading to death were assessed as related to filgotinib.

3. CLINICAL STUDY OBJECTIVES

3.1. Primary Objective

- To evaluate the efficacy of filgotinib in subjects in stable clinical remission on 200 mg filgotinib q.d. for whom the dose was decreased to 100 mg q.d. compared to subjects remaining on 200 mg q.d.

3.2. Secondary Objective(s)

- To evaluate the effect of dose de-escalation of filgotinib on time to flare.
- To evaluate the effect of dose de-escalation of filgotinib on disease-specific biomarkers and Inflammatory Bowel Disease Questionnaire (IBDQ).

– To evaluate the safety and tolerability of filgotinib.

[redacted]

4. ENDPOINTS AND ESTIMANDS

4.1. Primary Endpoint/Estimand

– Proportion of subjects in corticosteroid-free[2] clinical remission based on modified Mayo Clinical Score (mMCS)[3] at Week 48.

The primary estimand for the primary endpoint targets to estimate the effect of decreasing the filgotinib dose from 200 mg q.d. to 100 mg q.d. versus remaining on 200 mg q.d. on corticosteroid-free mMCS remission without ES-confirmed flare or discontinuation of treatment at Week 48, regardless of treatment interruptions, in subjects who are in stable clinical remission at study entry. The effect size will be estimated using the Mantel-Hanszel method and expressed as a difference in proportions.

[redacted].

[2] Free of corticosteroids for at least 12 weeks.

[3] mMCS score of ≤2, with endoscopic subscore of ≤1, stool frequency subscore of ≤1, and a rectal bleeding subscore of 0.

The primary estimand for the primary endpoint is described according to the following attributes:

Primary Endpoint	Primary Estimand
Treatment	Filgotinib 100 mg q.d. and filgotinib 200 mg q.d. as randomized.
Population	Subjects who are in stable clinical remission on filgotinib 200 mg q.d. defined through the appropriate inclusion / exclusion criteria.
Variable	Binary corticosteroid-free mMCS remission without ES-confirmed flare and without discontinuation of treatment at Week 48. Corticosteriod-free is defined as free of corticosteroids for at least 12 weeks.
Intercurrent events including strategy for addressing them	– ES-confirmed UC flare: Subjects randomized to the filgotinib 100 mg q.d. or 200 mg q.d. group will be considered as nonresponders for any visit after the re-escalation visit, for flares occurring prior to Week 48 (**Composite strategy**). – Permanent treatment discontinuation (not flare-related): Subjects who discontinue treatment prior to Week 48 will be considered as nonresponders in both the 100 mg q.d. and the 200 mg q.d. group (**Composite strategy**). – Any temporary treatment interruption: Data collected for subjects who temporarily interrupt treatment will be included as reported in the analysis (**Treatment policy strategy**).
Population-level summary	The treatment difference in the percentage of subjects meeting corticosteroid-free mMCS remission criteria between the filgotinib 100 mg q.d. group and 200 mg q.d. group at Week 48.
Estimator	The adjusted proportion difference (filgotinib 200 mg – filgotinib 100 mg) with corresponding 95% confidence interval (CI) as calculated by a stratified Mantel-Haenszel test (stratification factor: baseline ES [0 or 1]).

Refer to Section 9.3.4.1 for more information.

4.2. Secondary Endpoints

- Time to PRO2 flare[1].
- Time to ES-confirmed UC flare.
- Change from baseline in C-reactive protein (CRP) and fecal calprotectin (FCP) up to Week 48.
- Change from baseline in IBDQ at Week 48.

[1] Defined as a PRO2 (patient-reported outcome based on 2 items) score worsening of at least 2 points and an absolute PRO2 score of at least 3, with stool frequency subscore ≥2, and rectal bleeding subscore ≥1.

– Frequency and severity of treatment-emergent adverse events (TEAEs), treatment-emergent SAEs, and TEAEs leading to treatment discontinuation.

Refer to Section 9.3.4.2 for more information.

[redacted]

5. INVESTIGATIONAL PLAN

5.1. Clinical Study Design

This study is a Phase 3b, randomized, double-blind, controlled, multi-center study to evaluate the efficacy and safety of dose de-escalation of orally administered filgotinib in subjects with UC in corticosteroid-free clinical remission.

Approximately 80 subjects, who are in clinical remission on 200 mg filgotinib q.d. for at least 2 consecutive quarterly visits in the ongoing SELECTION-LTE study, are planned to be rolled over and randomized (1:1) to receive either 100 mg or 200 mg filgotinib q.d. Subjects will be stratified according to ES (0 or 1) at baseline to ensure treatment balance in each stratum.

[redacted]

The study will consist of the following study periods:

- screening period: a maximum of 28 days with at least 2 screening visits;
- treatment period:
  - During the blinded treatment period, study visits will be on Day 1 (randomization to blinded treatment), at Week 4, Week 12, and then every 12 weeks. Subjects will receive blinded treatment until the primary analysis time point (i.e. after the last subject completed their Week 48 postbaseline visit or has completed their Week 12 post re-escalation visit, or after the last follow-up of subjects discontinuing prior to Week 48, whichever comes last, see Section 6.4.2), with the exception of subjects with ES-confirmed UC flare who will be switched to open-label 200 mg q.d. (as explained below).
  - After unblinding at the study primary analysis time point, subjects will receive unblinded treatment and the frequency of study visits will be reduced to every 24 weeks (see Section 8.1.4).
- follow-up: 4 weeks after last dose (End of Study [EoS]) visit).

Sigmoidoscopy

The ES will be obtained from a sigmoidoscopy performed during screening, including collection of 2 biopsies for histology assessment.

Roll-over from SELECTION-LTE

Subjects in the SELECTION-LTE study who are in clinical remission with 200 mg filgotinib q.d. for at least 2 consecutive quarterly visits, will be provided the option to roll-over to the present study at any scheduled visit of the SELECTION-LTE study or at a separate visit.

Subjects will be requested to attend the site for at least 2 screening visits. Depending on the results of FCP (if applicable) and ES at screening, the subject will either be a screening failure (FCP >250 µg/g or ES >1) in the present study and will remain in SELECTION-LTE, or the subject will be eligible (FCP ≤250 µg/g and ES ≤1) and will need to perform the End of Treatment (EoT) assessments in SELECTION-LTE before being randomized to the present study. Subjects who fail screening in the present study may be re-screened once. Re-screening may only be conducted after approval from the sponsor's medical lead (see Section 8.1.3).

Further details on the timing of screening and Day 1 assessments are provided in Section 8.1.

Flare

When a subject experiences an increase in clinical symptoms, a stool sample will be obtained for culture for pathogenic bacteria, ova and parasite evaluation, and *Clostridium difficile* toxin assay.

An endoscopy will be performed in subjects who experience during treatment an increase in clinical symptoms defined as:

– an increase in rectal bleeding subscore by at least 1 point, AND an increase in stool frequency subscore by at least 2 points, AND a *Clostridium difficile* infection is excluded.

An ES-confirmed UC flare is defined as:

– an increase in rectal bleeding subscore by at least 1 point AND an increase in stool frequency subscore by at least 2 points AND an increase in endoscopic subscore by at least 1 point.

Subjects who experience an ES-confirmed UC flare during treatment will be "re-escalated" (see Definition of Terms) to open-label 200 mg filgotinib q.d. for at least 12 weeks, while maintaining the blind for the treatment at randomization, and should follow the Schedule of Activities after re-escalation (Section 8.9.2). An ES-confirmed UC flare should be reported as an adverse event (AE), as explained in Section 8.4.1.

Re-escalation

Subjects should follow the Schedule of Activities after re-escalation (Section 8.9.2).

– In case of further worsening of symptoms after Week 2 following re-escalation and/or no improvement in pMCS is detected at Week 4, addition of corticosteroid treatment (i.e. orally- and/or rectally-administered corticosteroids) can be considered with a maximum oral dose of 30 mg q.d. prednisone equivalent.
– If the subject does not respond to re-escalation therapy within a timeframe of maximum 12 weeks, the subject will be permanently discontinued from the treatment and invited to remain in the study up to Week 48 (see Section 5.4.1.1).
– If subject improvement is sufficient in the opinion of the investigator, the subject will restart the regular Schedule of Activities (Section 8.9.1), starting from the next 12-weekly visit assessments. The subject may continue on open-label 200 mg filgotinib q.d. until the end of the study. Corticosteroid treatment should be tapered off at the discretion of the investigator.

In case symptoms are worsening again after 12 weeks of re-escalation, the disease worsening criteria must be applied, as explained in Section 5.4.1.3.

Study duration

Each subject will be in the study for a minimum of approximately 56 weeks (28 days screening period + 48 weeks of treatment + 4 weeks follow-up) in countries where filgotinib will become commercially available, and for a maximum duration of 216 weeks (approximately 4 years) in case filgotinib will not become commercially available. In case of re-escalation, the subject will remain in the study at least until the next regular scheduled visit after the 12 weeks post re-escalation visit, or until the end of the study in that country, whichever is longer.

In countries where filgotinib becomes commercially available, the study will be terminated for the subjects who have already completed at least 48 weeks of treatment. Subjects will then be requested to attend the EoT visit as soon as possible. For the subjects who have not yet completed

the Week 48 visit when filgotinib becomes commercially available, the Week 48 visit can replace or occur on the same day as the EoT visit (see Section 8.1.2). When the EoT visit is performed, the subjects will be considered as having completed the treatment part of the study and can start taking commercial filgotinib or local standard of care the next day. In addition, subjects will be requested to attend a follow-up visit 4 weeks after the EoT visit. The study will be terminated in that country when the last subject in that country has completed the safety follow-up visit.

Reduction in study visits

After unblinding at the study primary analysis time point, the frequency of study visits will be reduced to every 24 weeks (see Section 8.1.4). All subjects should be invited for an unblinding visit no later than 4 weeks after the study primary endpoint unblinding. If no regular visit is scheduled within this time frame, an unscheduled visit should be performed for IP dispensing to ensure the subject has sufficient IP to cover the period until the next 24-weekly visit.

Subjects who discontinue the study will be asked to attend an early discontinuation (ED) visit.

A schematic diagram of clinical study design, procedures, and stages is provided in Figure 1.

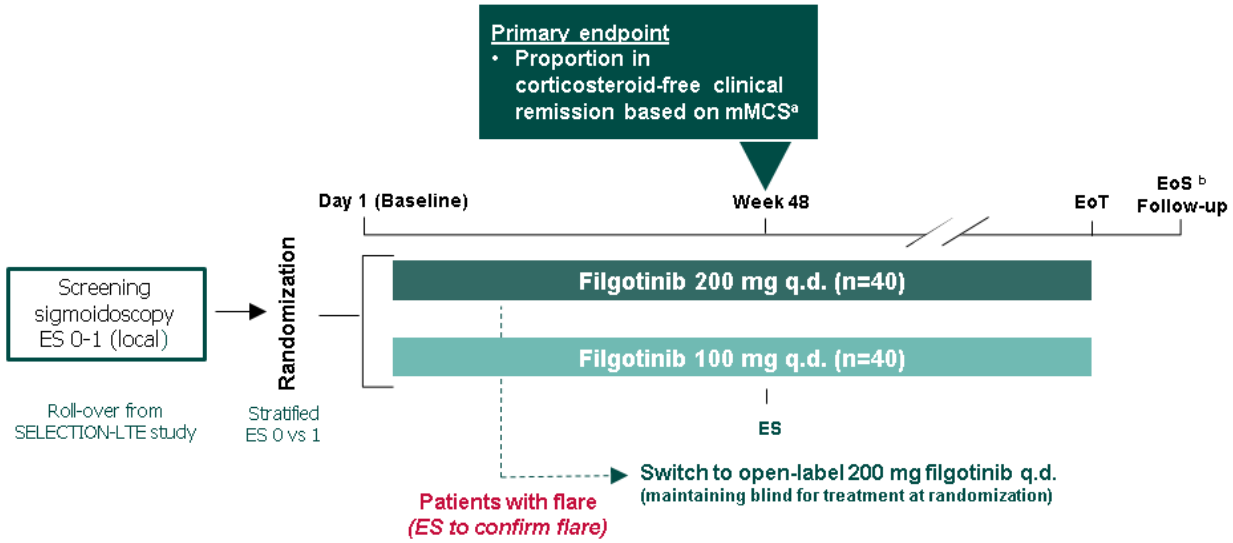


Figure 1: Schematic Diagram

EoT: End of Treatment; EoS: End of Study; ES: endoscopic score; mMCS: modified Mayo Clinical Score; n: number of subjects in the treatment group; q.d.: once daily.
[a] mMCS of ≤2 points, with endoscopic subscore of ≤1, stool frequency subscore of ≤1, and rectal bleeding subscore of 0.
[b] EoS: when the last subject has completed the safety follow-up visit in that country (i.e. after completing minimum 48 weeks of treatment and the follow-up visit) OR (in countries where filgotinib is not commercially available) when the last subject completes 216 weeks in the study.

5.2. Clinical Study Design Rationale

The study is designed to evaluate the efficacy and safety of dose de-escalation of orally administered filgotinib in subjects with UC in clinical remission.

Subjects must have been in clinical remission for at least 2 consecutive quarterly visits in the SELECTION-LTE study prior to and including screening of the present study, to ensure that subjects are stable and that possible effects on efficacy can be attributed to dose change. Since UC is a progressive disease and worsening symptoms and flares can occur due to external factors as well as natural disease progression, a control group that remains on 200 mg filgotinib q.d. is included in the study design. The selected population will be recruited from subjects currently in the SELECTION-LTE study.

While the main objective of the study evaluates the possibility to maintain clinical remission while lowering the dose, subjects who do experience a flare will re-escalate to 200 mg filgotinib q.d. to evaluate if and how rapidly a response can be re-established.

Filgotinib is now approved for the treatment of UC in the EU, UK, and Japan, and shows a positive benefit-risk profile in patients with UC. To reduce the subject's burden in terms of both travel and site attendance, and assessments required, a reduction of on-site visit frequency will be introduced. After study unblinding at the primary analysis time point (see Section 6.4.2), the frequency of study visits will be reduced to every 24 weeks. 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.

The maximum study duration for a single subject in the present study is 216 weeks (approximately 4 years). This maximum duration is calculated based on the last subject enrolled and still included in the SELECTION-LTE study. Since subjects are recruited from SELECTION-LTE, they will be provided the opportunity to have the same length of treatment as in SELECTION-LTE.

[redacted] Patients with an active disease state will have elevated IL-6 plasma concentrations reported to decrease activity of carboxylesterase (CES)2 (Li et al., 2021; Shen et al., 2019), the enzyme involved in the metabolism of filgotinib into the active metabolite. [redacted]

5.3. Dosing Rationale

Doses have been selected based on efficacy and safety data in the preceeding SELECTION and SELECTION-LTE studies.

5.4. Treatment Discontinuation, Subject Withdrawal

5.4.1. Treatment Discontinuation

The investigator, who may consult the medical monitor, can consider stopping the study treatment in case of concerns about the subject's safety, serious or severe AEs or worsening of

the disease condition, which in the investigator's opinion needs an alternative treatment approach not being covered in the clinical study. Every effort should be made to keep subjects in the study and on treatment, taking into account the subject's safety and well-being.

5.4.1.1. Permanent Treatment Discontinuation

Treatment with IP must be discontinued by the investigator (who may consult the medical monitor) for any of the following conditions:

a. any opportunistic infection, defined at the discretion of the investigator;
b. any serious infection that requires antimicrobial therapy or hospitalization, or any infection that meets SAE reporting criteria;
c. febrile neutropenia (temperature>38.3 °C or a sustained temperature of 38 °C for more than 1 hour) with absolute neutrophil count of <1000/mm^3;
d. symptomatic anemia (e.g. signs/symptoms including pallor, shortness of breath, new heart murmur, palpitations, lethargy, fatigue) with hemoglobin <7.5 g/dL, or if transfusion is indicated regardless of hemoglobin value;
e. complicated herpes zoster infection (with multi-dermatomal, disseminated, opthalmic, or central nervous system involvement);
f. evidence of active hepatitis C virus (HCV) during the study, as evidenced by HCV RNA positivity;
g. evidence of active hepatitis B virus (HBV) during the study, as evidenced by HBV DNA positivity;
h. any thromboembolic event that meets SAE reporting criteria;
i. 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 to be in the subjects's best interest;
j. subject's request to discontinue for any reason;
k. subject's noncompliance;
l. pregnancy;
m. subject's use of prohibited concurrent therapy;
n. laboratory criteria: After becoming aware of any of the below described abnormal laboratory changes occurring at any one time, an unscheduled visit (i.e. sequential visit) should occur to retest within 3 to 7 days (except creatinine, which should be retested 7 to 14 days apart).
   - 2 sequential platelet counts <75000 platelets/mm^3 (SI <75.0x10^9 cells/L);
   - 2 sequential aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >3 times the upper limit of normal range (ULN) and at least 1 of the following confirmed values:
     - total bilirubin >2x ULN;
     - or international normalized ratio (INR) >1.5;
     - or accompanied by symptoms consistent with hepatic injury.

   For any subject with an initial AST or ALT elevation >3x ULN, at the time of the second confirmatory blood draw, INR, prothrombin time (PT) and partial thromboplastin time (PTT) must also be assessed.

- 2 sequential AST or ALT elevations >5x ULN;
- 2 sequential values for estimated creatinine clearance (CrCl) <35 mL/min based on the Cockcroft-Gault formula[1].

o. disease worsening (refer to Section 5.4.1.3);
p. nonreponse to re-escalation therapy (refer to Section 5.1).
q. subjects diagnosed with malignancy during the study except successfully treated non-melanoma skin cancer or cervical carcinoma in situ.

Any subject who discontinues study treatment, regardless of reason, will be invited to remain in the study and complete the visits as scheduled up to Week 48.

When the subject is discontinued from the study, the subject will be requested to return for the ED visit.

5.4.1.2. Temporary Treatment Discontinuation

Where possible, IP should not be interrupted. In case IP interruption is needed as per the discretion of the investigator (e.g. for intercurrent illnesses, new infections, or elective or emergency surgeries), the medical monitor should be consulted prior to IP interruption when medically feasible.

IP interruption should be considered in the following circumstances:

– Subjects with newly positive (converted) or 2 indeterminate QuantiFERON® tuberculosis (TB) test (or centrally reported equivalent assay) result(s) should interrupt study drug dosing and be evaluated for active TB and latent TB by the investigator per local standard of care. An indeterminate result should be repeated once and the second result (if positive or negative) will be accepted. Positive or negative results must not be repeated.
  - Subjects diagnosed with latent TB (i.e. a subject who has newly identified positive diagnostic TB test result, in which active TB has been ruled out) may initiate an adequate course of prophylaxis as per local standard of care. Appropriate, ongoing, prophylactic treatment for latent TB must be initiated for a minimum of 4 weeks prior to the continuation of study medication. Subjects may resume study drug after investigator's consultation with medical monitor.
  - Subjects with positive or 2 indeterminate QuantiFERON® test result(s) who are determined as having neither latent nor active TB infection may continue participation in the study after consultation and approval from the medical monitor.
  - Any subject with active TB must be discontinued from the study.
  - Subjects who were previously treated for TB with a complete and adequate course of therapy as per local standard of care and as verified by the investigator do not need to have yearly QuantiFERON® tests. Subjects previously treated for TB should be

[1] Estimate of CrCl using serum creatinine level: CrCl (male) = ([140-age] × weight in kg)/(serum creatinine × 72); CrCl (female) = CrCl (male) × 0.85.

screened at least yearly for signs and symptoms consistent with reactivation of TB and any subject with active TB should be discontinued from the study.

- For subjects with absolute lymphocyte count less than 500 cells/mm^3, confirmed via retest within 3 to 7 days, filgotinib should be interrupted until grade returns to ≤Grade 2 (more than 500 cells/mm^3). If absolute lymphocyte count does not return to ≤Grade 2 within 4 weeks or returns to less than 500 cells/mm^3 following re-challenge with IP, then IPshould be permanently discontinued and the subject managed according to local practice.
- For subjects with absolute neutrophil counts <1000 cells/mm^3 (international system of units [SI]: <1.0 x 10^9 cells/L); an unscheduled visit should occur to retest within a reasonable timeframe after establishing, treating, and resolving any possible underlying condition (within 3-7 days). The IP should be interrupted until the retest result is available. If the abnormal neutrophil count has been confirmed by a retest, the IP will be interrupted until the value returns to ≥1000 cells/mm^3 (SI: ≥1.0 x 10^9 cells/L). If the neutrophil abnormality does not return to >=1000 cells/mm^3 within 4 weeks or recurs following a re-challenge with IP and is considered related to IP, then IP 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 CrCl ≥35 mL/min and <60 mL/min per Cockcroft-Gault formula) at any time during the study, 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 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.

Prior to resumption of IP, the investigator should discuss the case with the medical monitor.

5.4.1.3. Disease Worsening Criteria

When a subject becomes symptomatic, including worsening or return of disease activity, a stool sample will be obtained for culture for pathogenic bacteria, ova and parasite evaluation, and *Clostridium difficile* toxin assay.

Subjects who have been re-escalated after an ES-confirmed UC flare (Section 5.1) and who meet the following criteria will be permanently discontinued from study drug treatment and, if applicable, will be invited to remain in the study up to Week 48:

- Any subject with significant disease worsening or lack of response to therapy based on investigator judgment should discontinue study drug treatment.
- If a subject experiences significant worsening of underlying UC, which requires any of the prohibited medications (refer to Section 6.3.2.2), or surgical intervention at any point during the study, treatment should be discontinued.

5.4.2. Subject Withdrawal

Subjects will be informed prior to clinical study entry that they are allowed to withdraw from the clinical study. At any time and for any reason, a subject's participation in the clinical study may terminate at his/her request, without prejudice to their future medical care. The subject will be encouraged to share the reason(s) for withdrawal so this can be documented in the source documents, and to complete the assessments of the ED visit, but will not be obliged to do so.

A subject may be withdrawn from the clinical study at any time without the subject's consent If the investigator or sponsor determines that it is not in the best interest of the subject to continue participation. In such case, the reason for withdrawal will be documented in the source documents, and the subject will be asked to complete the assessments of the ED visit.

5.4.3. Lost to Follow-up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the site. The site must make every effort to contact the subject to assess and document their health status in the source documents, including checking the medical records and contacting general practitioner or relatives, if necessary.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.

5.5. Potential Risks and Benefits

Potential Benefits

Filgotinib 200 mg q.d. has shown a rapid and pronounced efficacy response in subjects with moderate to severe UC in both the SELECTION and SELECTION-LTE study.

Patients may benefit from a decrease in filgotinib dose if they can maintain remission (see below).

Potential Risks

- Serious infections:
  JAK inhibition is expected to increase the risk of infection based on the mechanism of action. Serious and opportunistic infections, and herpes zoster have been reported for participants in clinical studies receiving filgotinib and are considered Important Identified

Risks with filgotinib. Adult patients receiving immunomodulatory treatment without any evidence of immunity to varicella, may be at increased risk of primary varicella (chicken pox) infection should they contract the virus. Reactivation of varicella zoster virus latent infection causes herpes zoster (shingles) and is of concern in patients on immunomodulatory therapy, including JAK inhibitors. Herpes zoster is an AE of interest in the ongoing long-term safety evaluations. The underlying immune pathology and chronic use of drugs such as corticosteroids has also been associated with an increased risk of infection.

- Malignancy:
  There have been no nonclinical findings that are directly relevant to malignancy. However, the risk of malignancies is increased in patients with UC, and immunomodulatory medicines may increase this risk. Clinical studies are insufficient to assess the potential risk following exposure to filgotinib. Long-term safety evaluations are ongoing.
- Major adverse cardiovascular events (MACE) and hyperlipidemia:
  The association of JAK inhibitors and cardiovascular outcomes, including the potential for MACE as a result of elevations of lipid levels remains unclear. Filgotinib treatment was associated with dose-dependent increases in total cholesterol and high-density lipoprotein (HDL) levels, while low-density lipoprotein (LDL) levels were slightly increased, and LDL/HDL ratios were generally unchanged. Traditional cardiovascular risk factors (e.g. smoking, dyslipidemia, obesity, hypertension, diabetes mellitus, age, and cardiovascular history) may also apply to patients with UC. The Cardiovascular Safety Endpoint Adjudication Committee (CVEAC) will periodically review and adjudicate all potential MACE (refer to Section 10.1.1).
- Venous thromboembolism (deep vein thrombosis [DVT] and pulmonary embolism [PE]):
  DVT and PE have been reported in patients receiving JAK inhibitors including filgotinib, but there is currently insufficient evidence indicating a causal relationship between filgotinib treatment and DVT/PE occurrence. The CVEAC will periodically review and adjudicate all potential thromboembolic events (refer to Section 10.1.1).
- Embryolethality and teratogenicity:
  Embryolethality and teratogenicity were identified in nonclinical studies. It is not known whether these effects apply to humans exposed to filgotinib; however, similar effects from nonclinical studies with other medicinal products in the same class have been identified. The possible impact for a pregnant female participant taking filgotinib could be fetal death or a congenital anomaly. Filgotinib is contraindicated in pregnancy.
- Impaired spermatogenesis, leading to possible reduction in male fertility:
  Filgotinib-related findings were observed in the male reproductive system of both rats and dogs. Spermatogenic and histopathological effects were reversible at lower exposures but were not completely reversible at exposure margins of approximately 7- to 9-fold the exposure at the 200 mg q.d. dose in humans. Based on the results of ongoing male safety studies to examine the potential effect of filgotinib on sperm parameters, it was concluded that there is no evidence of filgotinib-related effects on measures of testicular function at the marketed dose of 200 mg once daily (details are provided in IB Edition 17, Section 6.3.2).

Information on important safety risks is included in the latest version of the IB and relevant addenda/errata.

Risk Mitigation

Due to the listed risk of infection, investigators are advised to monitor infections appropriately. Treatment interruption and discontinuation considerations surrounding infections are incorporated in the present protocol, and sites and investigators will be trained regarding such circumstances. Filgotinib should not be administered to patients with active TB. All subjects will be screened for TB and subjects with clinically significant active infections will be excluded. Use of live attenuated vaccines during filgotinib treatment is not recommended.

Given this study will be performed during a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, appropriate measures should be taken to minimize the risk of SARS-CoV-2 infection for subjects participating in the study as well as study site personnel. Local guidelines to prevent SARS-CoV-2 infection should be adhered to.

HBV Surveillance

- Subjects with positive HBV surface antigen (HBsAg) at screening were excluded from the parent UC studies (GS-US-418-3898 and GS-US-418-3899). Subjects who were positive for HBV surface antibody (HBsAb), but negative for both HBsAg and HBV core antibody (HBcAb) at screening were eligible to participate in the parent UC studies (GS-US-418-3898 and GS-US-418-3899) and are also eligible to participate in the present study.
- Subjects with positive HBcAb and HBV DNA below the lower limit of quantification (LLOQ) in a parent UC study will require ongoing HBV DNA monitoring every 12 weeks during the present study. After study primary analysis endpoint unblinding frequency will be reduced to every 24 weeks. These subjects may also require prophylactic treatment per investigator discretion in accordance with local guidelines/standard of care.
- Any subject who has HBV DNA ≥LLOQ will be discontinued from the present study (Section 5.4.1.1 and Section 6.2 item 10).

Malignancy has been reported in subjects on filgotinib. In the present study, subjects will be required to have up to date colorectal cancer screening and surveillance as per standard of care. Following SELECTION and SELECTION-LTE studies, subjects with recent malignancies will be excluded from the present study (Section 6.2, Item 9.1) and those diagnosed during the study will be discontinued, except successfully treated non-melanoma skin cancer or cervical carcinoma in situ.

Highly effective contraceptive measures are expected to mitigate the risk of fetal toxicity. Refer to Section 6.3.1 for further guidance on pregnancy precautions and contraceptive requirements.

For more details refer to the latest version of the IB and its relevant updates/addenda.

6. CLINICAL STUDY POPULATION

6.1. Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for participation in this study:

Signed Informed Consent Form

1. Subject must be able and willing to comply with the CSP requirements and must sign and date the informed consent form (ICF) as approved by the Independent Ethics Committee (IEC) / Institutional Review Board (IRB), prior to any screening evaluations.

Target Population

2. Criterion modified per amendment 1.
   2.1 Subjects must be participating in the SELECTION-LTE study, currently on 200 mg filgotinib q.d. and fulfill the following conditions:
   - pMCS remission[1] over a period of at least 2 consecutive quarterly visits in the SELECTION-LTE study prior to screening of the present study;
   - free of corticosteroids for at least 12 weeks prior to and including baseline;
   - FCP <=250 µg/g at last observation within 6 months prior to screening or FCP <=250 µg/g during the screening of the present study.
   - sigmoidoscopy ES of 0 or 1 (local score) at screening.
3. Subject must be able and willing to comply with restrictions on prior and concomitant medication (as described in Section 6.3.2).
4. Willing to refrain from live attenuated vaccines during the study and for 12 weeks after the last dose of filgotinib in the study.

Reproductive Status

5. Female subjects of childbearing potential must have a negative highly sensitive (serum beta human chorionic gonadotropin) pregnancy test during screening, and must agree to continued monthly urine dipstick pregnancy testing during filgotinib treatment.
6. Criterion modified per amendment 1.
   6.1 Female subjects of childbearing potential must agree to use highly effective contraception measures as defined in Section 6.3.1.1.2.

[1]pMCS score ≤2 points, with PGA ≤1, stool frequency subscore ≤1, and rectal bleeding subscore = 0.

6.2. Exclusion Criteria

Subjects meeting one or more of the following criteria cannot be selected for this clinical study.

Medical History and Concurrent Diseases

1. Any chronic medical condition (including but not limited to, cardiac or pulmonary disease, alcohol, or drug abuse) that, in the opinion of the investigator or sponsor would make the subject unsuitable for the study or would prevent compliance with the study protocol.

Previous and Concomitant Medications

2. Subject has taken any prohibited therapies before the planned first dose of IP.
3. Subject concurrently participates or participated in a drug, drug/device, or biologic investigational research study with the exception of the preceeding SELECTION-LTE study within 12 weeks or 5 half-lives of the IP, whichever is longer, prior to the first dose.

Allergies and Adverse Drug Reactions

4. Subject has a known hypersensitivity to filgotinib ingredients or history of a significant allergic reaction to filgotinib ingredients as determined by the investigator.

Other Exclusion Criteria

5. Female subject who is pregnant or breastfeeding, or intending to become pregnant or breastfeed, and/or plans to undergo egg donation or egg harvesting for the purpose of current or future fertilization, during the study and until the end of the study.
6. Criterion deleted per amendment 1.
7. Subject is unable or unwilling to comply with restrictions regarding prior and concomitant medication as described in the protocol.
8. Criterion modified per amendment 1.
   8.1 Subject has a positive QuantiFERON® TB test at screening or has 2 indeterminate QuantiFERON® TB test results that require IP treatment interruption, or subject has signs and symptoms of TB reactivation at screening.
9. Criterion modified per amendment 1.
   9.1 History of malignancy during or in the last 5 years prior to participation in the UC parent studies, except for subjects who have been successfully treated for nonmelanoma skin cancer or cervical carcinoma in situ.
10. Subject meets discontinuation criteria of the SELECTION-LTE study.
11. Investigator or other study staff or relative thereof who is directly involved in the conduct of the study.
12. Subject has any condition or circumstances that, in the opinion of the investigator, may make a subject unlikely or unable to complete the study or comply with study procedures and requirements (e.g. active alcohol or drug abuse).

13. Subject is institutionalized by virtue of an order issued by either the judicial or the administrative authorities, or has a dependence on the sponsor or investigator.

6.3. Prohibition and Restrictions

6.3.1. Precautions for Sexual Intercourse

For participation in this study, the use of highly effective contraception is required as outlined below for all female subjects who are of childbearing potential. In addition, during the study women of childbearing potential (WOCBP) must have at minimum a urine pregnancy test every 4 weeks.

6.3.1.1. Female Subjects

6.3.1.1.1. Definition of Childbearing Potential

Woman of Childbearing Potential

A female subject is considered of childbearing potential, i.e. fertile, following menarche and until becoming postmenopausal unless permanently sterile (see below).

Woman of Non-childbearing Potential

A female subject is considered of non-childbearing potential:

1. Premenopausal female with permanent infertility due to one of the following documented conditions:
   a. hysterectomy
   b. bilateral salpingectomy
   c. bilateral oophorectomy
   d. For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g. Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator judgment should be applied to determine study eligibility which should be properly documented.
2. Postmenopausal female:
   The postmenopausal state is defined as:
   - no menses for ≥12 months without an alternative medical cause
     AND
   - confirmed high follicle stimulating hormone (FSH) level in the postmenopausal range.
     Note: If the FSH level is below the postmenopausal range while the female subject is using hormonal therapy, the postmenopausal state will be assessed by the investigator taking into account the subject's age, medical records, medical examination, and/or medical history interview.

6.3.1.1.2. Contraceptive Methods

Contraception for Female Subjects of Childbearing Potential

The inclusion of female subjects of childbearing potential requires the use of highly effective contraceptive measures. Women must have a negative serum pregnancy test during screening of the present study. Urine pregnancy tests will be performed at monthly intervals thereafter during filgotinib treatment. Female subjects must agree to continue to use one of the following contraceptive methods from screening, during the study, and until the end of the study:

- 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 3 months after procedure).

Female subjects who utilize a hormonal contraceptive as one of their birth control methods must have consistently used the same method for at least 3 months prior to study dosing.

Hormonally-based contraceptive methods 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 the study and until the end of the study.

The used contraceptive methods for female subjects must be documented in the source documents.

Women of nonchildbearing potential are not required to use any contraceptive method.

For information on the timing and requirements for pregnancy testing or FSH testing, refer to Section 8.4.2 and the Schedule of Activities.

6.3.1.2. Male Subjects

Section deleted per amendment 1.

6.3.1.3. Unacceptable Birth Control Methods

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

6.3.1.4. 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 30 days of the last IP dose. Subjects who become pregnant or who suspect that they are pregnant during the study must report the information to the investigator and discontinue the IP intake immediately.

Instructions for reporting pregnancy, and pregnancy outcome are outlined in Section 11.3.3.

6.3.2. Prior and Concomitant Medications

6.3.2.1. Allowed Medications

Doses for allowed concomitant medications for UC must be maintained at a stable dose. Discontinuation or dose modifications within the limits of allowed doses are permitted at the discretion of the investigator.

The allowed medications for UC disease are as follows:

- oral and rectal 5-aminosalicylate (5-ASA) compounds;
- azathioprine, 6-mercaptopurine or methotrexate;
- rectally administered, nonsystemically absorbed steroids (except for at least 12 weeks prior to screening and including baseline of the present study);
- antidiarrheals (e.g. loperamide or diphenoxylate/atropine).

Oral and/or rectal corticosteroids are allowed in case of flare (see Section 5.1), and oral corticosteroids should not exceed prednisone 30 mg/day equivalents.

6.3.2.2. Prohibited Medications

A list of prohibited medications is provided in Table 1.

Table 1: Prohibited Medications

Drug Class	Prohibited Agents
Prohibited inflammatory bowel disease medication	
Corticosteroids (intravenous)[a]	
TNF alpha agonist	Infliximab, adalimumab, golimumab, certolizumab, or biosimilar agent
Integrin antagonist	Vedolizumab and natalizumab
Interleukin antagonist	Ustekinumab
JAK inhibitor	Any JAK inhibitors including, but not limited to, tofacitinib, baricitinib, and updadacitinib
Other (nonbiologics)	Cyclosporine, thalidomide, tacrolimus, ozanimod, leflunomide and any investigational agent
Investigational biologics	Any investigational biologic agent
Lymphocyte-depleting therapies	Alemtuzumab, cyclophosphamide, total lymphoid irradiation, rituximab, and any other lymphocyte-depleting therapy
Other probited Medications	
Chronic nonsteroidal anti-inflammatory drugs (NSAIDs)[b]	Aspirin, ibuprofen, naproxen, diclofenac, indomethacin, cyclooxygenase-2 (COX-2) inhibitors
Other biologics	Antibody based or other systemic biologics, e.g. denosumab, trastuzumab

[a] Oral and/or rectal corticosteroids may be used in case of a flare (see Section 5.1), and oral corticosteroids should not exceed prednisone 30 mg/day equivalents (except for at least 12 weeks prior to screening and including baseline of the present study).
[b] Occasional use for transient symptoms and daily use of aspirin up to 162.5 mg for the purpose of cardiovascular prophylaxis are permitted

6.3.3. Food and Beverage Restrictions

There are no specific food and beverage restrictions for this study. The IP can be taken with or without food. There are no specific requirements regarding IP and the dietary intake.

6.4. Measures to Minimize Bias

6.4.1. Randomization

Subjects will keep the subject number received in the SELECTION-LTE study. When a subject is confirmed to be eligible for the clinical study, the subject will be randomized. Allocation of each subject to a given treatment will be done using a centralized electronic system (randomization and trial supply management [RTSM]). Subjects will be randomized in a 1:1 ratio to 200 mg or 100 mg filgotinib q.d. Subjects will be stratified according to ES (score of 0 or 1) at baseline to ensure treatment balance in each stratum.

6.4.2. Blinding and Unblinding

This is a randomized, double-blind clinical study. The subjects and the entire clinical study team, including the investigators, clinical study coordinators, and sponsor personnel are blinded to

treatment assignment until the study primary analysis time point, with the exception of the sponsor's clinical study supply leader.

Unblinding will take place at the study primary analysis time point, i.e. after the last subject completed their Week 48 postbaseline visit or has completed their Week 12 post re-escalation visit (if baseline of re-escalation is within the first 48 weeks of the study), or after the last follow-up of subjects discontinuing prior to Week 48, whichever comes last. Unblinding at the Week 48 interim analysis is described in Section 9.3.2. In addition, [redacted] external functions specified in RTSM specification, will also be unblinded to treatment assignment.

Study medication provided to the sites will be packaged and labeled assuring the blinding of the IP. Unblinded study medication will be provided for treatment in case of re-escalation and for treatment after unblinding. Subjects who are re-escalated to 200 mg filgotinib q.d. will remain blinded to their treatment at randomization.

The blind can be broken only if the investigator deems it necessary for the safety of a subject. The investigator is encouraged to discuss considerations to break the blind with the medical monitor of the study, whenever possible and where the situation allows. However, the responsibility to break the treatment code in emergency situations resides solely with the investigator. The investigator is not required to discuss unblinding beforehand if he or she feels rapid emergency unblinding is necessary, but is required to inform the sponsor within 24 hours after unblinding has occurred.

The blind can be broken by the investigator via RTSM.

If the blind is broken for any reason during the course of the clinical study, all relevant information will be documented by the site. The reason for breaking the blind will be indicated and justified in the source documentation.

In case an AE leads to unblinding, that AE should be given as the reason for unblinding.

The pharmacovigilance department of the sponsor (or a representative thereof) may independently unblind cases for expedited reporting of suspected unexpected serious adverse reactions (SUSARs) to worldwide regulatory agencies (see Section 11.4).

7. INVESTIGATIONAL PRODUCT

7.1. Identity of the Investigational Product

Filgotinib is available as 200 mg and 100 mg strength tablets. Filgotinib tablets, 200 mg and 100 mg are beige, debossed with "GSI" on one side and "200" or "100" on the other, capsule-shaped, biconvex, film-coated tablets for clinical use. Each tablet contains the equivalent of 200 mg or 100 mg filgotinib free base in the form of filgotinib maleate. In addition to the active ingredient, filgotinib tablets contain the following inactive ingredients: microcrystalline cellulose, lactose monohydrate, fumaric acid, pregelatinized starch, silicon dioxide, magnesium

stearate, macrogol/polyethylene glycol (PEG) 3350, polyvinyl alcohol, talc, titanium dioxide, iron oxide yellow, and iron oxide red.

Placebo-to-match (PTM) 200 mg and 100 mg filgotinib tablets are identical in appearance to the respective active filgotinib tablets. PTM 200 mg and 100 mg 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.

7.2. Dosage and Administration

The IP needs to be taken q.d. at approximately the same time. Subjects will be asked to swallow the IP with a glass of water and to not chew the drug prior to swallowing. The IP can be taken with or without food. There are no specific requirements regarding IP and the dietary intake.

Blinded treatment up to the primary analysis time point

Doses of 100 mg or 200 mg filgotinib, as a combination of 2 tablets (filgotinib and PTM) for blinding purposes, will be taken q.d. orally.

Subjects will be provided with medication kits containing 2 bottles with blinded IP, either:

- 100 mg filgotinib tablets in bottle 1 and PTM 200 mg filgotinib tablets in bottle 2;
- 200 mg filgotinib tablets in bottle 1 and PTM 100 mg filgotinib tablets in bottle 2.

At the baseline visit (Day 1), IP will be administered on-site after predose assessments have been completed. If on Day 1, the subject has already taken the IP as assigned in the SELECTION-LTE study, the first dose as assigned in this study should be taken on Day 2.

Starting from Day 2, subjects will be instructed to take 1 tablet from each bottle q.d. (i.e. a total of 2 tablets).

Re-escalation

Subjects who are re-escalated to open-label 200 mg filgotinib q.d. will be provided with bottles containing unblinded IP (200 mg filgotinib tablets in 1 bottle). If the subject has already taken IP on the re-escalation baseline day, the first adjusted dose should be taken on re-escalation Day 2. Subjects will be instructed to take 1 tablet q.d.

Subjects who are re-escalated continue on open-label 200 mg filgotinib q.d. for at least 12 weeks. If the subject does not respond to re-escalation therapy within a timeframe of maximum 12 weeks, the subject will be permanently discontinued from the treatment. If subject improvement is sufficient in the opinion of the investigator, the subject may continue on open-label 200 mg filgotinib q.d. until the end of the study.

After unblinding at the primary analysis time point

For continued q.d. treatment after unblinding until the end of the study, subjects will be provided with bottles containing unblinded IP, either:

- 1 bottle with 100 mg filgotinib tablets;
- 1 bottle with 200 mg filgotinib tablets.

Subjects will be instructed to take 1 tablet q.d.

At each IP dispensing visit, subjects will receive IP to take home on non-study visit days and will be provided with instructions for dosing. Multiple medication kits can be provided to ensure the subject has sufficient tablets to cover the period until the next visit when IP dispensing is scheduled.

If a subject misses a dose (e.g. because he/she forgot to take the medication), he/she should take the missed dose as soon as possible during the same day of the planned intake time, or else that dose should be skipped. If a dose is not taken it should be returned to the bottle.

7.3. Packaging, Labeling, and Distribution

Filgotinib and PTM filgotinib tablets are packaged in white, high-density polyethylene 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, aluminum-faced liner. The IP to be distributed to centers in the United States (US), EU, and other participating countries shall be labeled to meet applicable requirements of the US Food and Drug Administration, EU Guideline to Good Manufacturing Practice – Annex 13 (Investigational Medicinal Products), and/or other local regulations, as applicable.

The distribution of IP to the site will only occur after the required local documentation is obtained, including clinical study approval by regulatory authorities and the IECs/IRBs, documentation on which the assessment of the investigator's qualifications was based (e.g. curriculum vitae), and the signed and dated clinical study agreement.

In case of travel restrictions (including due to SARS-CoV-2 pandemic), to ensure study subjects maintain dosing per protocol requirements during this study, special delivery services through Direct to Patient (DTP) shipments of IP to the subject can be implemented. DTP shipments should only be used in case of emergency when on-site IP dispensation is not possible, and if allowed per local regulations. Local guidelines must be followed and regulatory approval or notification of authorities may be required. Agreement of the subject to receive IP at home is required prior to the shipment of IP to the subject's home. The DTP shipment process used will be reviewed and approved by the sponsor. In case the DTP shipments originate from the site they will be coordinated by the investigational site(s) in collaboration with the local CRO without the involvement of the sponsor, to ensure clinical study integrity.

7.4. Storage

Sites must store IP supplies in a secure temperature-controlled area at room temperature (15-25 °C; excursions permitted between 15 °C and 30 °C) until dispensed. Sites are required to monitor the storage temperature by using at least a min-max temperature recording device and to record each working day the minimum and maximum temperature (either by the temperature recording device or in a temperature log). This is to establish a record of compliance with these storage conditions. The investigator will instruct subjects how the IP should be stored at home.

7.5. Treatment Compliance and Drug Accountability

The investigator must discuss treatment compliance with the subject prior to the start of the study. Missed doses should be discussed to try to ascertain the reason(s). Every effort should be made to ensure the proper subject dose. Subjects with poor compliance will be retrained by the site. IP administration as indicated by the subject (amounts as well as periods) will be recorded on the case report form (CRF).

The pharmacist or designated clinical study staff will maintain a log (paper or electronic) of the total amount of IP received at site, amount dispensed to the subject, and the amount of IP returned by the subject to the site. IP supplies for each subject will be inventoried and accounted for throughout the clinical study. On an ongoing basis and at the end of the treatment period, these records will be checked against the inventory by the study monitor. All clinical supplies will be stored in locked facilities.

Subjects will return any unused IP and empty IP packages at every dispensing visit, unscheduled visit, and/or ED visit. All used and unused IP, and packages are to be returned from the sites and/or any vendor involved in the clinical study supplies management activities to the agreed location (depot), if possible. Only in exceptional cases, upon sponsor approval, IP can be destroyed at the site. All returns and destructions must be properly documented.

8. CLINICAL STUDY ASSESSMENTS

Every effort must be made to ensure that CSP-required tests and procedures are completed as described in the Schedule of Activities (see Section 8.9.1 and Section 8.9.2). To avoid inter-observer variability, every effort should be made to ensure that clinical observations are performed by the same individual who made the initial baseline determinations.

8.1. Timing of Assessments

The study assessments described below will be performed at time points as specified in the Schedule of Activities in Section 8.9.1 and Section 8.9.2.

The ICF needs to be signed before any study procedure, including screening procedure, is carried out.

Subjects in the SELECTION-LTE study who are in clinical remission with 200 mg filgotinib q.d. for at least 2 consecutive quarterly visits, will be provided the option to roll over to the present study at any scheduled visit of the SELECTION-LTE study or at a separate visit.

Subjects will be requested to attend the site for at least 2 screening visits:

- Screening visit 1 (ICF signature) (S1) and other screening assessments as per Schedule of Activities in Section 8.9.1, including TB assessment and screening FCP assessment (if last FCP observation was >6 months prior to screening or most recent FCP value was >250 µg/g) in order to obtain the results prior to randomization.

  Depending on the screening FCP in the present study (if applicable) and the ES, the subject will either be a screening failure (FCP >250 µg/g or ES >1) in the present study and will remain in SELECTION-LTE, or the subject will be eligible (FCP ≤250 µg/g and ES ≤1) and will need to perform the EoT assessments in SELECTION-LTE and the remaining screening assessments before being randomized to the present study (refer to Schedule of Activities in Section 8.9.1).
- Screening visit 2 (S2), the EoT visit in SELECTION-LTE, and the Day 1 visit of the present study can occur on the same day or on 2 consecutive days.

Some data collected in SELECTION-LTE, as specified in the Schedule of Activities in Section 8.9.1, may be used in the present study.

In case a randomized subject is not able to attend a scheduled study visit on-site for reasons related to SARS-CoV-2 pandemic restrictions, a phone call or a televisit may be conducted (televisit after obtaining approval from the sponsor). It is strongly recommended to conduct planned study assessments for the applicable visit as per protocol as much as possible. If possible and if local regulations allow, and the subject agrees, trained site study staff are encouraged to perform study assessments at the study subjects' home or a local facility. Only staff trained in conducting the protocol planned assessments are authorized to perform home or local facility visit assessments and the alternative arrangements need to be adequately documented.

DTP shipments are possible, if needed, in case of travel restrictions (e.g. due to SARS-CoV-2 pandemic), and if allowed per local regulations (refer to Section 7.3).

8.1.1. Order of Assessments

For assessments to be performed at screening visits, refer to the Schedule of Activities in Section 8.9.1.

In case the following assessments are planned to be performed at the same time point, they need to be performed in the following order:

[redacted]

2. 12-lead electrocardiogram (ECG) and vital signs;
3. blood sampling for clinical laboratory assessments, [redacted]

For other assessments planned to be performed at the same time point, a random order is allowed.

[redacted]

8.1.2. End of Treatment Visit

In countries where filgotinib becomes commercially available, subjects will be requested to attend the EoT visit as soon as possible after the subject has completed at least 48 weeks of treatment (see Section 5.1). For the subjects who have not yet completed 48 weeks of treatment when filgotinib becomes commercially available, the Week 48 visit can replace or occur on the same day as the EoT visit. All assessments listed at the EoT visit can be conducted as part of the Week 48 visit; therefore the EoT assessments do not need to be repeated. If not performed on the same day, there should be a minimum of 1 week and maximum of 4 weeks between the 2 assessments, and the TB assessment at Week 48 suffices for TB assessment at EoT. Other assessments for the EoT visit should be performed according to the Schedule of Activities (Section 8.9).

8.1.3. Re-screening of Subjects

If a subject fails screening, it is allowed to re-screen the subject once. Re-screening may only be conducted after approval from the sponsor's medical lead. When a subject is re-screened, the subject needs to be reconsented and all screening assessments need to be repeated. The subject will be assigned a new subject number.

8.1.4. Unblinding of Subjects at the Study Primary Analysis Time Point

After unblinding at the study primary analysis time point, subjects will receive unblinded treatment and the frequency of study visits will be reduced to every 24 weeks. All subjects should be invited for an unblinding visit no later than 4 weeks after the study primary endpoint unblinding. If no regular visit is scheduled within this time frame, an unscheduled visit should be performed for IP dispensing to ensure the subject has sufficient IP to cover the period until the next 24-weekly visit. Assessments indicated as to be performed every 12 weeks will then be added to the assessments at Week 24.

The unblinded treatment duration depends on commercial availability of filgotinib in the country but will be limited to the maximum study duration for individual subjects of 216 weeks.

8.2. Unscheduled Visits

Additional visits can be performed at other time points for IP dispensing and /or any safety assessments, if clinically indicated. These unscheduled visits and outcomes of additional safety assessments need to be recorded in the source and, if it is a CSP-specified safety assessment performed before the subject's last visit per CSP, also in the CRF.

[redacted]

8.3. Efficacy Assessments

8.3.1. Endoscopy and Biopsy Sample Collection

A sigmoidoscopy will be performed at the visits specified in the Schedule of Activities in Section 8.9.1.

The ES for randomization purposes will be obtained from a sigmoidoscopy performed during the screening period (including biopsy collection for histology assessment). It is recommended that the screening sigmoidoscopy be performed only after the subject meets all other eligibility criteria.

In case of a suspected UC flare, an additional sigmoidoscopy is needed (refer to Section 5.1).

Subjects who discontinue the study prior to Week 48 need a sigmoidoscopy at the ED visit.

The endoscopy will be assessed by a local reader and scored using the Mayo scoring system (refer to Section 8.3.2).

[redacted]

8.3.2. Mayo Clinical Score

The Mayo scoring system for assessment of UC activity is shown in Appendix 2. The total MCS consists of 4 subscores (stool frequency, rectal bleeding, endoscopic findings, and PGA).

The primary efficacy objective will be assessed based on the mMCS. The mMCS is composed of 3 subscores: stool frequency, rectal bleeding, and endoscopic findings.

[redacted]

Stool frequency and rectal bleeding scores will be established based on the subject's e-Diary. PGA will be completed electronically by the investigator.

[redacted]

[redacted]

8.3.3.4. IBDQ

This disease-specific questionnaire comprises 32 questions divided into 4 health subscales:

- bowel symptoms (10 questions);
- systemic symptoms, including sleep disorders, and fatigue (5 questions);
- emotional function such as depression, aggression, and irritation (12 questions);
- social function, meaning the ability to participate in social activities and to work (5 questions).

8.4. Safety Assessments

This section describes methods for all safety assessments and recording. Additional assessments (e.g. unscheduled clinical laboratory evaluations or extra vital signs recordings) are allowed to ensure appropriate collection of safety data and to assess any perceived safety concerns. Retesting is allowed in case no results from the assessment(s) are available due to subject-independent external factors, such as, but not limited to, transport and/or technical issues.

Clinically significant abnormal findings should be recorded as AE as indicated in Section 11.1.5.

8.4.1. Adverse Events

The AE reporting period for safety surveillance begins when the subject signs the ICF and ends at their last scheduled visit.

Detailed definitions, reporting period, ratings and reporting requirements for AEs and SAEs are found in Section 11.

8.4.2. Clinical Laboratory Evaluations

The clinical laboratory evaluations (listed in Appendix 3) will be performed at visits and time points specified in the Schedule of Activities in Section 8.9.1 and Section 8.9.2 (see also Section 8.1, "Timing of Assessments"). Reference ranges will be supplied by the central laboratory. Clinical laboratory values outside the normal range will be flagged and clinical relevance will be assessed by the investigator. Only laboratory test abnormalities judged as clinically significant by the investigator should be recorded as AEs (see Section 11.1.5). At the discretion of the investigator, when following up AEs, additional laboratory parameters may be tested, and additional samples taken.

Clinical and clinically significant laboratory abnormalities will be managed according to uniform guidelines detailed in Appendix 4.

Blood and urine sample handling, and shipment instructions will be provided in a separate laboratory manual.

8.4.3. Physical Examination

Physical examinations, including height (only during screening) and weight, will be conducted by a physician or a trained physician's assistant, as acceptable according to local regulation at visits specified in the Schedule of Activities in Section 8.9.1 and Section 8.9.2 (see also Section 8.1, Timing of Assessments).

Physical examinations will be symptom-directed.

The person conducting the physical examination will document this in the subject's source documents.

8.4.4. Vital Signs

Vital signs (systolic and diastolic blood pressure, pulse, respiratory rate, and body temperature) will be measured.

Vital signs values will be recorded in a standardized manner at visits specified in the Schedule of Activities in Section 8.9.1 and Section 8.9.2 (see also Section 8.1, "Timing of Assessments"):

- systolic and diastolic blood pressure and pulse: after the subject has rested in a seated or supine position for 5 minutes;
- respiratory rate;
- body temperature: oral or tympanic (consistent method to be used at every time point within the same subject).

8.4.5. 12-lead Electrocardiogram

At the time points specified in the Schedule of Activities (see Section 8.9.1 and also Section 8.1, "Timing of Assessments"), a 12-lead ECG will be recorded.

12-lead ECG recordings will be performed before blood sampling and after subjects rested for 5 minutes in supine position. In case an indwelling catheter is used, ECGs may be recorded after blood sampling, provided that there is at least 30 minutes between catheter insertion and the ECG recording. When catheter insertion would fail, the 12-lead ECG needs to be taken before the venipuncture and at least 30 minutes after the failed attempt.

The following parameters need to be recorded: heart rate, PR interval, QRS interval, uncorrected QT interval, morphology, and rhythm analysis.

The ECG will be reviewed by the investigator to detect clinically significant abnormalities. This review during the visit needs to be documented in the subject's source documents.

[redacted]

[redacted]

8.7. Sample Management

8.7.1. Total Blood Volume

The total amount of blood to be taken during the screening and 48-week blinded treatment period for mandatory scheduled laboratory parameters will not exceed 340mL. [redacted]

The average amount of blood taken for mandatory scheduled laboratory parameters at each subsequent visit scheduled after the 48-week blinded treatment period will not exceed 36 mL.

[redacted]

A limited increase in amount of blood taken is possible in case repeat or unscheduled samples are taken for safety reasons or for technical issues with the samples.

This is considered to be within the acceptable limits based upon the standard of the World Health Organization (WHO, 1994).

8.7.2. Blood and Urine Samples for Routine Safety Tests

All blood and urine samples for routine safety tests (see Section 8.4.2) will be analyzed in a central laboratory and will be destroyed after analysis as per laboratory procedure (unless otherwise indicated in Section 8.8).

[redacted]

8.8. Optional Long-term Storage of Samples and Associated Data for Future Clinical and Research Assessments

Left-over samples from samples already collected during the study and associated data (e.g. sample type, quantity, treatment name) qualify for long-term storage for use as part of future scientific research if subjects have agreed to participate and provide their optional informed consent. Blood (serum and plasma), stool samples, and biopsy samples will be stored. Samples that qualify for long-term storage will be stored for 30 years or according to local legislation, for future scientific research.

The sample(s) and associated data collected for future scientific research will be stored in the Galapagos Biobank and may be used by the sponsor, sponsor partners, and/or other companies contracted by the sponsor. The objective of biobanking is to allow the gathering of additional knowledge on the compound GLPG0634 and/or diseases it may target both investigated during this study and beyond.

No characterization of human genetic material (genes, DNA, or RNA) will be undertaken on these sample(s).

Subjects are not required to consent for the long-term storage of sample(s) and associated data for future scientific research in order to participate in the study. Subjects will also be informed that consent to storage for future scientific research is voluntary and that they may withdraw their consent at any time. If a subject chooses to withdraw consent for the storage of sample(s) and

associated data for future research after the end of the study, then the investigator or designated personnel must inform the sponsor (withdrawal@glpg.com).

Withdrawal from the study or [redacted] does not, by itself, implicate withdrawal of consent for the storage of sample(s) and associated data for future research. Likewise, withdrawal of consent for the storage of sample(s) and associated data for future research does not implicate withdrawal from the study or [redacted]

In the event of subject's death or loss of competence, the already collected sample(s) and data will continue to be used as part of the future scientific research only for the purposes as described in the ICF that was signed by the subject.

The sample(s) and associated data for future research, e.g. body fluids, solid tissue, and derivatives thereof (e.g. protein, peptides) will be destroyed no later than 30 years after the end of the study or according to local legislation. The sample(s) and associated data storage period will be in accordance with the IRB/EC-approved ICF and applicable legislation (e.g. regulatory authority requirements).

The subject will receive additional information specific to the long-term processing of their personal data for future scientific research purposes, as required by the EU General Data Protection Regulation. This includes information about the broader scientific purposes of future research, the lawful bases of the processing activities involved, as well as the retention period of their personal data for these additional purposes. The details are included in the optional ICF.

8.9. Schedule of Activities

For additional information on the timing of the clinical study procedures, please see Section 8.1, "Timing of Assessments".

8.9.1. Regular Schedule of Activities

EVENT	SCREENING PERIOD		TREATMENT PERIOD							FOLLOW-UP PERIOD
Study Day (D)/ Week (W)	**S1[a]**	**S2**	**Day 1[b]**	**W4**	**W12 and then every 12 weeks**	**W24 and then every 24 weeks**	**W48 [c] and then every 48 weeks**	**ED**	**EoT[d]**	**4 weeks after last IP dose (EoS)**
	D-28 to D-1			**± 3 days**	**± 7 days**	**± 7 days**	**± 7 days**			**± 3 days**
Informed consent	✓									
TB assessment [e]	✓ [f]						✓		✓	
Sigmoidoscopy [g] including biopsy collection	✓ [h]						✓	✓ [i]		

[a] Screening visit 1 (S1) may occur at the same time as any scheduled visit of the SELECTION-LTE study or as a separate visit.
[b] Screening visit 2 (S2) and the Day 1 visit can occur on the same day or on 2 consecutive days.
[c] After unblinding at the study primary analysis time point, subjects will receive unblinded treatment and the frequency of study visits will be reduced to every 24 weeks with an allowed window of ±10 days (see Section 8.1.4).
[d] In countries where filgotinib becomes commercially available, the study will be terminated for the subjects who have already completed at least 48 weeks of treatment. Subjects will then be requested to attend the EoT visit as soon as possible (see Section 5.1). For the subjects who have not yet completed 48 weeks of treatment when filgotinib becomes commercially available, the Week 48 visit can replace or occur on the same day as the EoT visit. All assessments listed at the EoT visit can be conducted as part of the Week 48 visit; therefore EoT assessments do not need to be repeated.
[e] Subjects who have been previously treated for TB with a complete and adequate course of therapy as per local standard of care and as verified by the investigator and do not need to have yearly QuantiFERON® tests should only be screened for signs and symptoms of reactivation at the time of screening and at visits as indicated in the Schedule of Activities.
[f] Blood sample for QuantiFERON® test, if applicable, at S1 needs to be taken after signing ICF, preferably 4 weeks before Day 1 to obtain the TB assessment result before randomization. An indeterminate result should be repeated once and the second result (if positive or negative) will be accepted. Subjects who had 2 sequential indeterminate QuantiFERON® tests or a positive QuantiFERON® test during any of the visits of the SELECTION-LTE but do not have active or latent TB at the time of screening, as

EVENT	SCREENING PERIOD		TREATMENT PERIOD							FOLLOW-UP PERIOD
Study Day (D)/ Week (W)	**S1[a]**	**S2**	**Day 1[b]**	**W4**	**W12 and then every 12 weeks**	**W24 and then every 24 weeks**	**W48 [c] and then every 48 weeks**	**ED**	**EoT[d]**	**4 weeks after last IP dose (EoS)**
	D-28 to D-1			**± 3 days**	**± 7 days**	**± 7 days**	**± 7 days**			**± 3 days**
Inclusion/exclusion criteria	✓		Prerandom-ization							
Demographics	✓									
Medical history	✓									
Pregnancy test	✓ [j]			✓ [j]	✓ [j]			✓ [j]	✓ [j]	✓ [j]
FSH test [k]	✓									
Physical examination (symptom-directed)		✓[l]		✓	✓			✓	✓	✓
Vital signs		✓[l]		✓	✓			✓	✓	✓
Height	✓									
Weight	✓ [l]			✓	✓			✓	✓	✓

verified by the investigator, or had latent TB and underwent adequate treatment and continued in the SELECTION-LTE, are not required to have a screening QuantiFERON® test. In this case, the subject must be screened for signs and symptoms of TB reactivation.

[g] Sigmoidoscopy during screening, at Week 48 and every 48 weeks thereafter, and ED (if applicable), in fasting condition, as per local guidance. In case of a suspected UC flare, an additional sigmoidoscopy is needed. Two biopsies should be collected during every sigmoidoscopy performed during the study.

[h] Bowel preparation for screening sigmoidoscopy can only start after signing ICF.

[i] Subjects who discontinue the study prior to Week 48 require a sigmoidoscopy at the ED visit.

[j] WOCBP only. Serum pregnancy test during screening; urine dipstick pregnancy test at the Week 4 visit, thereafter at the site every 12 weeks, and in-between every 4 weeks at home (±3 days). If a urine test cannot be confirmed as negative (e.g. an ambiguous result), a serum pregnancy test is required to confirm.

[k] For postmenopausal women only.

[l] Could be taken from SELECTION-LTE. In case assessments listed at S2 are conducted as part of the EoT visit in SELECTION-LTE, the assessments do not need to be repeated and assessment results may be used.

EVENT	SCREENING PERIOD		TREATMENT PERIOD							FOLLOW-UP PERIOD
Study Day (D)/ Week (W)	**S1[a]**	**S2**	**Day 1[b]**	**W4**	**W12 and then every 12 weeks**	**W24 and then every 24 weeks**	**W48 [c] and then every 48 weeks**	**ED**	**EoT[d]**	**4 weeks after last IP dose (EoS)**
	D-28 to D-1			**± 3 days**	**± 7 days**	**± 7 days**	**± 7 days**			**± 3 days**
Hematology		✓ [l, m]		✓	✓			✓	✓	✓
Chemistry		✓ [l, m]		✓	✓			✓	✓	✓
Lipid profile (fasted [n])		✓ [l, m]				✓			✓	
Urine analysis		✓ [l, m]				✓			✓	
HBV DNA monitoring [o]		✓ [l]			✓				✓	
12-lead ECG		✓ [l]					✓		✓	
Serum immunoglobulin		✓ [l]				✓			✓	
CRP		✓ [l]		✓	✓			✓	✓	
Fecal calprotectin [p]	✓ [q]	✓ [l,r]		✓	✓			✓	✓	

[m] Screening clinical laboratory results may only be available after randomization. In that case, these results will be reviewed after randomization and subjects with laboratory results meeting discontinuation criteria, will be discontinued from the study.
[n] Subjects should remain fasted for at least 8 hours, excluding water.
[o] Only subjects with positive HBcAb and HBV DNA <LLOQ in a parent UC study will require ongoing HBV DNA monitoring every 12 weeks during the present study, and after study primary endpoint unblinding every 24 weeks.
[p] Stool samples need to be taken prior to bowel preparation for endoscopy. Stool samples can be collected within 24 hours prior to the visit or during the visit.
[q] FCP should be assessed during screening if the last assessment during SELECTION-LTE was >6 months prior to screening or the most recent value was >250 µg/g.
[r] This FCP assessment should be obtained at the EoT visit in SELECTION-LTE (i.e. performed after the subject is fully eligible to roll over to the present study) and will be the baseline of the present study. In case FCP was not obtained at the EoT visit of SELECTION-LTE, an unscheduled stool sample should be collected within 24 hours prior to or during Day 1 (i.e. predose).

EVENT	SCREENING PERIOD		TREATMENT PERIOD							FOLLOW-UP PERIOD
Study Day (D)/ Week (W)	S1[a]	S2	Day 1[b]	W4	W12 and then every 12 weeks	W24 and then every 24 weeks	W48 [c] and then every 48 weeks	ED	EoT[d]	4 weeks after last IP dose (EoS)
	D-28 to D-1			± 3 days	± 7 days	± 7 days	± 7 days			± 3 days
[redacted]										
e-Diary instruction & review [u]			✓	✓	✓			✓	✓	✓
[redacted]										
modified Mayo Clinical Score[w]	✓						✓	✓		
[redacted]										

[redacted]

[t] For subjects who consent to participate in the optional PK substudy, PK blood samples will be collected either at the Week 4 or Week 12 visit, or if more convenient, at any [redacted]

[u] Training and dispensation of the e-Diary on Day 1; review subject e-Diary and retrain, if necessary, at all subsequent time points; return of e-Diary at EoS (follow-up visit). Subjects will record the following in the e-Diary: stool frequency, rectal bleeding, and normal stool count.

[redacted]

[w] mMCS calculation during screening (baseline value for all subjects), every 48 weeks, and at ED visit (if applicable). Screening mMCS will be calculated using rectal bleeding, stool frequency subscores from SELECTION-LTE during the screening period, and endoscopic subscore from screening sigmoidoscopy. mMCS at other study specified timepoints will be calculated using rectal bleeding, stool frequency, and endoscopic subscores during the present study.

[redacted]

EVENT	SCREENING PERIOD		TREATMENT PERIOD							FOLLOW-UP PERIOD
Study Day (D)/ Week (W)	**S1[a]**	**S2**	**Day 1[b]**	**W4**	**W12 and then every 12 weeks**	**W24 and then every 24 weeks**	**W48 [c] and then every 48 weeks**	**ED**	**EoT[d]**	**4 weeks after last IP dose (EoS)**
	D-28 to D-1			**± 3 days**	**± 7 days**	**± 7 days**	**± 7 days**			**± 3 days**
Randomization [y]			✓							
Dispense IP			✓	✓	✓ [z]					
Review IP compliance				✓	✓			✓	✓	
Concomitant medications	✓ [v]		✓	✓	✓			✓	✓	✓
Dose IP			q.d. throughout the treatment period starting Day 1 [aa]						✓	
AE assessment	✓ [v]		throughout the study [bb]							

AE: adverse event; CRP: C-reactive protein; ECG: electrocardiogram; ED: early discontinuation; EoS: End of Study; EoT: End of Treatment; FSH: follicle stimulating hormone; HBV: hepatitis B virus; [redacted]; IP: investigational product; [redacted]; q.d.: once daily; S1: Screening visit 1; S2: Screening visit 2; TB: tuberculosis; UC: ulcerative colitis.

[y] Randomization only after performing all screening procedures and after completion of the EoT visit in SELECTION-LTE.
[z] Frequency of IP dispensation after study unblinding at the primary analysis time point will be every 24 weeks.
[aa] If on Day 1 the subject has already taken the IP as assigned in the SELECTION-LTE study, the first dose as assigned in this study should be taken on Day 2.
[bb] AEs ongoing at the end of the subject's participation in the SELECTION-LTE study should be recorded as medical history.

8.9.2. Schedule of Activities After Re-escalation

Event	TREATMENT PERIOD					
Study Day (D)/ Week (W)	baseline	W2[a]	W4	W8	W12	After Week 12:
		± 3 days	± 3 days	± 7 days	± 7 days	Continue with the regular Schedule of Activities, starting with assessments of the next 12-weekly visit until end of the study
Physical examination (symptom-directed)	✓		✓	✓	✓	
Vital signs	✓		✓	✓	✓	
Weight	✓		✓	✓	✓	
Hematology	✓		✓	✓	✓	
Chemistry	✓		✓	✓	✓	
Urine pregnancy test [b]	✓		✓	✓	✓	
CRP	✓		✓	✓	✓	
[redacted]						
e-Diary instruction & review	✓	✓	✓	✓	✓	

[a] Phone contact
[b] Only for women of childbearing potential

Event	**TREATMENT PERIOD**					
Study Day (D)/ Week (W)	**baseline**	**W2**[a]	**W4**	**W8**	**W12**	After Week 12:
		± 3 days	**± 3 days**	**± 7 days**	**± 7 days**	
[redacted]						
Dispense IP	✓		✓	✓	✓	12-weekly visit until end of the study
Concomitant medications	✓	✓	✓	✓	✓	
Dose IP	q.d. starting from dispensing of unblinded re-escalated IP [c]					
AE assessments	throughout the study					

AE: adverse event; CRP: C-reactive protein; [redacted] q.d.: once daily.

[c] If the subject has already taken IP on the re-escalation baseline day, the first adjusted dose should be taken on Day 2 of re-escalation.

9. STATISTICAL METHODS

All statistical methods shall be detailed in a statistical analysis plan (SAP). The SAP will be finalized prior to the interim analysis (see Section 9.3.2) and unblinding. All relevant data collected in this clinical study will be documented using summary tables, figures, and subject data listings.

Any deviations from the CSP are to be justified in the SAP.

9.1. Determination of Sample Size

The primary objective is to estimate the difference in remission rates at Week 48 between 200 mg filgotinib q.d. and 100 mg filgotinib q.d. No formal hypothesis testing will be conducted.

The sample size is determined based on the desired level of precision (half width of the 95% CI) of the estimated treatment difference between 200 mg filgotinib q.d. and 100 mg filgotinib q.d. in the percentage of subjects meeting corticosteroid-free[1] mMCS remission criteria at Week 48. The level of precision determines the range in which the treatment difference is estimated to be. This range is expressed in percentage points.

The highest variability in the estimation of the treatment effect (i.e. CI with the lowest precision, or largest width) is observed when the remission rate is 50%. Figure 2 shows the worst-case precision for a range of observed treatment differences when the remission rate is 50% in at least one treatment group for a fixed set of possible sample sizes ranging from 30 subjects to 70 subjects per group (assuming 2 groups of equal size). Continuity-corrected Newcombe confidence limits were used to calculate the precision. The precision is better if the actual observed remission rates differ from 50%. A sample size of 40 subjects per group will guarantee a worst-case precision of maximum 22.5%.

[1] Free of corticosteroids for at least 12 weeks.

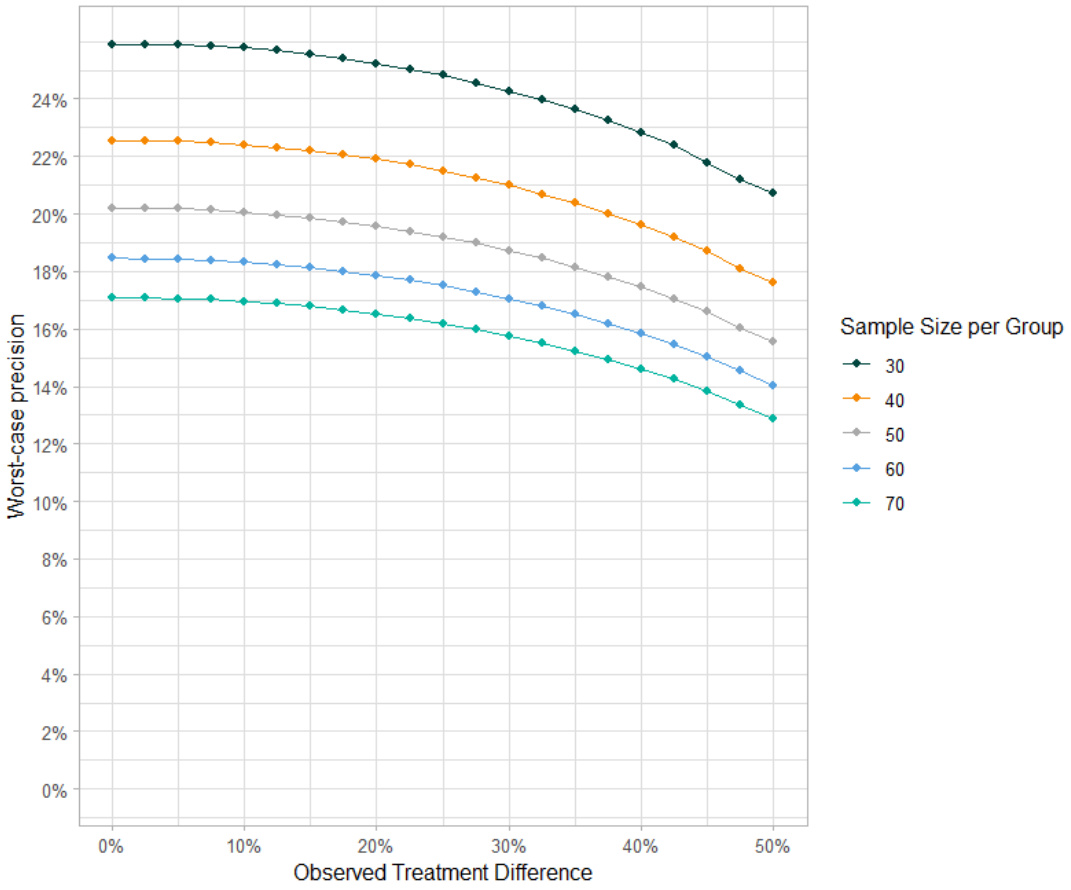


Figure 2: Worst-case Precision for a Range of Sample Sizes Using Newcombe Continuity-corrected CIs With 50% Remission Rate in at Least 1 Group

Figure 3 shows the precision achieved for a range of potential treatment differences for a sample size of 80 subjects. With 40 subjects per group, the estimated half width of the 95% CI for the treatment difference between filgotinib 200 mg q.d. and 100 mg q.d. will lie within 11% and 22.5%.

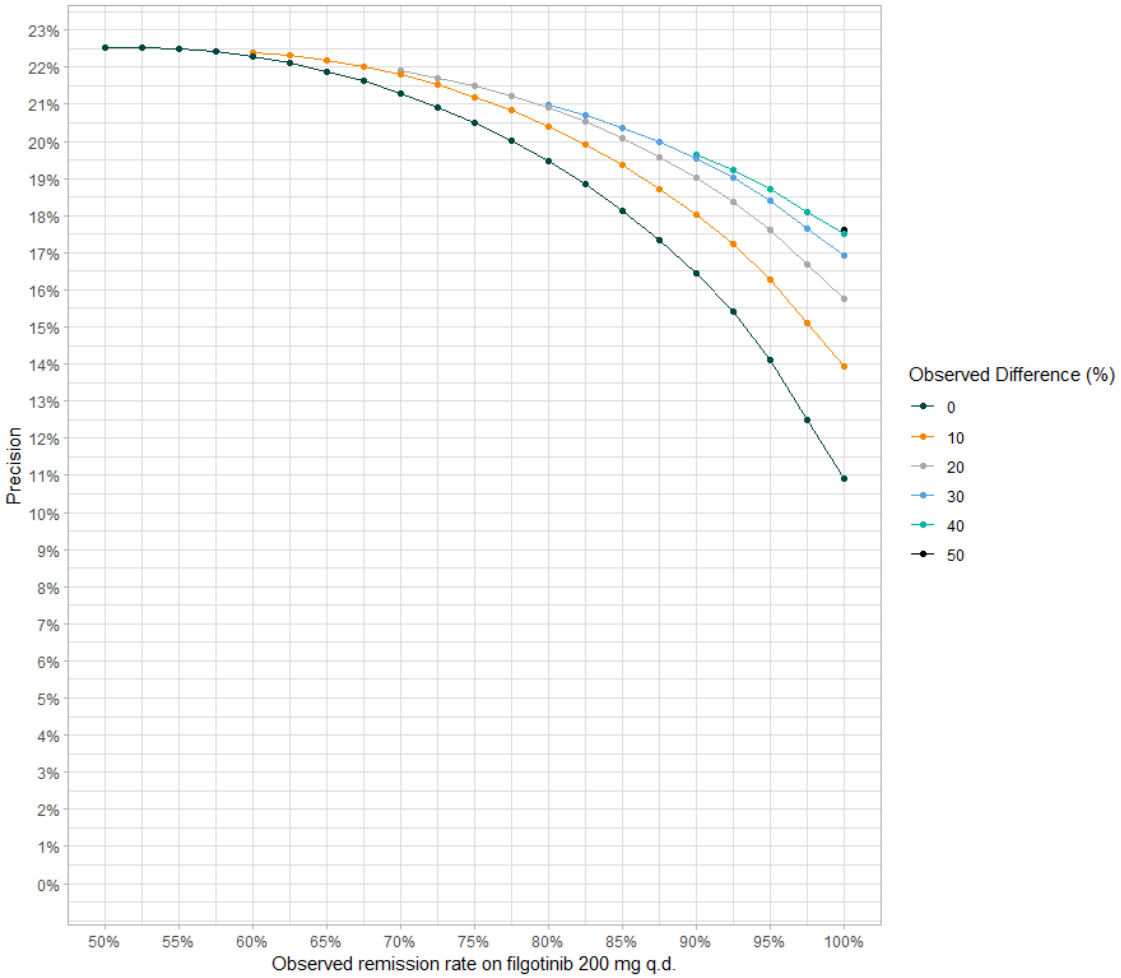


Figure 3: Precision for a Sample Size of 40 Subjects per Group Using Newcombe Continuity-corrected CIs

9.2. Population for Analyses

9.2.1. All Screened Subjects

All subjects who signed and dated an ICF.

9.2.2. All Randomized Subjects

All screened subjects who were randomized into the clinical study.

9.2.3. Full Analysis Set

All randomized subjects who have received at least 1 dose of IP.

9.2.4. Safety Analysis Set

All randomized subjects who received at least 1 dose of IP (same as full analysis set [FAS]).

[redacted]

9.3. Statistical Analyses

9.3.1. General Statistical Considerations

Summary tabulations will be presented and will display the number of observations, mean, standard deviations (SDs) and/or standard error (SE) (as appropriate), median, minimum and maximum (for continuous variables), and the number and percentage per category (for categorical data). In addition to tabulated descriptive statistics, graphical data displays may be used to summarize the data.

Baseline is defined as the last available assessment prior to the first intake of IP in the current study.

9.3.2. Interim Analysis

An interim analysis is planned for this clinical study.

The data collected from this study will be analyzed at 2 time points. An unblinded interim analysis of the clinical study data will be performed by the sponsor on cleaned and locked data, after the last subject completed their Week 48 postbaseline visit or has completed their Week 12 post re-escalation visit (if baseline of re-escalation is within the first 48 weeks of the study), or after the last follow-up of subjects discontinuing prior to Week 48, whichever comes last. This analysis will be the primary analysis. The analyses will be conducted on efficacy data up to Week 48 and safety data up to the data cut-off date, to be able to evaluate the primary, secondary, and exploratory efficacy endpoints, and safety. The subjects and the clinical study team will be unblinded at the time of the Week 48 analysis (for details, refer to Section 6.4.2).

The final analysis will be performed after the global end of the study (i.e. date of the last visit for the last subject in the last country) and the database is cleaned and locked. At the final analysis, all available efficacy and safety data will be summarized using descriptive statistics.

Details on the interim analysis and the final analysis will be further described in the SAP.

9.3.3. Analyses of Demographics and Baseline Characteristics

Subject disposition (including reasons for ED), CSP deviations, demographics, baseline characteristics, medical history, and concomitant therapies will be analyzed descriptively. Baseline will be defined as the last measurement before the first dose of IP in the present study.

9.3.4. Analyses of Efficacy Parameters

No hypothesis testing will be performed. The de-escalation effect will be described using standard descriptive statistics, but also with model-based estimates for the differences with 95% CIs as appropriate. For binary efficacy data, the number and proportion of responders will be presented by treatment group. The continuous data and change from baseline will be summarized descriptively by treatment group.

Besides the efficacy analyses specified in the protocol, additional estimands may be defined and sensitivity analyses performed for the efficacy assessments. More details on efficacy analyses will be described in the SAP.

9.3.4.1. Analysis for Primary Efficacy Endpoint

9.3.4.1.1. Primary Efficacy Estimand

The primary estimand for the primary endpoint targets to estimate the effect of decreasing the filgotinib dose from 200 mg q.d. to 100 mg q.d. versus remaining on 200 mg q.d.on corticosteroid-free mMCS remission without ES-confirmed flare or discontinuation of treatment at Week 48, regardless of treatment interruptions, in subjects who are in stable clinical remission at study entry. The effect size will be estimated using the Mantel-Hanszel method and expressed as a difference in proportions.

The primary estimand for the primary endpoint is described according to the following attributes:

Primary Endpoint	Primary Estimand
Treatment	Filgotinib 100 mg q.d. and filgotinib 200 mg q.d. as randomized.
Population	Subjects who are in stable clinical remission on filgotinib 200 mg q.d. defined through the appropriate inclusion / exclusion criteria.
Variable	Binary corticosteroid-free mMCS remission without ES-confirmed flare and without discontinuation of treatment at Week 48. Corticosteriod-free is defined as free of corticosteroids for at least 12 weeks.
Intercurrent events including strategy for addressing them	– ES-confirmed UC flare: Subjects randomized to the filgotinib 100 mg q.d. or 200 mg q.d. group will be considered as nonresponders for any visit after the re-escalation visit, for flares occurring prior to Week 48 (**Composite strategy**). – Permanent treatment discontinuation: Subjects who discontinue treatment prior to Week 48 will be considered as nonresponders in both the 100 mg q.d. and the 200 mg group q.d. (**Composite strategy**). – Any temporary treatment interruption: Data collected for subjects who temporarily interrupt treatment will be included as reported in the analysis (**Treatment policy strategy**).
Population-level summary	The treatment difference in the percentage of subjects meeting corticosteroid-free mMCS remission criteria between the filgotinib 100 mg q.d. group and 200 mg q.d. group at Week 48.
Estimator	The adjusted proportion difference (filgotinib 200 mg – filgotinib 100 mg) with corresponding 95% CI as calculated by a stratified Mantel-Haenszel test (stratification factor: baseline ES [0 or 1]).

Details on sensitivity analyses for the primary estimand will be described in the SAP.

9.3.4.1.2. Secondary Efficacy Estimand

The secondary estimand for the primary endpoint targets to estimate the effect of decreasing the filgotinib dose from 200 mg q.d. to 100 mg q.d. versus remaining on 200 mg q.d. on corticosteroid-free mMCS remission at Week 48, regardless of flare, permanent treatment discontinuation, or temporary treatment interruptions, in subjects who are in stable clinical remission at study entry. The effect size will be estimated using the Mantel-Hanszel method and expressed as a difference in proportions.

The secondary estimand for the primary endpoint is described according to the following attributes:

Primary Endpoint	Secondary Estimand
Treatment	Filgotinib 100 mg q.d. and filgotinib 200 mg q.d. as randomized.
Population	Subjects who are in stable clinical remission on filgotinib 200 mg q.d. defined through the appropriate inclusion / exclusion criteria.
Variable	Binary corticosteroid-free mMCS remission at Week 48.
Intercurrent events including strategy for addressing them	– ES-confirmed UC flare: Data collected for subjects randomized to the filgotinib 100 mg q.d. or 200 mg q.d. group for any visit after the re-escalation visit will be included in the analyses (**Treatment policy strategy**). – Permanent treatment discontinuation: Data collected for subjects who discontinue treatment prior to Week 48 will be included in the analyses (**Treatment policy strategy**). – Any temporary treatment interruption: Data collected for subjects who temporarily interrupt treatment will be included as reported in the analysis (**Treatment policy strategy**).
Population-level summary	The treatment difference in the percentage of subjects meeting corticosteroid-free mMCS remission criteria between the filgotinib 100 mg q.d. group and 200 mg q.d. group.
Estimator	The adjusted proportion difference (filgotinib 200 mg – filgotinib 100 mg) with corresponding 95% CI as calculated by a stratified Mantel-Haenszel test (stratification factor: baseline ES [0 or 1]).

In both the primary and secondary estimands for the primary endpoint, any subjects with missing data at Week 48 will primarily be considered as nonresponders. Additional sensitivity analyses may be defined in the SAP.

9.3.4.2. Analyses for Secondary Efficacy Endpoints

9.3.4.2.1. Analyses for Continuous Efficacy Data

Analyses for endpoints analyzed at Week 48

The primary estimand for the secondary endpoint that is analyzed at Week 48 (i.e. change from baseline in IBDQ) targets to estimate the effect of decreasing the filgotinib dose from 200 mg q.d. to 100 mg q.d. versus remaining on 200 mg q.d. in subjects who are in stable clinical remission at study entry, regardless of temporary treatment interruptions, under the hypothetical condition that no subject had an ES-confirmed UC flare and all subjects remained on treatment. The effect size will be estimated using an analysis of covariance and expressed as the mean treatment difference.

The primary estimand for the secondary endpoint that is analyzed at Week 48 is described according to the following attributes:

Continuous Endpoint	**Primary Estimand**
Treatment	Filgotinib 100 mg q.d. and filgotinib 200 mg q.d. as randomized.
Population	Subjects who are in stable clinical remission on filgotinib 200 mg q.d. defined through the appropriate inclusion / exclusion criteria.
Variable	Change from baseline in IBDQ at Week 48.
Intercurrent events including strategy for addressing them	– ES-confirmed UC flare: Data collected for subjects randomized to the filgotinib 100 mg q.d. or 200 mg q.d. group for any visit after the re-escalation visit will be considered missing and will be imputed using Last Observation Carried Forward (LOCF), if the flare occurred prior to Week 48 (**Hypothetical strategy**). – Permanent treatment discontinuation: Data collected after permanent treatment discontinuation prior to Week 48 will be considered missing and will be imputed using LOCF (**Hypothetical strategy**). – Any temporary treatment interruption: Data collected for subjects who temporarily interrupt treatment will be included as reported in the analysis (**Treatment policy strategy**).
Population-level summary	The mean treatment difference between the filgotinib 100 mg q.d. group and 200 mg q.d. group at Week 48.
Estimator	The adjusted mean difference between the 2 treatments (filgotinib 200 mg – filgotinib 100 mg) and its corresponding 95% CI will be estimated using an analysis of covariance (ANCOVA) with treatment group and the ES at baseline (0 versus 1) as factors and baseline scores as covariate.

The secondary estimand for the secondary endpoint that is analyzed at Week 48 (i.e. change from baseline in IBDQ) targets to estimate the effect of decreasing the filgotinib dose from 200 mg q.d. to 100 mg q.d. versus remaining on 200 mg q.d. in subjects who are in stable clinical remission at study entry, regardless of flare, permanent treatment discontinuation, or temporary treatment interruptions. The effect size will be estimated using an analysis of covariance and expressed as the mean treatment difference.

The secondary estimand for the secondary endpoint that is analyzed at Week 48 is described according to the following attributes:

Continuous Endpoint	Secondary Estimand
Treatment	Filgotinib 100 mg q.d. and filgotinib 200 mg q.d. as randomized.
Population	Subjects who are in stable clinical remission on filgotinib 200 mg q.d. defined through the appropriate inclusion / exclusion criteria.
Variable	Change from baseline in IBDQ at Week 48.
Intercurrent events including strategy for addressing them	– ES-confirmed UC flare: Data collected for subjects randomized to the filgotinib 100 mg or 200 mg q.d. group for any visit after the re-escalation visit will be included in the analyses (**Treatment policy strategy**). – Permanent treatment discontinuation: Data collected after permanent treatment discontinuation prior to Week 48 will be included in the analyses (**Treatment policy strategy**). – Any temporary treatment interruption: Data collected for subjects who temporarily interrupt treatment will be included as reported in the analysis (**Treatment policy strategy).**
Population-level summary	The mean treatment difference between the filgotinib 100 mg q.d. group and 200 mg q.d. group at Week 48.
Estimator	The adjusted mean difference between the 2 treatments (filgotinib 200 mg – filgotinib 100 mg) and its corresponding 95% CI will be estimated using an analysis of covariance (ANCOVA) with treatment group and the ES at baseline (0 versus 1) as factors and baseline scores as covariate.

In both the primary and secondary estimands for the secondary endpoint that is analyzed at Week 48, any missing data will be handled using LOCF.

Analyses for endpoints analyzed over time up to Week 48

The primary estimand for the secondary endpoints that are measured over time targets to estimate the effect of decreasing the filgotinib dose from 200 mg q.d. to 100 mg q.d. versus remaining on 200 mg q.d. in subjects who are in stable clinical remission at study entry, regardless of temporary treatment interruptions, under the hypothetical condition that no subject had an ES-confirmed UC flare and all subjects remained on treatment. The effect size will be estimated using a linear mixed effects model and expressed as the mean treatment difference.

The primary estimand for the secondary endpoints that are measured over time is described according to the following attributes:

Continuous Endpoint	Primary Estimand
Treatment	Filgotinib 100 mg q.d. and filgotinib 200 mg q.d. as randomized.
Population	Subjects who are in stable clinical remission on filgotinib 200 mg q.d. defined through the appropriate inclusion / exclusion criteria.
Variable	– Change from baseline in CRP up to Week 48. – Change from baseline in FCP up to Week 48.
Intercurrent events including strategy for addressing them	– ES-confirmed UC flare: Data collected for subjects randomized to the filgotinib 100 mg q.d. or 200 mg q.d. group for any visit after the re-escalation visit will be considered missing, if the flare occured prior to Week 48, and will be handled in a linear mixed effects model (**Hypothetical strategy**). – Permanent treatment discontinuation: Data collected after permanent treatment discontinuation prior to Week 48 will be considered missing and will be handled in a linear mixed effects model (**Hypothetical strategy**). – Any temporary treatment interruption: Data collected for subjects who temporarily interrupt treatment will be included as reported in the analysis (**Treatment policy strategy**).
Population-level summary	The mean treatment difference between the filgotinib 100 mg q.d. group and 200 mg q.d. group at all postbaseline visits up to Week 48.
Estimator	The adjusted mean difference between the 2 treatments (filgotinib 200 mg – filgotinib 100 mg) and its corresponding 95% CI will be estimated using a linear mixed effects model with baseline value, treatment group, the ES at baseline (0 versus 1), visit, and treatment group by visit interaction, all as fixed effects, and subject as a random effect.

Details on sensitivity analyses for the primary estimand for the secondary endpoints that are measured over time will be described in the SAP.

The secondary estimand for the secondary endpoints that are measured over time targets to estimate the effect of decreasing the filgotinib dose from 200 mg q.d. to 100 mg q.d. versus remaining on 200 mg q.d. in subjects who are in stable clinical remission at study entry, regardless of flare, permanent treatment discontinuation, or temporary treatment interruptions.

The effect size will be estimated using a linear mixed effects model and expressed as the mean treatment difference.

The secondary estimand for the secondary endpoints that are measured over time is described according to the following attributes:

Continuous Endpoint	**Secondary Estimand**
Treatment	Filgotinib 100 mg q.d. and filgotinib 200 mg q.d. as randomized.
Population	Subjects who are in stable clinical remission on filgotinib 200 mg q.d. defined through the appropriate inclusion / exclusion criteria.
Variable	– Change from baseline in CRP up to Week 48. – Change from baseline in FCP up to Week 48.
Intercurrent events including strategy for addressing them	– ES-confirmed UC flare: Data collected for subjects randomized to the filgotinib 100 mg or 200 mg q.d. group for any visit after the re-escalation visit will be included in the analyses (**Treatment policy strategy**). – Permanent treatment discontinuation: Data collected after permanent treatment discontinuation prior to Week 48 will be included in the analyses (**Treatment policy strategy**). – Any temporary treatment interruption: Data collected for subjects who temporarily interrupt treatment will be included as reported in the analysis (**Treatment policy strategy**).
Population-level summary	The mean treatment difference between the filgotinib 100 mg q.d. group and 200 mg q.d. group at all postbaseline visits up to Week 48.
Estimator	The adjusted mean difference between the 2 treatments (filgotinib 200 mg – filgotinib 100 mg) and its corresponding 95% CI will be estimated using a linear mixed effects model with baseline value, treatment group, the ES at baseline (0 versus 1), visit, and treatment group by visit interaction all as fixed effects, and subject as a random effect.

In both the primary and secondary estimands for the secondary endpoints that are measured over time, any missing data will be handled using a linear mixed effects model where missing values are assumed to be missing at random.

9.3.4.2.2. Analyses for Time-to-Event Data

For time-to-event endpoints, the time to occurrence of the first event of interest will be estimated in each treatment group using the Kaplan-Meier method.

The median time-to-event (if reached) will be reported for each treatment group.

The Cox proportional hazards model, stratified by ES (0 or 1), will be used to estimate outcome differences between treatment groups. Hazard ratios and 95% CIs will be provided to quantify the treatment difference.

[redacted] [redacted]

[redacted]

[redacted]

[redacted]

[redacted] [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

9.3.5. Analyses of Safety Data

All safety analyses will be performed using the safety analysis set (Section 9.2.4). All safety data will be summarized descriptively by treatment group according to the filgotinib dosing regimen actually received at randomization.

For the primary safety analysis, any data collected after ES-confirmed UC flare will not be included in the analyses.

For the secondary safety analysis, data will be included regardless of flare.

Additionally, safety data may be analyzed in the subgroup of subjects who are initially assigned to 100 mg filgotinib q.d. and are re-escalated later to 200 mg q.d. in the safety analysis set.

Missing data for safety endpoints will not be imputed.

Clinical safety will be addressed by assessing AEs, laboratory assessments, physical examinations, ECG, and vital signs.

9.3.5.1. Extent of Exposure

A subject's extent of exposure to the IP will be generated from the IP administration page of the CRF. Exposure data will be summarized by treatment group. Duration of exposure to the IP will be expressed as the number of weeks between the first and last dose of IP, inclusive, regardless of temporary interruptions in IP administration, and summarized by treatment group.

9.3.5.2. Adverse Events

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

The following AEs will be considered as treatment-emergent adverse events (TEAEs):

Any AE with an onset date on or after the IP start date and no later than 30 days after last dose of IP, or any worsening of any AE on or after the IP start date.

Summaries (number and percentage of subjects) of TEAEs per subject by SOC and Preferred Term will be provided by treatment group. TEAEs will also be summarized by causal relationship to the IP and severity. In addition, TEAEs leading to treatment interruption or permanent discontinuation of the IP will be summarized and listed. Also, all SAEs, including the non-treatment-emergent SAEs, will be listed.

9.3.5.3. Clinical Laboratory Evaluations

Laboratory assessments will be analyzed descriptively. Changes from baseline and shifts according to normal ranges and/or a laboratory abnormality grading scale will be presented as well. Analyses will be done per treatment group.

9.3.5.4. Vital Signs

Vital signs will be analyzed descriptively. Changes from baseline will be presented as well. Analyses will be done per treatment group.

9.3.5.5. 12-lead Electrocardiogram

A descriptive analysis will be done for the 12-lead ECG. Summary analyses of abnormalities will be presented as well.

[redacted]

9.3.9. Subgroups

Selected efficacy analyses may be repeated for the subgroups by stratification factor ES (0 versus 1).

Other subgroup analysis can be added to the SAP.

9.3.10. Additional Statistical Considerations

Not applicable.

10. DATA MONITORING

10.1. Data Monitoring Committee

In this study subjects will receive the recommended filgotinib dose for UC (approved in EU, UK, and Japan) and/or a lower dose, and in case of flare, subjects will be re-escalated to 200 mg filgotinib q.d. and addition of corticosteroids can be considered. Subjects will be monitored through standard medical and safety monitoring processes. Therefore, no data monitoring committee will be installed.

10.1.1. Cardiovascular Safety Endpoint Adjudication Committee

An independent adjudication committee will be formed to periodically review and adjudicate all potential MACE and thromboembolic events in a blinded manner.

The CVEAC's specific activities will be governed by a mutually agreed charter, which will define the CVEAC's membership, conduct, and meeting schedule.

The following events will be adjudicated and classified by the CVEAC:

- cardiovascular death;
- myocardial infarction;
- stroke;
- arterial thromboembolism;
- venous thromboembolism (e.g. deep venous thrombosis, pulmonary embolism).

Further details will be specified in the CVEAC Charter.

11. SAFETY REPORTING

11.1. Definitions of Adverse Events, Serious Adverse Events, and Special Situations

11.1.1. Adverse Events

An AE is any untoward medical occurrence, new or worsening of any preexisting condition, in a clinical study subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related. AEs may also include pre- or post-treatment complications that occur as a result of CSP-specified procedures, worsening of the targeted disease, overdose, drug abuse/misuse reports, or occupational exposure. Preexisting conditions that increase in severity or change in nature during or as a consequence of participation in the clinical study will also be considered AEs.

11.1.2. Serious Adverse Events

An SAE is defined as an AE that:

- Results in death.
- Is 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).
- Requires in-patient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly / birth defect.
- Is medically significant (medical and scientific judgment should be exercised in deciding whether other situations should be considered serious such as important medical events that might not be immediately life-threatening or result in death or hospitalization but might jeopardize the subject or might require intervention to prevent 1 of the other outcomes listed in the definition above).

11.1.3. Unlisted (Unexpected) Adverse Events/ Reference Safety Information

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

11.1.4. Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Not applicable.

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

Laboratory abnormalities or other abnormal safety assessments (e.g. ECG, radiography, vital signs) without clinical significance based on the investigator's judgment are not considered AEs or SAEs. However, laboratory abnormalities (e.g. clinical chemistry, hematology, and urinalysis) or other abnormal (clinical study-specific) assessments (e.g. ECG, radiography, vital signs) that require medical or surgical intervention, are associated with signs and/or symptoms, and/or lead to IP interruption, modification, or discontinuation must be recorded as an AE or SAE if they meet the definition as described in Sections 11.1.1 and 11.1.2, respectively. If the laboratory abnormality is part of a syndrome, the syndrome or diagnosis is to be reported (e.g. anemia instead of decreased hemoglobin).

Management of clinical and clinically significant laboratory abnormalities is detailed in Appendix 4.

11.1.6. Special Situations

Special situations are situations that have a possible impact on the safe use of the IP. These situations might be or might not be associated with AEs.

- Pregnancy.
- Exposure to IP via breastfeeding.
- Abuse or misuse of IP.
  - Abuse of IP is defined as the persistent or sporadic, intentional excessive use of the IP, which is accompanied by harmful physical or psychological effects.
  - Misuse of IP is defined as a situation where the IP is intentionally and inappropriately used not in accordance with the protocol/patient information.
- Drug interaction with IP.
  - A drug interaction with IP is defined as any drug/drug, drug/food, or drug/device interaction.
- Medication error with IP.
  - A medication error with IP is defined as an unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the subject.
- Overdose with IP.

  An overdose with IP is defined as an accidental or intentional administration of a quantity of the IP given per administration or cumulatively, which is above the maximum recommended dose as per protocol or in the product labeling (as it applies to the daily dose of the subject in question). When applying this definition, clinical judgment should always be applied.
- Occupational exposure to IP.
  - Occupational exposure to IP is defined as an exposure to the IP as a result of one's professional or nonprofessional occupation.
- Unexpected benefit of IP.

- Unexpected benefit of IP is defined as an unintended therapeutic effect where the results are judged to be desirable and beneficial.

– Transmission of infectious agents via the IP.
  - Transmission of infectious agents via the IP is defined as any suspected transmission of an infectious agent through the IP.
– Counterfeit or falsified medicine.
  - Any IP with a false representation of a) its identity, b) its source, or c) its history.
– Product complaint or quality defect of IP.
  - Product complaint or quality defect of IP is defined as complaints or defects of the IP arising from potential deviations in the manufacture, packaging, or distribution of the IP.

11.2. Assessment of Adverse Events and Serious Adverse Events

The investigator is responsible for assessing AEs and SAEs for causality and severity. This is the basis for the sponsor's final review and confirmation of accuracy and completeness of event information and causality assessments.

11.2.1. Assessment of Causality

Investigators should use their knowledge of the subject, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an AE is considered to be related to the study drug, indicating "related" or "not related" accordingly. The following guidance must be taken into consideration (see also Table 2):

– Temporal relationship of event onset to the initiation of study drug.
– Course of the event, with special consideration of the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable).
– Known association of the event with the study drug or with similar treatments.
– Known association of the event with the disease under study.
– Presence of risk factors in the subject or use of concomitant medications known to increase the occurrence of the event.
– Presence of non-treatment-related factors that are known to be associated with the occurrence of the event.

Table 2: Causal Attribution Guidance

Is the adverse event suspected to be caused by the study drug on the basis of facts, evidence, science-based rationales, and clinical judgment?	
Related	There is a plausible temporal relationship between the onset of the adverse event and administration of the study drug, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study drug; and/or the adverse event abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge.
Not related	An adverse event will be considered related, unless it fulfills the criteria specified below. Evidence exists that the adverse event has an etiology other than the study drug (e.g. preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of the study drug (e.g. cancer diagnosed 2 days after first dose of study drug).

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

11.2.2. Assessment of Severity

The severity of AEs must be graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. If a CTCAE criterion does not exist, the investigator must 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 AE. For purposes of consistency with the CTCAE, these intensity grades are defined in Table 3.

Table 3: Grading of AE 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[a]
Grade 3	Severe	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[b]
Grade 4	Life-threatening	Urgent intervention indicated
Grade 5	Death	Death-related AE

ADL = Activities of Daily Living.
a Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
b Self-care ADL refers to bathing, dressing, and undressing, feeding self, using the toilet, taking medications, and not bedridden.

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.

Management of clinical and clinically significant laboratory abnormalities is detailed in Appendix 4. This is upon the investigator's assessment.

If there is a worsening of an AE, it must be recorded.

11.3. Instructions for Reporting Adverse Events, Serious Adverse Events, Pregnancies, and Other Special Situations

11.3.1. Adverse Events

The AE reporting period for safety surveillance begins when the subject signs the ICF and ends at the subject's last scheduled visit. In this period, all new AEs, regardless of cause or relationship, derived by spontaneous, unsolicited reports of subjects, by observation, and by routine open questioning (such as "How do you feel?") need to be recorded in the source and in the CRF.

In case an AE is ongoing at the time of the last follow-up visit, the investigator needs to follow-up on the subject until AE resolution or reasonable stabilization and to document in the subject's source documentation. No related updates or additional data on the AE should be reported in the CRF.

If a subject is documented as lost to follow-up, ongoing/unknown outcome AEs will not be followed-up.

If the AE meets the criteria for seriousness, the SAE must be reported as indicated in Section 11.3.2.

11.3.2. Serious Adverse Events

Subjects experiencing an SAE or an emergency situation will be examined by a physician as soon as possible. The subject will remain under observation as long as medically indicated. Appropriate additional examinations will be performed until all parameters return to normal or are otherwise explained or stable.

All SAEs, whether or not deemed IP-related, must be recorded in the eCRF database and from there transmitted to the sponsor. The investigator must report each SAE immediately, and under no circumstances should this exceed 24 hours following the knowledge of the SAE, as indicated on page 2 under "Emergency Contact Information".

If for any reason it is not possible to record SAE information electronically, i.e. the eCRF database is not functioning, record the SAE on a SAE form and submit the SAE within 24 hours by e-mail to: [redacted]

Every SAE reported via form must be transcribed into the eCRF database as soon as possible according to instructions in the eCRF completion guidelines.

The SAE reporting must at least contain identifiers of the subject and the reporter, SAE term and statement of relatedness to the IP, and at a later stage if not yet available within 24 hours, the form needs to be completed with a clearly written narrative describing signs, symptoms, and treatment of the event, diagnostic procedures, as well as any relevant laboratory data and any sequelae.

Follow-up and outcomes must be reported and documented in the source documents for all subjects that experience an SAE.

Copies of additional laboratory tests, consultation reports, post-mortem reports, hospital case reports, autopsy reports, and other documents must be sent when requested and available. Only subject identifiers (subject number) should appear on the copies, and all names and initials must be blackened and rendered illegible. Follow-up reports relative to the subject's subsequent course must be submitted until the event has subsided or, in case of permanent impairment, until the condition stabilizes.

Any SAEs that occur after the post-treatment follow-up visit but within 30 days of the last dose of IP(s), regardless of causality, should also be reported (Emergency Contact Information on page 2) but not entered in the source. Investigators are not obligated to actively seek SAEs after the CSP-defined follow-up period. However, if the investigator is informed about an SAE that occurs at any time after the subjects' post-treatment follow-up visit and the event is deemed relevant to the use of IP(s), he/she must promptly document and report the event to the sponsor by using the SAE form.

11.3.3. Pregnancy

All initial reports of pregnancy in female subjects included in the clinical study must be recorded and documented in the source documents and on the pregnancy form. The investigator must report each pregnancy immediately, and under no circumstances should this exceed 24 hours following the knowledge of the pregnancy, as indicated on page 2 under "Emergency Contact Information".

All pregnancies should be followed-up until delivery or pregnancy interruption. The investigator will contact the subject after acquiring consent, at the expected time of delivery for follow-up and for information regarding the outcome of the newborn. Abnormal pregnancy and/or abnormal newborn outcomes are considered SAEs and must be reported using the SAE form.

11.3.4. Reporting of Special Situations (Other Than Pregnancy) With or Without Associated Adverse Events

In case a special situation is not associated with an AE, the special situation must be reported within 24 hours by using the Special Situations form as indicated on page 2 under "Emergency Contact Information".

In case a special situation is associated with an AE, the special situation must be reported within 24 hours by using the Special Situations form and the associated AE must be reported as specified in Section 11.3.1.

In case a special situation is associated with an SAE, the special situation must be reported within 24 hours by using the SAE form (and not the Special Situations form) and the associated SAE must be reported as specified in Section 11.3.2.

11.4. Sponsor Reporting Requirements

Depending on relevant local legislation or regulations the sponsor may be required to expedite to worldwide regulatory agencies reports of SAEs and serious adverse drug reactions or SUSARs. The sponsor or a specified designee will notify worldwide regulatory authorities and the relevant IEC/IRB in concerned Member States of applicable SUSARs as outlined in current regulations.

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

All concerned investigators will receive a safety letter notifying them of relevant SUSAR reports associated with any IP(s). The investigator must notify the IEC/IRB of SUSAR reports as soon as is practical, where this is required by local regulatory authorities, and in accordance with the local institutional policy.

12. SPONSOR'S AND INVESTIGATOR'S RESPONSIBILITIES

This clinical study will be conducted in compliance with this CSP, the current ICH Guideline E6 "Good Clinical Practice (GCP)", and applicable local ethical and legal requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of clinical study subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki (1996 and successive amendments), and that the clinical study data are credible.

The contact details of each third party vendor involved in the conduct of the clinical trial will be available in the investigator's (as appropriate) and sponsor's files.

12.1. Sponsor's Responsibilities

12.1.1. Regulatory Authority Approval

Prior to clinical study start, this CSP together with all relevant documentation needs to be submitted to the respective regulatory authorities for review and approval in compliance with current regulations before the study can start.

12.1.2. Clinical Study Closure Considerations

The sponsor reserves the right to close the site or end the clinical study at any time for any reason. In case of an early termination of the clinical study, i.e. premature end of the study for any reason before the conditions specified in the protocol are complied with, or temporary halt by

the sponsor, the IEC/IRB, and regulatory authorities will be notified according to local requirements, unless more strict requirements are specified by IEC/IRB and/or regulatory authorities. The notification will include a detailed written explanation of the reasons for the termination/halt.

Reasons for the closure of a site may include, but are not limited to:

- successful completion of the clinical study at the site;
- the overall required number of subjects for the clinical study has been recruited;
- failure of the investigator to comply with the CSP, ICH-GCP guidelines, or local requirements;
- inadequate recruitment of subjects by the investigator.

Reasons for early termination of a clinical study by the sponsor may include, but are not limited to:

- safety concerns;
- sufficient data suggesting lack of efficacy.

The end of clinical study declaration will be submitted to the regulatory authorities and IEC/IRB after the complete clinical study has ended in all participating sites, in all countries. This notification will also be submitted according to local requirements of the end of the clinical study in a given country/member state.

12.1.3. Indemnification

Under the conditions of a contract concluded between investigator, site, and sponsor or designee, which shall prevail, the sponsor shall, except in case of gross negligence or willful misconduct, indemnify and hold harmless the investigator and his/her medical staff from any claim arising from the clinical study activities carried out in compliance with the CSP, sponsor's instructions, and applicable local regulations.

The investigator must notify the sponsor immediately upon notice of any claims or lawsuits.

12.1.4. Insurance

The sponsor shall maintain insurance coverage that is sufficient to cover its obligations and that is consistent with human clinical study local regulations. Provided that the subject has been treated according to the CSP and sponsor's instructions, any injury caused to a subject, which is the direct result of his/her participation to the clinical study shall be covered by the sponsor's insurance, except in case of gross negligence or willful misconduct by the investigator.

12.1.5. Archiving

The sponsor will archive the content of the trial master file (TMF) for at least 25 years after the end of the clinical study.

12.2. Reporting

Where required by IEC/IRB per local requirements, at least once a year, the investigator will provide the IEC/IRB with a progress report to allow review of the clinical study (see Section 12.7.1).

The results of the unblinded Week 48 interim analyses (primary, secondary, and exploratory efficacy endpoint results up to Week 48 and safety up to the data cut-off date) will be reported by the sponsor in an interim clinical study report. At the global end of the clinical study, the final results of the clinical study will be reported in a final clinical study report by the sponsor. A summary or full report, depending on the requirements, will be provided by the sponsor to the investigators, to the relevant regulatory authorities, and IECs/IRBs (if required by the applicable regulatory requirements) within 1 year after the end of the clinical study.

12.3. Publication

It is understood by the investigator that the sponsor shall be free to use the compound-related information, which is generated during the clinical study and may disclose it to other clinical investigators and to regulatory agencies. As a consequence, the investigator agrees to provide all clinical study results and data generated during this clinical study to the sponsor.

The investigator shall not be authorized to submit the results of this clinical study and any data for public disclosure (e.g. publication or presentation) without the prior written approval of the sponsor, which shall not be unreasonably withheld.

However, it is understood and agreed by the investigators that their results and/or findings shall not be authorized for publication prior to sponsor's publication of the overall clinical study results. The investigator agrees that prior to the publication of any results, he/she shall provide the sponsor with a draft copy of the intended publication. The sponsor shall have the right to review it and to make any comments. In accordance with generally accepted scientific collaboration principles, co-authorship with any staff member sponsor involved in the clinical study, will be discussed and mutually agreed upon before submission of any manuscript to a publisher.

12.4. Investigator's Responsibilities

12.4.1. Financial Disclosure

The disclosed financial interest of any (sub-)investigator participating in this study must be collected before the investigator is permitted to begin participation in the study. The investigator is required to promptly update this information if any relevant changes occur during the course of the study and for 1 year following the completion of the study.

Any (sub)-investigator participating in the study must complete the Financial Disclosure Form prior to site activation.

12.4.2. Source Data and Data Capture

The nature and location of all source documents need to be identified and documented to ensure that all sources of original data required to complete the CRF are known and are accessible for verification by the monitor.

Data transferred from third partners (e.g. laboratory data) may be directly captured as source data. The CRF completion guidelines will be provided to each site.

It is required that the author of an entry in the source documents is identifiable. Following ICH-GCP guidelines, direct access to sponsor's representatives to source documents must be granted for the purpose of verifying that the data recorded on the CRF are consistent with the original source data.

12.4.3. Archiving

Unless local legislation requires archiving for a longer period, the investigator shall archive the content of the clinical investigator site file for at least 25 years after the end of the clinical study. However, the medical files of subjects shall be archived in accordance with national law.

The investigator should take measures to prevent accidental or premature destruction of these documents.

Under no circumstance shall the investigator relocate or dispose any clinical study documents before having obtained a written approval of the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this clinical study, the investigator must permit access to such reports. The subject is granting access to his/her source data by signing the ICF.

Any difficulty in storing original documents must be discussed with the monitor prior to the initiation of the clinical study.

12.4.4. Participation Cards

If the subjects are not under 24-hour supervision of the investigator or site staff, they must be provided with a subject participation card indicating the investigator's name, and the site's 24-hour emergency contact number. The subjects should be advised to keep the participation card with them at all times.

12.5. Confidentiality

The subject will receive all information as required by the EU General Data Protection Regulation (i.e. the identity and contact details of the controller, the contact details of the data protection officer, the clinical research purposes, the legal basis for the processing, the recipients of the personal data, the transfer of the personal data to third countries and respective safeguards, the retention periods, the fair processing of his data, and all his/her data subject's rights) or by any other (locally) applicable requirements and/or regulations. All details are listed in the ICF.

All information concerning the product and the sponsor's operations (such as patent applications, formulae, manufacturing processes, basic scientific data, or formulation information supplied to the investigator by the sponsor and not previously published) is considered confidential and must not be disclosed by the investigator to any third party without the sponsor's prior written approval. The investigator agrees to use this information only in accomplishing the clinical study and will not use it for other purposes.

In order to permit easy identification of the individual subject during and after the clinical study, the investigator is responsible for keeping an updated Subject Identification Code List. The monitor will review this document for completeness. However, the investigator must guarantee the subject's anonymity will be maintained. Therefore, in order to ensure subject confidentiality, the Subject Identification Code List must remain at the site and no copy will be made.

12.6. Protection of Personal Data

The subject will receive all information as required by the EU General Data Protection Regulation (i.e. the identity and contact details of the controller, the contact details of the data protection officer, the clinical research purposes, the legal basis for the processing, the recipients of the personal data, the transfer of the personal data to third countries and respective safeguards, the retention periods, the fair processing of his data, and all his/her data subject's rights) and/ or by any other (locally) applicable requirements and/or regulations. All required information is listed in the ICF.

The sponsor is considered as a controller in respect to the personal data of the study subjects that are collected in connection with the study, and shall act in accordance with the relevant data protection laws in relation to the collection and processing of that personal data. The personal data of the subjects will be pseudonymized as indicated above (see Section 12.5), making sure that the identity of the subjects is not disclosed. Personal data such as health status, year of birth, age, and demographics (sex, race, and ethnicity) will be collected. Samples for safety analysis may include subject number, panel number, sex, year of birth. Samples collected for bioanalysis will contain either subject number or panel number. All other personal data will be kept at the site. The study subject's personal data shall be collected and processed for the purposes (and the corresponding legal bases) as described in the ICF. The study subjects' personal data might be processed for such purposes by other parties including: the sponsor's affiliates and licensing partners, its business partners, processors, regulatory agencies and other health authorities, and IECs. The study subjects' data may also be further de-identified and added to research databases and used in the future by the sponsor and its affiliates for certain additional statistical, clinical research purposes.

Personal data is securely protected to prevent accidental or unlawful destruction, unauthorized access, disclosure, alteration, or loss of the personal data. Access to personal data is restricted so that only staff members who are required to access personal data as part of their job role can do so. All staff members who access personal data are bound by a duty of confidentiality.

Technical requirements for the electronic storage and use of data by the sponsor and vendor are as follows:

- All personal data is pseudonomized by assigning a code to the subject, which replaces his or her name.
- All personal data is stored on password-protected computers.
- Computers storing electronic personal data are protected by antivirus software and the network on which computers are linked is protected by industry-grade firewalls.
- Off-site staff members can only access networked computers through a virtual private network (VPN).
- Electronic access to data is limited according to users' roles and tracked (Privileged Access Management).
- Regular audits of certain applications and systems.
- Incident management system and patch management is in place.
- All data is backed up regularly and stored in a protected location.
- Regular inspections of emergency equipments.
- Encryption of the computer, firewalls, and anti-malware software(s).

Organizational arrangements are as follows:

- The premises are secured by key-card access.
- Data Protection Policies Framework is adopted (Global Internal Data Protection Policy, ICF including a Privacy Statement, Privacy Statement toward Staff Members and External Contractors, Electronic Communication Policy; etc.).
- Data Protection Procedures are in place (Data Subject Rights Procedures, Maintenance of Record of Processing Activities Procedure, etc.).
- Homeworking Policy and Password Policy.
- Physical files containing personal data are stored within locked cabinets that can only be accessed by authorized personnel.
- Sponsor due diligence and assessment of third parties is accomplished via a Vendor Risk Assessment process before entering into any contractual relationship.
- Data security and/or confidentiality provisions are included in Data Processing Agreements and Data Sharing Agreements with pre-assessed third parties.
- Documented back-up and disaster recovery procedures are in place.
- Internal audit and compliance functions of the sponsor provide regulatory oversight.
- Additionally, the sponsor's staff members - contractually bound by a duty of confidentiality - receive regular awareness training in this matter.

Concerning Personal Data Security Breach Management, the sponsor has a comprehensive process in place for identifying, assessing, resolving, and reporting any potential personal data breach. All staff are trained in the identification of potential personal breaches. Potential breaches are managed by appropriately trained personnel in accordance with SOPs. After robust assessment, data breaches deemed serious will be reported to the supervisory authority not later than 72 hours and/or to study subjects without undue delay after having become aware of it.

12.7. Ethical Considerations

12.7.1. Independent Ethics Committee / Institutional Review Board

This clinical study can only be undertaken after IEC/IRB approval of this CSP together with all relevant documentation. This approval document must be dated and clearly identify the clinical study and the related clinical study documents being approved, including the subject compensation programs, if applicable.

During the course of the clinical study, at least the following documents have to be submitted to the IEC/IRB, per local requirements:

- changes to the IB;
- reports of AEs that are serious, unlisted, and associated with the IP (in compliance with IEC/IRB, per local requirements);
- CSP amendments;
- ICF amendments.

The IEC/IRB is responsible for continuous review of the clinical study. Where required by IEC/IRB, per local requirements, at least once a year the investigator will provide the IEC/IRB with a progress report to allow review of the clinical study. Additional progress reports should be provided according to local legal requirements. These requests and (re-)approvals, if applicable, should be documented in writing.

12.7.2. Informed Consent

The investigator or designated personnel must explain the clinical study and the implications of participation (e.g. objectives, methods, anticipated benefits, possible risks) to potential subjects according to applicable regulations prior to any clinical study-related activity. Subjects will be informed that their participation is voluntary and that they may withdraw from the clinical study at any time. They will be informed that choosing not to participate or to withdraw from the clinical study will not have an impact on the care the subject will receive for the treatment of their disease.

The subject will be given sufficient time to read the ICF and to ask additional questions. After this explanation and before entry in the clinical study, the subject's consent must be appropriately recorded by means of the subject's personally dated signature and by the dated signature of the investigator or their authorized delegate. After having obtained the consent, a copy of the signed and dated ICF must be given to the subject.

If new information becomes available relevant to the subject's willingness to participate in the clinical study, the subject will be informed in a timely manner by means of an amended ICF. This amended ICF will be signed and dated by the subject and the investigator to document the willingness of the subject to continue with the clinical study.

This signed and dated amended version will be filed together with the initially signed and dated ICF.

[redacted]

12.8. Data Quality Control/Assurance

12.8.1. Monitoring

Data quality will be assured through monitoring, medical monitoring, and other relevant activities as described in the study plans available in the TMF. This clinical study will be monitored by sponsor representatives according to their current SOPs.

To guarantee adequate protection of the subjects and to guarantee the quality of the data, the sponsor will ensure oversight of any clinical study-related duties and functions carried out on its behalf, including clinical study-related duties and functions that are subcontracted to another party by the sponsor's contracted CRO(s).

A Risk Management process is in place that includes risk identification, risk analysis, risk evaluation, risk control, risk communication, risk review, and risk reporting. A Risk Management Tool is prepared for the study that evaluates potential risks and defines Quality Tolerance Limits in relation to rights, safety, and well-being of the study subjects as well as the data quality. Risks are considered at study level (e.g. personnel, vendors, IP, study design, data collection, and recording).

12.8.2. Audit and Inspection

To ensure compliance with relevant regulations, an independent quality assurance representative, regulatory authorities, and/or IECs/IRBs may review this clinical study. This implies that auditors/inspectors will have the right to inspect the site(s) at any time during and/or after completion of the clinical study and will have access to the data generated during the clinical study, source documents, and subject's files. By participating in this clinical study, investigators agree to this requirement.

13. REFERENCES

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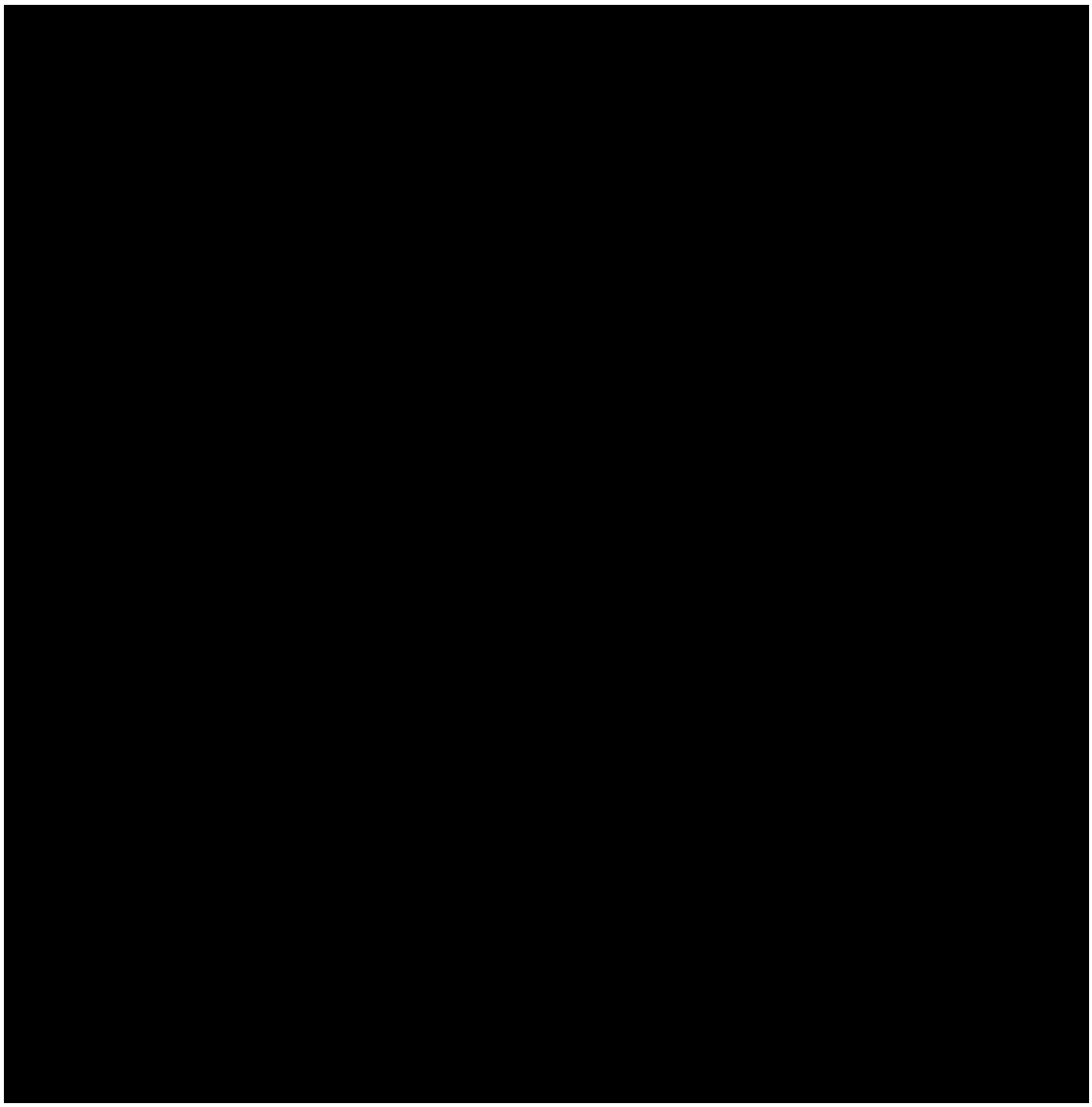
14. APPENDICES

[redacted]



[redacted]

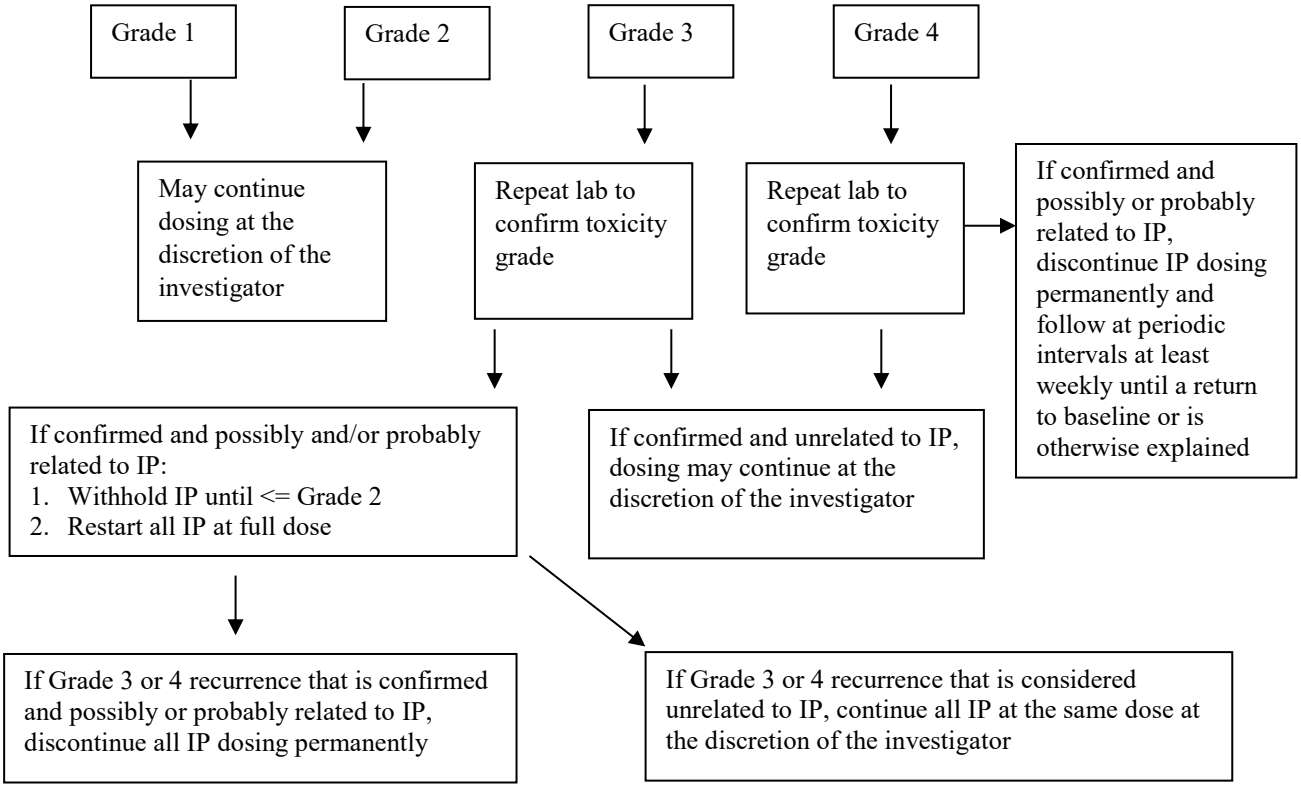
Appendix 2: Mayo Scoring System for Assessment of Ulcerative Colitis Activity

Stool Frequency–Each subject serves as his or her own control to establish the degree of abnormality of the stool frequency	□ 0	Normal number of stools for subject
	□ 1	1 to 2 stools per day more than normal
	□ 2	3 to 4 stools more than normal
	□ 3	≥5 stools more than normal
Rectal Bleeding–The daily bleeding score represents the most severe bleeding of the day	□ 0	No blood seen
	□ 1	Streaks of blood with stool less than half the time
	□ 2	Obvious blood with stool half or more than half of the time
	□ 3	Blood alone passes
Endoscopic findings–Assessed by local reader (include only for MCS assessment)	□ 0	Normal or inactive disease
	□ 1	Mild disease (erythema, decreased vascular pattern)
	□ 2	Moderate disease (marked erythema, lack of vascular pattern, friability, erosions)
	□ 3	Severe disease (spontaneous bleeding, ulceration)
Physician's Global Assessment–The physician's global assessment acknowledges the 3 other criteria, the subject's daily recollection of abdominal discomfort and general sense of well-being, and other observation, such as physical findings and the subject's performance status	□ 0	Normal
	□ 1	Mild disease
	□ 2	Moderate disease
	□ 3	Severe disease

Appendix 3: Clinical Laboratory Assessments

Hematology	Chemistry	Urinalysis	Other
Hematocrit Hemoglobin Platelet count Red blood cell (RBC) count White blood cell (WBC) count Differentials (absolute and percentage), including: Lymphocytes Monocytes Neutrophils Eosinophils Basophils Reticulocyte count Mean corpuscular volume (MCV)	Alkaline phosphatase Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Total bilirubin Direct and indirect bilirubin Total protein Albumin Bicarbonate Blood urea nitrogen Calcium Chloride Serum creatinine Creatinine clearance (CrCl) Cockcroft-Gault formula Glucose Phosphorus Magnesium Potassium Sodium Creatine phosphokinase (CPK) **Lipids (fasted)** Triglycerides Cholesterol and its subfractions (high-density lipoprotein [HDL] and low-density lipoprotein [LDL])	Appearance: Blood Color Glucose Leukocyte esterase pH Protein Urobilinogen **Pregnancy** In females of childbearing potential: Serum pregnancy Urine pregnancy In postmenopausal females: Serum FSH test at screening	C-reactive protein (CRP) Fecal (stool) Calprotectin Bacterial stool culture *Clostridium difficile* toxin Ova and parasites Serum biomarkers Serum immunoglobulins QuantiFERON® (or centrally reported equivalent assay) Prothrombin time (PT) Partial Thromboplastin time (PTT) International Normalized Ratio (INR) HBV DNA

Appendix 4: Management of Clinical and Laboratory Adverse Events



SIGNATURE PAGE – SPONSOR

Study Title:	A randomized, double-blind, controlled, multi-center study to evaluate the efficacy and safety of dose de-escalation of orally administered filgotinib in subjects with ulcerative colitis in clinical remission		
CSP Version:	2.0	Date:	17-Mar-2023
Amendment:	1		

This CSP has been reviewed and approved by the sponsor to ensure compliance with this CSP, the current ICH-GCP Guideline E6, and applicable local ethical and legal requirements.

An electronic signature for the sponsor is provided at the end of the document.

Medical Leader	Signature	Date

SIGNATURE PAGE – INVESTIGATOR

Study Title:	A randomized, double-blind, controlled, multi-center study to evaluate the efficacy and safety of dose de-escalation of orally administered filgotinib in subjects with ulcerative colitis in clinical remission		
CSP Version:	2.0	Date:	17-Mar 2023
Amendment:	1		

I, the undersigned, have read this CSP and will conduct the study as described in compliance with this CSP, the current ICH-GCP Guideline E6, and applicable local ethical and legal requirements.

Investigator Name	Signature	Date

Signature Page for glpg0634-cl-341-protocol-amend1 20975

Approval	[redacted] Associate Medical Director Clinical Development 21-Mar-2023 11:28:17 GMT+0000

Signature Page for glpg0634-cl-341-protocol-amend143952_37012_115917