Galápagos
Pioneering for patients

STATISTICAL ANALYSIS PLAN

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

Development Phase:	3		
Status:	Final		
Version:	2.0	Date:	5-Jan-2024
EudraCT:	2022-000719-30	IND:	129647
Sponsor:	Galapagos NV, Generaal De Wittelaan L11 A3, 2800 Mechelen, Belgium		
Biostatistician:	[redacted]		
Medical Leader:	[redacted]		

Confidentiality Statement

TABLE OF CONTENTS

VERSION HISTORY

SAP Amendment #	Date	Description of changes
SAP Version 1.0	13-Oct-2023	Initial version
SAP Version 2.0	05-Jan-2024	Status corrected from Draft to Final (administrative change only)

LIST OF ABBREVIATIONS

AE	adverse event
AEI	adverse event of interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical
BMI	body mass index
CI	confidence interval
CSP	clinical study protocol
CRF	case report form
CRP	C-reactive protein
CSR	clinical study report
ECG	Electrocardiogram
ED	early discontinuation
EMA	European Medicines Agency
ES	endoscopic score
FAS	full analysis set
FCP	fecal calprotectin
H	high, above the upper limit of the normal range
IBDQ	inflammatory Bowel Disease Questionnaire
ICF	informed consent form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
INF	infinity
L	low, below the lower limit of the normal range
LLN	lower limit of the normal range
MCS	Mayo Clinical Score
mMCS	modified Mayo Clinical Score
MedDRA	medical dictionary for regulatory activities
N	normal, within the limits of the normal range
PGA	Physician's Global Assessment
[redacted]	[redacted]
pMCS	partial Mayo Clinical Score
PRO2	patient-reported outcome based on 2 items

PT	preferred term
q.d.	once daily (quaque die)
RTSM	randomization and trial supply management
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SDTM	study data tabulation model
SE	standard error
SOC	system organ class
SSG	statistical support group
TEAE	treatment-emergent adverse event
TLF	tables, listings and figures
UC	ulcerative colitis
ULN	upper limit of the normal range
WHO	World Health Organization

Definition of Terms

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

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical analyses of study GLPG0634-CL-341 (CAPYBARA), a Phase 3b dose de-escalation study.

Due to the limited number of patients rolled over into this study, the number of patients needed to ensure adequate precision in the estimations and to draw meaningful conclusions did not materialize, leading to the decision to prematurely terminate the CAPYBARA study. This decision was taken after consultation with the European Medicines Agency (EMA).

In light of the above, it was decided to limit the analyses to the primary, key secondary and safety endpoints. Since the study was stopped prior to subjects reaching the primary analysis timepoint, the presented results will also be limited to observed data and may deviate from the planned analyses.

The results will be presented in an abbreviated clinical study report (CSR).

General mock tables, listings and figures (TLFs) and TLF programming rules will be presented in the Mock Standards Phase 2/3 document. Study-specific mock TLFs and TLF programming rules will be presented in the Programming Requirements Document.

The statistical analysis will process and present the results following the International Council for Harmonization (ICH) standards, particularly the ICH-E3, ICH-E6, ICH-E9, ICH-R9 (R1) and ICH-E14 guidelines.

2. STUDY DESIGN AND OBJECTIVES

2.1. Study Objectives & 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[a] clinical remission based on modified Mayo Clinical Score (mMCS)[b] at Week 48.

[a] Free of corticosteroids for at least 12 weeks.
[b] mMCS of ≤2 points, with endoscopic subscore of ≤1, stool frequency subscore of ≤1, and a rectal bleeding subscore of 0.

Objectives	Endpoints
Secondary	
To evaluate the effect of dose de-escalation of filgotinib on time to flare.	– Time to PRO2 flare[c]. – 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.
[redacted]	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[c] 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.

[redacted]

2.2. 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 are stratified according to ES (0 or 1) at baseline to ensure treatment balance in each stratum.

The study consists 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), 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.
- 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.

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. An ES-confirmed UC flare should be reported as an adverse event (AE).

Re-escalation

- 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.
- If subject improvement is sufficient in the opinion of the investigator, the subject will restart the regular Schedule of Activities, 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.

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. 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.

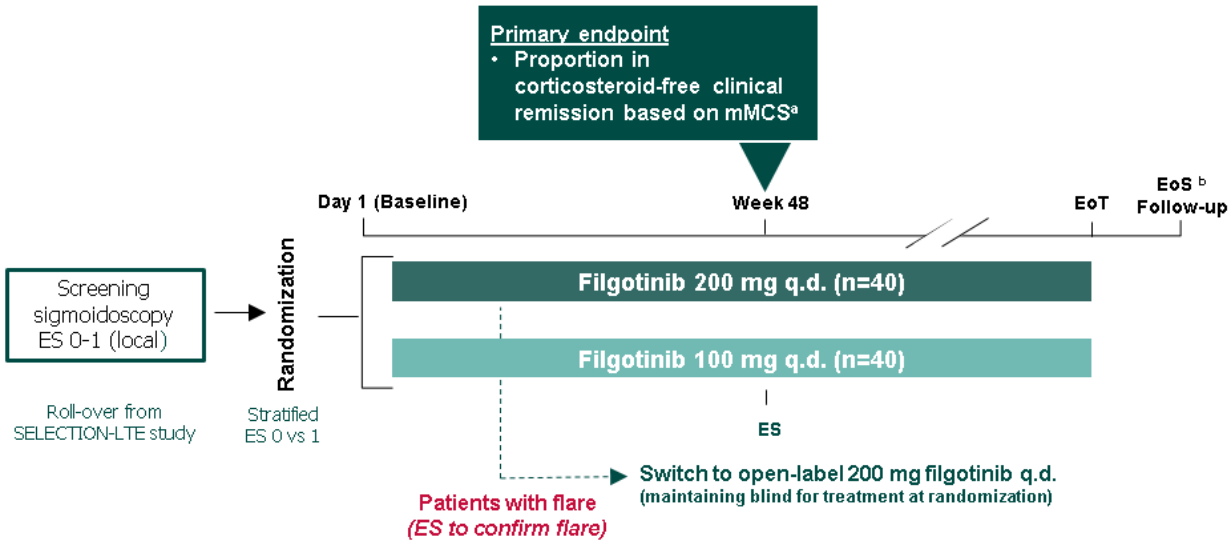


Figure 1: Schematic Diagram

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.

2.3. Clinical Study Protocol (CSP) and CSP Amendments

This SAP was based on the protocol version 2.0 / Amendment 1, dated 17-mar-2023.

2.4. Schedule of Assessments

2.4.1. 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 CSP 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 CSP 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 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.

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]			✓	✓			✓	✓	✓
Hematology		✓ [l, m]		✓	✓			✓	✓	✓

[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.
[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.

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**
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]		✓	✓			✓	✓	
[redacted]										

[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).
[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**
[redacted]										
e-Diary instruction & review [u]			✓	✓	✓			✓	✓	✓
[redacted]										
modified Mayo Clinical Score[w]	✓						✓	✓		
[redacted]										
Randomization [y]			✓							
Dispense IP			✓	✓	✓ [z]					
Review IP compliance				✓	✓			✓	✓	

[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]

[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.

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**
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.

[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.

2.4.2. Schedule of Activities After Re-escalation

Event	TREATMENT PERIOD					
Study Day (D)/ Week (W)	baseline	W2[a]	W4	W8	W12	
		± 3 days	± 3 days	± 7 days	± 7 days	After Week 12: 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	✓	✓	✓	✓	✓	
[redacted]						

[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**	
Dispense IP	✓		✓	✓	✓	Continue with the regular Schedule of Activities, starting with assessments of the next 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.

2.4.3. Sample Size Justification

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[a] 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%. A sample size of 40 subjects per group will guarantee a worst-case precision of maximum 22.5% (CSP section 9.1).

Due to early termination of the study, the sample size was limited to 22 randomized subjects.

2.5. Randomization and Blinding

When a subject is confirmed to be eligible for the clinical study (CSP section 6.1 and 6.2), the subject will be randomized. 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.

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.

Due to early termination of the study however, the unblinding is to take place prior to the study primary analysis time point. Further details on blinding are described in section 6.4.2 of the CSP.

3. STUDY ESTIMANDS

For an overview of the planned estimands to be analyzed, see CSP section 9.3.4. Due to the early termination of the study however, a different analysis approach will be taken which will be detailed in section 6.

4. GENERAL METHODOLOGY

4.1. Analysis Sets

The analysis set will always be indicated in a subtitle in the table, listing or figure.

4.1.1. All Screened Analysis Set

All subjects who signed an informed consent form to participate in this study.

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

4.1.2. All Randomized Analysis Set

All screened subjects who were randomized in this study.

4.1.3. Safety Analysis Set

All randomized subjects who were administered study drug at least once (Same as Full Analysis Set).

4.1.4. Full Analysis Set

All randomized subjects who were administered study drug at least once.

[redacted]

4.2. Randomized Versus Actual Treatment Group

For subject information, efficacy and safety parameters, the treatment group as assigned by the randomization will be used in the analysis (i.e. as-randomized analysis).

Differences between the randomized and actual assigned treatment group (disregarding any difference between randomized treatment and actual treatment due to dose re-escalation) will be listed.

4.3. Relative Days, Analysis Phases, Analysis Windows and Baseline

4.3.1. Relative Day

The timing of an assessment or an event relative to a reference date will be calculated as follows:

When the concerned date is before the reference date:

Relative day (days) = concerned date - reference date

When the concerned date is the equal to or later than the reference date:

Relative day (days) = concerned date - reference date + 1 day

Where:

- The *concerned date* could be the measurement date of the assessment, or the start or end date of the event.
- The *reference date* default is the date of the first dose of study drug administration, unless specified otherwise.

– *Date* implies a complete date having day, month and year available. Unless otherwise specified, the *relative day* will remain missing when it cannot be calculated due to absence or incompleteness of the concerned and/or reference dates.

The general terms of this formula also apply when similar relative timings are required in other time units, for example in minutes.

4.3.2. Analysis Phases

General Information

For each treated subject, analysis phases will be defined in order to embed the subject's event-type data and assessments (and other assessments as needed per analysis requirements).

Analysis phases describe patient-level segments (phases) of time throughout the conduct of a trial where the boundaries marking the end of one phase also denote the beginning of the next (seamless boundaries).

The last analysis phase will always end on the date of last contact in the study.

Applicable Analysis Phases

All event-type data (e.g., adverse events) and assessments will be allocated to analysis phases according to Table 1.

Table 1 Analysis Phases

Analysis Phase	Start Analysis Phase	End Analysis Phase
Screening	Date of signing the ICF	Date of first study drug administration
Treatment	Date of first study drug administration	Date of last study drug administration + 30 days
Post-Treatment#	Date of last study drug administration plus 30 days	Date of last contact in the study

ICF: informed consent form
If the date of last study drug administration plus 30 days is after the date of last contact in the study, the study will not include a post-treatment phase. The last analysis phase will end on the date of last contact in the study.

4.3.3. Analysis Windows

All assessments, including data collected on unscheduled visits, will be allocated to analysis windows based on the relative day of the assessment (see Section 4.3.1).

If applicable, study assessments will be allocated according to one of the algorithms in the tables below.

Table 2 Analysis Windows for Laboratory Assessments (Hematology, Chemistry)

Analysis Window Label	Target Day	Interval Lower Bound	Interval Upper Bound
Baseline	1	-INF	1
Week 4	29	2	57
Week 12	85	58	127
Week 24	169	128	211
Week 36	253	212	295
Week 48	337	296	379

Table 3 Analysis Windows for FCP & CRP

Analysis Window Label	Target Day	Interval Lower Bound	Interval Upper Bound
Baseline	1	-INF	1
Week 4	29	15	43
Week 12	85	71	99
Week 24	169	155	183
Week 36	253	239	267
Week 48	337	323	351

Table 4 Analysis Windows for Lipid Profile, Urine Analysis, Serum Immunoglobin

Analysis Window Label	Target Day	Interval Lower Bound	Interval Upper Bound
Baseline	1	-INF	1
Week 24	169	2	253
Week 48	337	254	421

Definition of Baseline

Baseline is defined as the last non-missing value before the first study drug administration. Unless specified otherwise, if multiple values qualify as last value, the mean of these values will be used in the analysis for continuous values. For categorical values the best-case selection (e.g. normal instead of abnormal) will be used.

In case of re-escalation, a re-escalation baseline is defined as the last non-missing value before the first open-label study drug administration.

For electrocardiogram (ECG), where triplicate results are measured, the baseline is defined as the mean of the last recorded triplicate before the first study drug administration. If no triplicate is available before the first dose of study medication intake, the last ECG value will be considered as baseline.

Selection of Visits

Per parameter and analysis window, the value closest to the target date will be used in analysis tables and figures. Other values will be listed only. If more than one value is located at the same distance from the target day, then the latest in time will be selected. If - after the previous selection - still multiple values qualify, the mean of continuous values will be used in the analysis. For categorical values the worst-case selection will be used post-baseline.

For composite endpoints, the value selection within each analysis window will be done on the level of the individual components, after which the composite is calculated on the selected component-level data.

4.4. Handling of Data

4.4.1. Handling of Missing Data

4.4.1.1. Handling of Missing Date-Time Data

Unless specified otherwise, no imputations will be done in case of missing date (time) fields, nor for the missing parts of partially known date (time) fields.

Assessments with missing date (time) will be omitted from the analysis.

Event-type data (e.g. adverse events, concomitant medications) with missing date (time) will be allocated to analysis phases using a worst-case approach as explained in the respective sections.

4.4.1.2. Handling of Missing Result Data

Missing data within an analysis window resulting from stopping the study will not be imputed. Due to the early termination of the study, all results will be presented as observed.

4.4.1.3. Censoring of Time-to-Event Data

Time-to-event endpoints include time to PRO2 flare and time to ES-confirmed flare.

Subjects who do not report the event at the time of the analysis, are censored at the date of last contact. The date of last contact is defined as the latest date collected in the CRF from the date of death, visit or assessment dates, AE dates, concomitant treatment dates, drug intake dates or lab test dates and trial completion date.

4.4.2. Handling of Values Below or Above a Threshold

Values below (above) the detection limit will be imputed by the value one unit smaller (larger) than the detection limit itself. In listings, the original value will be presented.

Example: if the database contains the value “<0.04”, then for the descriptive statistics the value “0.03” will be used. The value “>1000” will be imputed by “1001”.

4.4.3. Handling of Outliers

There will be no outlier detection, all measured values will be included in the analyses.

4.4.4. Stratification Factors

In case there is a discrepancy in stratification reported in the Randomization and Trial Supply Management (RTSM) system versus in the case report form (CRF), then the stratum reported in the CRF will be used in analyses and analysis models. Any discrepancies will be listed.

4.5. Presentation of Results

4.5.1. Presentation of Treatment Groups

In the section Subject Information (excluding Concomitant Medications), a grand total "All Subjects" will be added to summarize all subjects over all treatment groups in tables and figures.

Treatment groups will be presented as randomized, regardless of potential treatment switches to open-label 200 mg filgotinib.

4.5.2. Calculation of Descriptive Statistics

For continuous parameters, descriptive statistics will be presented when $N \geq 2$. When $N = 1$, the observation will not be shown in the tables or figures but only listed.

Descriptive statistics will include:

- the number of non-missing data points (N)
- the arithmetic mean
- the standard error (SE) and standard deviation (SD)
- the median, minimum and maximum
- 95% confidence interval (CI) of the mean (if indicated in the relevant section).

4.5.3. Calculation of Percentages

Frequencies and percentages will be generated for categorical parameters.

For event-type data (e.g. adverse events), the denominator will be all subjects in the analysis set and analysis phase. For other data (e.g. worst-case analysis of assessments), the denominator will be all subjects with non-missing data for the parameter, in the analysis set and analysis window/phase.

5. INTERIM ANALYSES & SAFETY MONITORING REVIEW

In light of the early termination of the CAPYBARA study, only one final analysis will be conducted.

Subjects were monitored through standard medical and safety monitoring processes. No data monitoring committee was considered needed. See CSP section 10.1 for details.

6. STATISTICAL ANALYSES

6.1. Changes to the Planned Analyses, Not Covered by Protocol Amendments

Due to the termination of the CAPYBARA study and the decision to write an abbreviated CSR, it was decided to limit the analyses to the primary and secondary efficacy endpoints and safety endpoints. Since the study was stopped prior to any subjects reaching the primary analysis time point at Week 48, the analyses described in this SAP will deviate from the planned analyses found in the protocol.

A summary of the modified analyses can be found in Table 5 below.

Table 5 Changes to Planned Analyses

Section SAP	Endpoint	Planned analysis as per Protocol	Revised analysis
PRIMARY ENDPOINTS			
6.3.1	Corticosteroid-free clinical remission based on modified Mayo Clinical Score at Week 48	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, calculated using Mantel-Haenszel test (stratification factor: baseline ES [0 or 1])	Available data on the primary endpoint will be listed.

SECONDARY ENDPOINTS			
6.3.2	Change from baseline in C-reactive protein (CRP) and fecal calprotectin (FCP) up to Week 48	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, using a linear mixed effects model	The available CRP and FCP data will be summarized as observed by treatment group, by visit.
6.3.2	Change from baseline in IBDQ at Week 48	The adjusted mean difference between the filgotinib 100 mg q.d. group and 200 mg q.d. using an analysis of covariance (ANCOVA)	The available IBDQ subscores and total score data will be listed.
6.3.3	Time to PRO2 flare	Estimate outcome differences between treatment groups using a Cox proportional hazards model	Listing with event details will be provided
6.3.3	Time to ES-confirmed flare	Estimate outcome differences between treatment groups using a Cox proportional hazards model	Listing with event details will be provided
6.4	Frequency and severity of treatment-emergent adverse events (TEAEs), treatment-emergent SAEs, and TEAEs leading to treatment discontinuation.	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.	Only the primary safety analysis will be conducted. Vital signs and ECG data will be listed

[redacted]

6.2. Subject Information

Subject information will be tabulated using the Safety Analysis Set. No inferential testing will be performed, nor will p-values be provided.

Subject information will be tabulated with descriptive statistics per treatment group and overall.

6.2.1. Demographic and Baseline Disease Characteristics

The following parameters will be summarized:

- Date of ICF signature (listed)
- Sex
- Age at signing the ICF (years)
- Age, categorized (years): $18 \leq$ age < 65; age ≥ 65
- Race and ethnicity
- Height at baseline (cm)
- Weight at baseline (kg)
- Body mass index (BMI) at baseline (kg/m^2) $= \frac{weight\ (kg)}{height^2\ (m^2)}$
  (BMI will not be recalculated if already available in the database)
- Endoscopic score at baseline

6.2.2. Disposition Information

The following tabulations will be provided, by treatment group and overall:

- The number of subjects screened, randomized and not-randomized, with the reason for not being randomized.
- Number (percent) of subjects randomized per country and investigator.
- The number (percent) of subjects in each analysis set as defined in Section 4.1.

- The number (percent) of subjects who completed/discontinued the study drug administration and the reasons for discontinuation.
- The number (percent) of subjects who completed/discontinued the study and the reasons for discontinuation.

Randomization schemes and codes will be listed overall and by site.

6.2.3. Protocol Deviations and Eligibility

Major protocol deviations are determined and recorded while the study is ongoing, and the list is finalized prior to database lock (and unblinding). For more details, please refer to the Protocol Deviations Plan.

All available information concerning major protocol deviations will be listed.

6.2.4. Medical History and Concomitant Diseases

Frequency tabulations per system organ class and preferred term will be provided for the medical history findings (i.e. condition no longer present at the start of the study) as well as for the concomitant diseases (i.e. conditions present at the start of the study).

6.2.5. Prior and Concomitant Therapies

6.2.5.1. Coding of Reported Terms

All prior and concomitant therapy terms will be coded in the database using the World Health Organization (WHO) drug coding dictionary.

6.2.5.2. Classification of Therapies

All prior and concomitant therapy records will be categorized as follows, considering their date and flags indicating the relative timing versus study (drug) start or end (before, after, ongoing…):

- Prior only: when the record ended before the first study drug administration date.
- Concomitant only: when the record started on or after the first study drug administration date.
- Prior and concomitant: when the record started before the date of first study drug administration, and ended on or after this point, or continued.

When the start or end date of the prior and concomitant therapy records are incomplete (and no flags indicating relative timing are available), the date of first study drug administration will be considered to the same level of information provided by these incomplete dates to categorize the timing of these records. This means that a record only having month and year will be categorized comparing only to the month and the year of the date of first study drug administration. Missing start dates without other information to indicate relative timing will be assumed to have occurred prior to first study drug, and missing end dates without timing information will be assumed to be ongoing at the end of the study.

6.2.5.3. Calculation of Relative Days

For both the start and the end dates of the concomitant therapy records, their day relative to the day of first study drug administration will be calculated as described in Section 4.3.1.

6.2.5.4. Presentation of Results

A detailed listing of the prior medications (defined as 'prior only' and 'prior and concomitant') will be provided as well as of the concomitant medications (defined as 'concomitant only' and 'prior and concomitant').

6.2.6. Exposure to Study drug and Compliance

6.2.6.1. Derivation Rules

Derived Parameters: Extent of Exposure to Study Drug

- *Total treatment duration* (days) = last study drug administration date – first study drug administration date + 1 day.
- *Total treatment duration, fully compliant* (days): Number of days with study drug administration, as planned per CSP.

Derived Parameters: Compliance

- Overall compliance (%) $= 100 \times \frac{number\ of\ doses\ actually\ used}{number\ of\ doses\ that\ should\ have\ been\ used}$
- Percent days fully compliance (%) $= 100 \times \frac{total\ treatment\ duration, fully\ compliant}{total\ treatment\ duration}$

6.2.6.2. Presentation of Results

Summary statistics will be provided for the exposure and compliance parameters.

6.3. Efficacy Analyses

Efficacy analyses will be performed on the Full Analysis Set (same as Safety Analysis Set).

Tabulations will be shown per treatment group.

6.3.1. Primary Efficacy Parameter(s)

6.3.1.1. Definition

The primary endpoint is defined as corticosteroid-free mMCS remission at Week 48.

6.3.1.2. Derivation Rules

The MCS system is a composite index of 4 disease activity variables. Each variable is scored individually on an integer scale of 0 to 3, inclusive, with higher scores indicating greater disease activity. The individual components of the MCS include stool frequency (SF), rectal bleeding (RB), endoscopic subscore (ES), and the physician's global assessment (PGA).

The mMCS is calculated as the sum of the 3 subscores excluding the physician's global assessment, ranging from 0 to 9. In case one of the subscores is missing, the mMCS will be set to missing as well. More details on the MCS-based scores and the calculation rules can be found in Appendix I.

mMCS remission is defined as a total score of score ≤2, with endoscopic subscore of ≤1, stool frequency subscore of ≤1, and a rectal bleeding subscore of 0. Corticosteroid-free mMCS remission is defined as being free of corticosteroids for at least 12 weeks.

6.3.1.3. Analysis Methods

Due to the early termination of the CAPYBARA study prior to the primary analysis time point, any data collected on the mMCS scores will be listed, including mMCS and ES at baseline, at early discontinuation (ED) and at any re-escalation visits if applicable. Corticosteroid-free status will be derived for any visit beyond week 12 where mMCS is assessed. Corticosteroids are defined as any drugs in the following ATC classes:

- A01AC
- A07EA
- H02A
- H02B
- H02CA

Corticosteroid-free is defined as no corticosteroid use for at least 12 weeks.

6.3.2. Key Secondary Efficacy Parameter(s)

Biomarkers

For the secondary endpoints CRP and FCP the actual values and changes from baseline will be tabulated and summarized for each available timepoint per treatment group. Any biomarker data collected after ES-confirmed flare will be excluded from the tabulation and will be listed only. Only biomarker data collected using the Siemens assay will be included in the analysis.

IBDQ

This disease-specific questionnaire comprises 32 questions divided into four 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); and social function, meaning the ability to participate in social activities and to work (5 questions).

For this secondary endpoint, any data collected on the four subscales and total scores will be listed at all available visits (including baseline, any re-escalation visits and early discontinuation visits).

6.3.3. Key Secondary Time-to-Event Endpoints

For time to PRO2 flare and time to ES-confirmed flare, any occurring events will be listed.

[redacted]

6.3.5. Subgroup Analyses

No subgroup analyses will be performed.

6.4. Safety Analyses

Safety analyses will be performed on the Safety Analysis Set.

Safety tables will be presented by treatment group.

Safety parameters will be analysed descriptively (see Section 4.5.2 and Section 4.5.3). No formal testing will be performed to compare the treatment groups.

6.4.1. Adverse Events

All adverse events (AEs) and changes in attributes (worsening and improvement) of AEs are reported in the database. An identification number serves to link the records considered by the investigator as describing the evolution of one and the same event.

6.4.1.1. Definition of Treatment-Emergent Adverse Events

The analysis of AEs will be based on treatment-emergent events (TEAE).
A TEAE is defined as

- An AE having a start date equal to or after the date of the first administration of study drug in this study and no later than 30 days after last administration of study drug.

– And is either a newly reported event, or a worsening[b] of an existing event. Improvements are not considered treatment-emergent.

6.4.1.2. Coding of Reported Terms

All AE terms will be coded in the database using the MedDRA coding dictionary.

All tables will show the AE preferred terms grouped into system organ classes. Subject listings will also show the reported terms. Any other coding levels will only be shown in a listing summarizing coding unless explicitly mentioned otherwise.

6.4.1.3. Allocation of Adverse Events to Analysis Phases

All AEs will be placed into analysis phases considering their start date, aiming to report the incidence of these events only in the analysis phase during which they started.

The general rule for allocation of AEs to analysis phases follows:

$$\text{Analysis phase start date} \leq \text{AE start date} \leq \text{analysis phase end date}$$

If the start date of an AE is missing or incomplete to a level preventing a clear allocation of the AE to one single analysis phase and no flag indicating timing relative to study medication is available, a worst-case consideration (see below) will be done aiming to allocate the AE to one single analysis phase, if possible. When a worst-case consideration is needed, the end date of the AE, if and as available, should also be considered; if such AEs clearly end on a given point, this will exclude the possibility to allocate the AE to an analysis phase after that point.

– An AE which according to the available information of its start date could belong to the screening as well as to the analysis phase with treatment will only be placed in the analysis phase with treatment.
– An AE which according to the available information of its start date could belong to an analysis phase with treatment as well as to a next analysis phase for which no treatment is defined (e.g. follow-up phase) will only be placed in the analysis phase with treatment.
– An AE which according to the available information of its start date could belong to two (or more) subsequent analysis phases with treatment will be allocated to all the matching analysis phases with treatment (i.e. these AEs will be replicated and reported once in each of these matching analysis phases).
– An AE with a missing start date will be allocated to all analysis phases with treatment (i.e. these AEs will be replicated and reported once in each of these analysis phases).

[b] 'Worsening' is defined as worsening in at least one of the following attributes: seriousness, severity, relationship and/or action taken.

6.4.1.4. Treatment Relatedness

Following the guideline ICH-E3 Structure and Content of Clinical Study Reports (Step 4 Version), the originally reported relatedness to study drug of an AE will be dichotomized as follows:

- *Not related*: all non-missing weaker levels of relatedness than 'possibly drug related'.
- *Related*: 'possibly drug related' and all stronger levels of relatedness (this class also includes any missing drug relatedness, as a worst-case consideration).

Only this dichotomized relatedness will be used in tables and can apply to different study drugs when relatedness has been collected separately per study drug; relatedness as originally reported will only be listed.

6.4.1.5. Worst-Case Selections

When cross-tabulating AE preferred terms versus an AE attribute (like severity), only the worst-case within each same preferred term, and same subject will be considered, i.e. when the same subject has more than once the same AE preferred term reported in the same treatment phase, the subject will be counted only once and will be shown under the worst outcome (like the worst severity for that AE in the concerned treatment phase).

6.4.1.6. Calculation of Relative Days and Duration

For each newly reported event, and reported worsening or improvement of an existing event, the start day in the study (the day of the AE start date relative to the date of first study drug administration), the start day in the analysis phase, and the duration (in days) will be calculated. In addition, the relative day and duration will be derived for the entire event; that is, the full evolution of the event, including the initial reporting and all subsequent worsenings and/or improvements.

Relative days and durations will only be listed.

See Section 4.3.1 for the calculation of relative days.

6.4.1.7. Adverse Events of Interest

Adverse events of interest (AEIs) are defined according to standardized MedDRA queries (SMQs) and/or custom MedDRA queries (CMQs) as specified in

Table 6. A frequency tabulation per AEI by system organ class and preferred term of subjects with TE AEIs by treatment arm will be provided. The custom MedDRA queries search list is provided in Appendix II.

Table 6 Adverse Events of Interest

Adverse Event of Interest	Definition
Major Adverse Cardiovascular Event (MACE)	Event positively adjudicated (see CSP section 10.1.1)
Arterial Systemic Thromboembolic Event (ASTE)	
Venous Thromboembolic Event (VTE)	
Infection	AEs within SOC 'Infections and infestations' with high level group term (HLGT) not equal to 'Ectoparasitic disorders' and 'Helminthic disorders'
Serious Infection	Serious AEs within SOC 'Infections and infestations' with HLGT not equal to 'Ectoparasitic disorders' and 'Helminthic disorders'
Opportunistic Infection	All Preferred Terms (PT) within SMQ 20000235, narrow
Malignancy excl. Non-melanoma Skin Cancer	CMQ
Non-melanoma Skin Cancer (NMSC)	CMQ
Gastrointestinal Perforation	CMQ
Herpes Zoster	CMQ
Fracture	All PTs that can be part of the 'Fractures' HLGT (n.b. the primary pathway of these terms may be different)

6.4.1.8. Presentation of Results

The analysis will focus on AEs reported during the treatment phase up to the time of ES-confirmed flare. Any AEs reported outside of that period will be listed.

All AE tables will show the number of subjects with applicable TEAEs.

A summary table will be provided, showing the number (percent) of subjects with at least one:

- TEAE,
- serious TEAE,
- TEAE leading to death,
- TEAEs by worst severity,
- IP-related TEAE,
- TEAE leading to study drug interruption,
- TEAE leading to permanent study drug discontinuation,
- TEAE leading to permanent study discontinuation.

Frequency tabulations, by system organ class and preferred term, of the number (percent) of subjects with a TEAE will be presented. Similar tables will be provided for related TEAEs and serious TEAEs.

Serious adverse events, AEs leading to death or leading to study drug discontinuation will be listed.

6.4.1.9. EudraCT Adverse Events Reporting

For the purpose of EudraCT reporting, the following tabulations will be created:

Frequency tabulations, by system organ class and preferred term, of the number (percent) of subjects with non-serious TEAE will be presented.

6.4.2. Laboratory Safety

6.4.2.1. Available Data

Laboratory tests scheduled are described in the protocol.

The statistical analyses will only present results in Standard International (SI) units. Other units will not be presented.

Only data provided by the central laboratory will be used in tables. Results from local labs will be listed only.

6.4.2.2. Derivation Rules

Fasted and Non-Fasted Results

Laboratory tests that are sensitive to the fasting status: glucose, triglycerides.

For these laboratory tests, only results from blood samples drawn in a fasted state will be included in the analysis. Results from blood samples taken in a non-fasted state will be listed only, no toxicities or abnormalities will be calculated. Laboratory results for which the fasting status is missing will be considered as taken non-fasted.

6.4.2.3. Definition of Toxicity Grades

Toxicity grades will only be derived for laboratory tests for which toxicity grades are available.

The CTCAE Version 5 will be used to assign toxicity grades (0 to 4) to laboratory results for analysis.

6.4.2.4. Definition of Non-Graded Abnormalities

For laboratory tests provided by the laboratory, the position of the actual analysis values versus their normal ranges will be determined directly by using the position indicator provided in the database as reported by the lab, expressing the classes for these analysis values as low (L), normal (N) or high (H). L, N and H are further referred to as non-graded abnormalities.

6.4.2.5. Urinalysis Tests with Categorical Results

Results of urinalysis with qualitative results will be tabulated by time point. No toxicity grading or non-graded abnormalities will be derived.

6.4.2.6. Treatment-Emergent Principle

Toxicity Grades

A post-baseline toxicity grade 1, 2, 3 or 4 is defined as treatment-emergent when higher than the toxicity grade of the baseline result. If the baseline result is missing, a post-baseline toxicity grade 1, 2, 3 or 4 will be considered as treatment-emergent.

Non-graded Abnormalities

A post-baseline non-graded abnormality class L or H is defined as treatment-emergent when it differs from the abnormality class of the baseline result. If the baseline result is missing, a post-baseline abnormality L or H will be considered as treatment-emergent.

6.4.2.7. Worst-Case Principle

Toxicity Grades

The worst-case post-baseline toxicity grade 0, 1, 2, 3 or 4 will be determined per subject, per laboratory test (and sense, if below and above), using all non-missing post-baseline records (including unscheduled and follow-up visits, but excluding local lab results).

The worst-case toxicity grade is the highest toxicity grade scored for the laboratory test (in each sense, if below and above).

Non-graded Abnormalities

The following worst-case post-baseline abnormalities L, N or H will be determined per subject, per laboratory test , using all non-missing post-baseline records (including unscheduled and follow-up visits, but excluding local lab results):

- L = low: at least one post-baseline result is classified as L.
- N = normal: all post-baseline results are classified as N.
- H = high: at least one post-baseline result is classified as H.

If, for a subject, both L and H are reported, the subject will be counted twice in the table: once with a worst-case L and once with a worst-case H.

6.4.2.8. Hepatotoxicity

Hepatotoxicity will be investigated by tabulating the aspartate aminotransferase (AST) and alanine aminotransferase (ALT) values categorized as >3, >5, >10 and >20 times their upper limit of normal (per analyte and over both analytes combined) and total bilirubin as ≥ 2 times the upper limit of normal.

To assess the potential of the drug to cause severe liver damage, possible Hy's Law cases will be identified. These subjects are defined as having any elevated AT (AST or ALT) of >3×ULN, alkaline phosphatase (ALP) <2×ULN, and associated with an increase in total bilirubin >2×ULN at the same post-baseline visit during the same treatment and at least once.

6.4.2.9. Presentation of Results

No formal inferential statistics (p-values) will be derived.

Continuous laboratory tests will be summarized by means of descriptive statistics (including 95% CI of the mean change) by laboratory test, treatment group and analysis window.

The analysis of abnormalities will focus on assessments reported during the treatment phase, i.e. the period during which events can be considered as treatment-emergent. Results reported outside of that period will only be listed.

A frequency table of the number (percent) of subjects with treatment-emergent worst-case abnormalities/toxicity grades per laboratory test, treatment group and analysis phase will be presented.

6.4.3. Electrocardiogram

6.4.3.1. Available Data

The following electrocardiogram (ECG) parameters will be listed: heart rate, PR interval, QRS interval, uncorrected QT interval.

If ECG is collected in triplicates, the values of the original members of a triplicate will be listed.

6.4.4. Vital Signs

6.4.4.1. Available Data

The following vital signs parameters will be listed: pulse, respiratory rate, diastolic and systolic blood pressure and temperature.

6.4.5. Physical Examinations

Clinically relevant results from physical examinations will be reported in the CRF as medical history or adverse events depending on their onset versus first study drug intake. No specific analyses on physical examinations will be performed.

[redacted]

[redacted]

[redacted]

7. REFERENCES

ICH E3 Structure and Content of Clinical Study Reports (Step 4 Version).

ICH E9 Statistical Principles for Clinical Trials (Step 4 Version).

ICH E14 The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs (Step 4 Version).

ICH E6 Intergrated Addendum to ICH E6 (R1): Guideline for good clinical practice (Step 4 Version).

ICH E9(R1) Estimands and Sensitivity Analysis in Clinical Trials (Step 2 Version).

APPENDIX

APPENDIX I: Calculation of Mayo Clinic Score and Component Subscores

For the purposes of calculation of the specific MCS and component subscores an anchor date is assigned and stool frequency and rectal bleeding records prior to the anchor date are used in the calculation of the subscores. For screening calculations of mMCS, the anchor date is considered the date of the endoscopy. As endoscopic subscore will be only evaluated over screening and not at Day 1 baseline.

For all calculations at other visits, including baseline [redacted], mMCS and [redacted] postbaseline, the anchor date is the date of the study visit.

Because the preparation for endoscopy procedure may impact the validity of the diary data, the patients reported daily stool frequency and rectal bleeding records collected 1 day prior to, the day of, and the day after the procedure will not be used in the calculation of stool frequency and rectal bleeding subscores. These above mentioned days are considered as non-evaluable days for those 2 subscores.

Calculation of mMCS at Screening/Baseline

The calculation of the screening stool frequency subscore and screening rectal bleeding subscores for the purposes of calculation of baseline mMCS is as follows:

1) The endoscopic procedure date is defined as the E-Day 1.

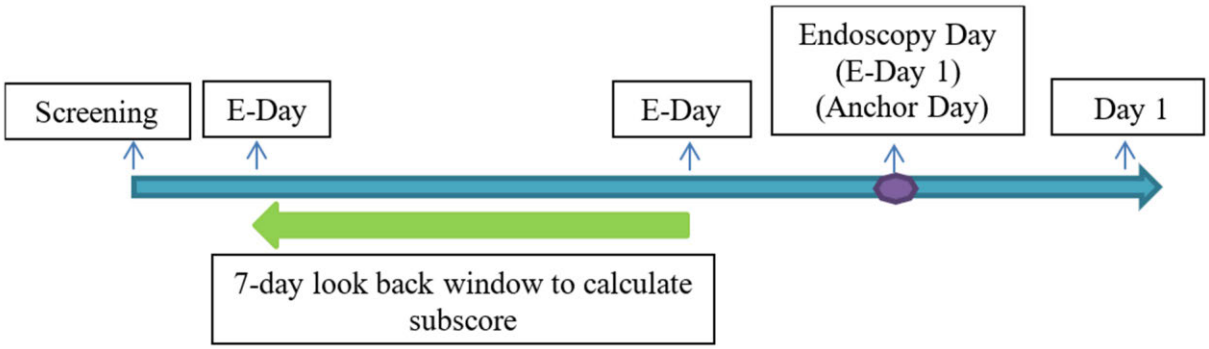
2) A 7-day window is defined in which the start of the window begins 7 days prior to the endoscopic procedure date and the window ends on the day prior to the endoscopic procedure date.

3) The subscore is calculated as the average of the 3 evaluable dairy data entries within the 7-day window closest to the endoscopic procedure date (discarding the day prior to endoscopy) and rounded to the nearest integer.

4) If a subject does not have 3 evaluable diary day entries within the 7-day window, this subject will have a missing subscore and missing baseline mMCS.

5) The PGA subscore used in the baseline mMCS is that recorded during the screening period (prior to Day1).

Appendix Figure 1. Stool Frequency and Rectal Bleeding Subscores Calculations at Screening



Calculation of Partial MCS, Stool Frequency and Rectal Bleeding at Baseline, and Postbaseline mMCS and [redacted]

The calculation of baseline stool frequency score, rectal bleeding score and [redacted], and postbaseline mMCS and [redacted] use the study visit date as the anchor date. For baseline rectal bleeding score, stool frequency score and [redacted], the visit date is the Day 1 visit. The calculations are as follows:

1) Subject diary data collected within 7 days prior to the visit day will be used for calculation, and some of the days within this 7-day window may be considered non-evaluable due to the endoscopy procedure and its preparation (ie, the day of the endoscopy and the day prior to the endoscopy).

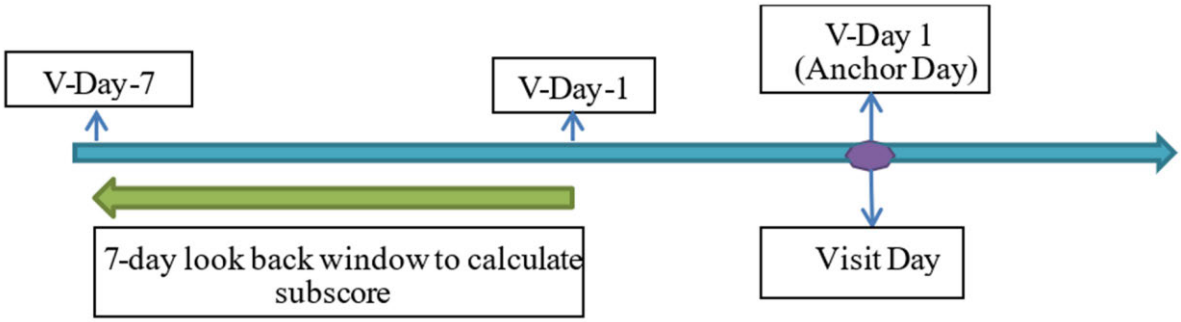
2) The average of the 3 evaluable diary day entries within the 7-day window closest to the visit day (V-Day 1), rounded to the nearest integer, will be considered the stool frequency and rectal bleeding subscore for that visit

3) The PGA subscore used in the calculation of baseline [redacted] is the PGA subscore recorded on Day 1. At subsequent visits, the PGA subscore used in calculation of MCS and [redacted] is that recorded within the visit window

4) If there are 2 or less evaluable diary day entries for stool frequency or rectal bleeding within the 7-day window, no missing data imputation will be done. mMCS and [redacted] will be considered as missing.

5) For mMCS, if endoscopic subscore is missing, mMCS will be left as missing. [redacted]

Appendix Figure 2. Stool Frequency and Rectal Bleeding Subscores Calculations at Baseline and Postbaseline



APPENDIX II: Overview of Custom MedDRA Queries

Appendix Table 1. Herpes Zoster – Custom medDRA Query Search List

Herpes Zoster - Galapagos Search Term List
MedDRA Version 26.0

TERM_CODE	TERM_NAME	TERM_TYPE
10019974	Herpes zoster	PT
10030865	Ophthalmic herpes zoster	PT
10061208	Herpes zoster infection neurological	PT
10063491	Herpes zoster oticus	PT
10065038	Herpes zoster disseminated	PT
10072210	Genital herpes zoster	PT
10074241	Varicella zoster gastritis	PT
10074243	Varicella zoster oesophagitis	PT
10074245	Herpes zoster pharyngitis	PT
10074248	Herpes zoster meningoencephalitis	PT
10074251	Herpes zoster meningomyelitis	PT
10074253	Herpes zoster necrotising retinopathy	PT
10074254	Varicella zoster pneumonia	PT
10074259	Herpes zoster meningitis	PT
10074297	Herpes zoster cutaneous disseminated	PT
10074298	Varicella zoster sepsis	PT
10075611	Varicella zoster virus infection	PT
10076667	Disseminated varicella zoster vaccine virus infection	PT
10079327	Herpes zoster meningoradiculitis	PT

Herpes Zoster - Galapagos Search Term List
MedDRA Version 26.0

TERM_CODE	TERM_NAME	TERM_TYPE
10080516	Herpes zoster reactivation	PT
10082717	Herpetic radiculopathy	PT
10084396	Disseminated varicella zoster virus infection	PT
10086594	Oral herpes zoster	PT
10086746	Varicella encephalitis	PT
10086747	Varicella meningitis	PT
10087746	Varicella zoster viraemia	PT

Malignancies, Excluding Nonmelanoma Skin Cancers - Galapagos Search Term List
MedDRA Version 26.0

TERM_CODE	TERM_NAME	TERM_TYPE
10000583	Acral lentiginous melanoma	PT
10000585	Acral lentiginous melanoma stage I	PT
10000586	Acral lentiginous melanoma stage II	PT
10000587	Acral lentiginous melanoma stage III	PT
10000588	Acral lentiginous melanoma stage IV	PT
10000739	Acute erythroid leukaemia	PT
10000830	Acute leukaemia	PT
10000846	Acute lymphocytic leukaemia	PT
10000847	Acute lymphocytic leukaemia (in remission)	PT
10000860	Acute megakaryocytic leukaemia	PT
10000871	Acute monocytic leukaemia	PT
10000872	Acute monocytic leukaemia (in remission)	PT
10000880	Acute myeloid leukaemia	PT
10000881	Acute myeloid leukaemia (in remission)	PT
10000890	Acute myelomonocytic leukaemia	PT
10001019	Acute promyelocytic leukaemia	PT
10001141	Adenocarcinoma	PT
10001150	Adenocarcinoma gastric	PT
10001167	Adenocarcinoma of colon	PT
10001197	Adenocarcinoma of the cervix	PT

Malignancies, Excluding Nonmelanoma Skin Cancers - Galapagos Search Term List
MedDRA Version 26.0

TERM_CODE	TERM_NAME	TERM_TYPE
10001244	Adenosquamous carcinoma of the cervix	PT
10001245	Adenosquamous cell lung cancer	PT
10001247	Adenosquamous cell lung cancer recurrent	PT
10001248	Adenosquamous cell lung cancer stage 0	PT
10001249	Adenosquamous cell lung cancer stage I	PT
10001250	Adenosquamous cell lung cancer stage II	PT
10001251	Adenosquamous cell lung cancer stage III	PT
10001254	Adenosquamous cell lung cancer stage IV	PT
10001388	Adrenocortical carcinoma	PT
10001413	Adult T-cell lymphoma/leukaemia	PT
10001416	Adult T-cell lymphoma/leukaemia recurrent	PT
10001417	Adult T-cell lymphoma/leukaemia refractory	PT
10001418	Adult T-cell lymphoma/leukaemia stage I	PT
10001419	Adult T-cell lymphoma/leukaemia stage II	PT
10001420	Adult T-cell lymphoma/leukaemia stage III	PT

Nonmelanoma Skin Cancers - Galapagos Search Term List
MedDRA Version 26.0

TERM_CODE	TERM_NAME	TERM_TYPE
10004146	Basal cell carcinoma	PT
10004178	Basosquamous carcinoma	PT
10004179	Basosquamous carcinoma of skin	PT
10006059	Bowen's disease	PT
10007390	Carcinoma in situ of skin	PT
10011677	Cutaneous T-cell lymphoma	PT
10011678	Cutaneous T-cell lymphoma recurrent	PT
10011679	Cutaneous T-cell lymphoma refractory	PT
10011680	Cutaneous T-cell lymphoma stage I	PT
10011681	Cutaneous T-cell lymphoma stage II	PT
10011682	Cutaneous T-cell lymphoma stage III	PT
10023284	Kaposi's sarcoma	PT
10023286	Kaposi's sarcoma AIDS related	PT

Nonmelanoma Skin Cancers - Galapagos Search Term List
MedDRA Version 26.0

TERM_CODE	TERM_NAME	TERM_TYPE
10023288	Kaposi's sarcoma classical type	PT
10023347	Keratoacanthoma	PT
10029266	Neuroendocrine carcinoma of the skin	PT
10037732	Queyrat erythroplasia	PT
10039495	Sarcoma of skin	PT
10040808	Skin cancer	PT
10041823	Squamous cell carcinoma	PT
10041834	Squamous cell carcinoma of skin	PT
10057070	Dermatofibrosarcoma protuberans	PT
10063609	Porocarcinoma	PT
10064755	Atypical fibroxanthoma	PT
10068784	Sebaceous carcinoma	PT
10069680	Eccrine carcinoma	PT
10072891	Skin angiosarcoma	PT
10073087	Malignant sweat gland neoplasm	PT
10073088	Hidradenocarcinoma	PT
10075614	Pilomatrix carcinoma	PT
10076248	Marjolin's ulcer	PT
10079945	Cutaneous lymphoma	PT
10080660	Trichoblastic carcinoma	PT
10081136	Skin squamous cell carcinoma recurrent	PT
10085518	Cutaneous B-cell lymphoma	PT

Gastrointestinal Perforations - Galapagos Search Term List
MedDRA Version 26.0

TERM_CODE	TERM_NAME	TERM_TYPE
10002248	Anastomotic ulcer perforation	PT
10003012	Appendicitis perforated	PT
10013832	Duodenal perforation	PT
10013849	Duodenal ulcer perforation	PT
10013850	Duodenal ulcer perforation, obstructive	PT
10017815	Gastric perforation	PT

Gastrointestinal Perforations - Galapagos Search Term List

MedDRA Version 26.0

TERM_CODE	TERM_NAME	TERM_TYPE
10017835	Gastric ulcer perforation	PT
10017836	Gastric ulcer perforation, obstructive	PT
10018001	Gastrointestinal perforation	PT
10021305	Ileal perforation	PT
10021310	Ileal ulcer perforation	PT
10022694	Intestinal perforation	PT
10023174	Jejunal perforation	PT
10023178	Jejunal ulcer perforation	PT
10023804	Large intestine perforation	PT
10030181	Oesophageal perforation	PT
10034354	Peptic ulcer perforation	PT
10034358	Peptic ulcer perforation, obstructive	PT
10038073	Rectal perforation	PT
10041103	Small intestinal perforation	PT
10052211	Oesophageal rupture	PT
10052488	Oesophageal ulcer perforation	PT
10052497	Large intestinal ulcer perforation	PT
10052498	Small intestinal ulcer perforation	PT
10061248	Intestinal ulcer perforation	PT
10061820	Diverticular perforation	PT
10061975	Gastrointestinal ulcer perforation	PT
10062065	Perforated ulcer	PT
10066993	Umbilical hernia perforation	PT
10074065	Procedural intestinal perforation	PT
10074442	Abdominal hernia perforation	PT
10075254	Inguinal hernia perforation	PT
10078413	Upper gastrointestinal perforation	PT
10078414	Lower gastrointestinal perforation	PT
10085627	Duodenal rupture	PT