CLINICAL PROTOCOL

A MULTI-CENTER, OPEN-LABEL STUDY OF CP-690,550 IN SUBJECTS WITH MODERATE TO SEVERE ULCERATIVE COLITIS

Compound:	CP-690,550
Compound Name:	Tofacitinib
US IND Number:	CCI [redacted]
European Clinical Trial Database (EudraCT) Number:	2011-004581-14
Protocol Number:	A3921139
Phase:	Phase 3

Document History

Document	Version Date	Summary of Changes and Rationale
Amendment 11	18 June 2019	This global amendment incorporates the provisional measures on the restrictions for prescriptions of tofacitinib set forth on 17 May 2019 by the European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC) in the European Union. Subjects receiving tofacitinib 10 mg BID who are identified as having one or more of the contraindicated risk factors for pulmonary embolism as described by PRAC will have their dose reduced to tofacitinib 5 mg BID. Any subject identified as having one or more of the contraindicated risk factors for pulmonary embolism as described by PRAC will not be permitted to receive tofacitinib 10 mg BID. A risk factor check for pulmonary embolism is added for each visit beyond Month 36, since at the time of this amendment, all subjects have crossed the Month 36 study visit. The following sections have been updated to reflect these changes: Schedule of Activities, Section 3 (Study Design), Section 5.5 (ConcomitantMedications), Section 5.8 (Tofacitinib Dose Adjustment Guidelines), Section 6.1.8 and Section 6.1.9 (Study Visit Procedures) and newly added Section 7.3.12 (Risk Factor Check for Pulmonary Embolism). Appendix 15 (Abbreviations) was also updated.
Amendment 10	22 October 2018	This amendment specifies the end of the trial will be approximately July 2020. This 2 year extension of the study will allow for additional collection of long term safety and efficacy data in UC patients on tofacitinib. This trial end date has been updated in several sections throughout the protocol. Schedule of Activities footnote 8 was updated to clarify that tuberculosis (TB) testing is not required at the early termination (ET) visit for specific countries that require annual TB testing to be performed. Language related to eligibility criteria for enrollment in Study A3921288 has been updated to be consistent with the updated study protocol for Study A3921288. Section 5.8 Tofacitinib Dosage Adjustment

		Guidelines have been revised to provide additional clarification for the definition of loss of response and flare for subjects who need to increase their dose back up to 10 mg BID after experiencing a flare on 5 mg BID. Section 7.3.4 Electrocardiogram (ECG) was updated to clarify that ECGs performed at ET should be submitted to the central lab. Administrative edits, such as updating the name of the TB testing performed by the central lab, have been made throughout the protocol.
Amendment 9	13 July 2017	This amendment specifies that subjects who enroll into Study A3921139 on tofacitinib 10 mg BID, and who are in stable remission on tofacitinib 10 mg BID for at least 6 months may have the opportunity to enter Study A3921288 (A Phase 3b/4, Multi-Center, Double-Blind, Randomized, Parallel Group Study of Tofacitinib in Subjects with UC in Stable Remission) if they meet the eligibility criteria. Study A3921288 will evaluate the efficacy and safety of tofacitinib in subjects in stable remission on 10 mg BID who decrease the dose to and remain on 5 mg BID compared to subjects who remain on 10 mg BID. Section 6.1.5 (Month 12, Early Termination or Evaluation Visit for Entry into Study A3921288), and Schedule of Activities have been revised to include additional assessment and information for subjects being evaluated for entry into Study A3921288. Appendix 3 monitoring and discontinuation requirements for CK testing have been revised for consistency.
Amendment 8	06 August 2015	This amendment specifies the study procedures to be performed beyond Month 36. The schedule of activities and Section 6 have been revised to reflect these procedures. ECGs and urinalysis beyond Month 36 have been removed. Frequency of collection and the number of patient reported outcomes have been reduced beyond Month 36. Addition of exclusion criterion 8 to exclude subjects who have evidence of colonic malignancy or any dysplasia identified on endoscopic exam during study A3921096. Clarifications to the following sections have been made: Section 5.5 (Concomitant

		Medications), Section 5.7 (Rescue Therapy), and Section 5.8 (Tofacitinib Dose Adjustment Guidelines). Estimated number of subjects to be enrolled has been increased. Annual TB re-testing requirements for specific countries have been added (Section 7.3.6). This amendment also incorporates updates to Section 7 (Assessments) as well as to standard Pfizer protocol text in Section 8 (Adverse Event Reporting) and Section 15 (Publication of Study Results). Section 4.5 Sponsor's Qualified Medical Personnel added per Pfizer protocol template. Additional editorial changes made throughout the protocol.
CCI [redacted]	[redacted]	[redacted]
CCI [redacted]	[redacted]	[redacted]
Amendment 5	28 September 2012	This amendment updates standard Pfizer protocol text, including safety language in various sections, including Administration, Reproductive Status of Female Subjects and Adverse Event Reporting. Also included in this amendment are updates to the summary of safety section for tofacitinib to be consistent with the revised Investigator's Brochure, updates to the secondary study endpoints, schedule of activities flowchart, prohibited medication list, guidelines for dosage adjustment and added guidance on temporary withholding of study drug.
CCI [redacted]	[redacted]	[redacted]
CCI [redacted]	[redacted]	[redacted]
Amendment 2	04 January 2012	Added Austria specific requirement of monthly

	(Country specific: AUSTRIA)	pregnancy testing for females of childbearing potential.
CCI [redacted]	[redacted]	[redacted]
Original protocol	30 September 2011	N/A

This amendment incorporates all revisions to date, including amendments made at the request of country Health Authorities, IRB/ERB, etc.

PROTOCOL SUMMARY

Indication:

Tofacitinib, also known as tofacitinib citrate or CP-690,550, is being developed for the treatment of patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy.

Background and Rationale:

Tofacitinib is a potent, selective inhibitor of the JAK family of kinases with a high degree of selectivity against other kinases in the human genome. In kinase assays, tofacitinib inhibits JAK1, JAK2, JAK3, and to a lesser extent TyK2. In cellular settings where JAK kinases signal in pairs, tofacitinib preferentially inhibits signaling by heterodimers containing JAK3 and/or JAK1 with functional selectivity over JAK2 homodimer signaling. Inhibition of JAK1 and JAK3 by tofacitinib blocks signaling through the common gamma chain containing receptors for several cytokines, including IL-2, -4,-7,-9, -15 and -21. These cytokines are integral to lymphocyte activation, proliferation, and function, and inhibition of their signaling may thus result in modulation of multiple aspects of the immune response. In addition, inhibition of JAK1 will result in attenuation of signaling by additional pro-inflammatory cytokines, such as IL-6 and IFNγ. At higher exposures, inhibition of erythropoietin, prolactin and other hormones could occur via inhibition of JAK2 homodimer signaling.

The broad effects of JAK1/3 inhibition on multiple cytokine pathways provides the rationale for developing tofacitinib as treatment for several diseases in which lymphocyte activation/proliferation plays a pathogenic role. Tofacitinib is being studied as an oral treatment for ulcerative colitis (UC), Crohn's disease, as a disease-modifying anti-rheumatic drug (DMARD) for the treatment of RA, as treatment for plaque psoriasis and for the prevention of renal allograft rejection.

Objectives and Endpoints:

Primary Objective

- To assess the safety and tolerability of long-term tofacitinib therapy in subjects with UC.

Secondary Objectives

- To evaluate the efficacy of long-term tofacitinib therapy in subjects with UC.
- To evaluate the effect of long-term tofacitinib therapy on quality-of-life in subjects with UC.

Primary Efficacy Endpoint

- As this is an open-label extension study, there will be no primary efficacy endpoint.

Secondary Efficacy Endpoints

- The proportion of subjects in remission at Month 2, Month 12, Month 24 and Month 36. Remission in this study is defined as a Mayo score ≤2 with no individual subscore >1, and rectal bleeding subscore of 0.

- The proportion of subjects in clinical remission at Month 2, Month 12, Month 24 and Month 36. Clinical remission in this study is defined as a Mayo score ≤2 with no individual subscore >1.

- The proportion of subjects in partial Mayo score (PMS) remission over time. PMS remission in this study is defined as a partial Mayo score ≤2 with no individual subscore >1.

- The proportion of subjects who achieve mucosal healing at Month 2, Month 12, Month 24 and Month 36. Mucosal healing is defined as a Mayo endoscopic subscore of 0 or 1.

- The proportion of subjects with total score in Inflammatory Bowel Disease Questionnaire (IBDQ) ≥170 over time.

Safety Endpoints

- Incidence and severity of adverse events (AEs).

- Incidence of serious infections.

- Incidence and severity of clinical laboratory abnormalities and change from baseline in clinical laboratory values.

- Incidence of vital sign abnormalities and change from baseline in vital signs.

- Incidence of clinically significant changes in physical examinations from baseline.

- Incidence of electrocardiogram (ECG) abnormalities during treatment.

- Summary of adjudicated safety events (eg, cardiovascular, malignancy, opportunistic infections).

- Proportion of subjects with addition of lipid lowering agents.

Study Design:

This is a Phase 3, multi-center, open-label study in subjects who have completed or demonstrated treatment failure in the maintenance study A3921096, or who were non-responders after completing induction studies A3921094 or A3921095. Approximately 900 subjects are expected to become eligible for the study. This study will continue up to approximately July 2020. Individual subject duration of participation will vary depending on when the subject was enrolled into the study and the end date of approximately July 2020. Therefore, the duration of participation for an individual subject may range from approximately 4 years to more than 7 years. If the study continues beyond year 6 for an individual subject, the investigator should continue to follow the same visit schedule and study procedures outlined during the study visits of year 4.

Subjects who completed Study A3921096 or had early withdrawal due to treatment failure as defined in the A3921096 protocol may be eligible to enroll in this study, A3921139. In addition, subjects who complete induction Study A3921094 or A3921095 and are classified as non-responders may be eligible to enroll in this study. The eligibility of a subject for this study will be assessed based on study data collected at Week 8/9 of Study A3921094 or A3921095 (for non-responders) or the Week 52/53 visit (for completers) or early termination visit (early withdrawals due to treatment failure) of Study A3921096. The study data collected at the Week 8/9 visit for Study A3921094 or A3921095 (for non-responders) or the Week 52/53 visit or early termination visit of Study A3921096 will be recorded as the baseline data for Study A3921139.

Eligible subjects will be assigned to either tofacitinib 5 mg twice a day (BID) or 10 mg BID depending on whether the subject is in remission at baseline of Study A3921139. Remission is defined by a total Mayo score ≤2 with no individual subscore >1, and rectal bleeding subscore of 0. Eligible subjects who are in remission at Week 52 of Study A3921096 will be assigned to receive tofacitinib 5 mg BID. For treatment assignment at baseline, the central read assessment of the Mayo endoscopic subscore will be used to determine if a subject is in remission. Subjects who complete Study A3921096 but do not meet the remission definition or who are early withdrawals due to treatment failure in Study A3921096 are eligible to receive tofacitinib 10 mg BID. Treatment failure is defined by an increase in Mayo score of at least 3 points from baseline value of the maintenance study (A3921096), accompanied by an increase in rectal bleeding subscore by at least 1 point, and an increase of endoscopic subscore of at least 1 point (yielding an absolute endoscopic subscore of ≥2) after a minimum of 8 weeks of treatment in the maintenance study. In the scenario where the endoscopic subscore is a '3', and the maintenance baseline endoscopic subscore is already a '3' (maximum value), then an increase by at least 1 point will not be needed in order to meet treatment failure. However, all other components of the treatment failure criteria will still need to be met. Subjects who complete induction studies A3921094 or A3921095 and are classified as non-responders are also eligible to receive tofacitinib 10 mg BID.

Tofacitinib dose can be adjusted from 5 mg BID to 10 mg BID for efficacy and from 10 mg BID to 5 mg BID after meeting specific laboratory abnormalities or other protocol defined criteria regarding efficacy (see Section 5.8 for dose adjustment guidelines). Dose adjustments can only occur after a subject has received at least 8 weeks of treatment in Study A3921139.

Subjects who enroll into this study who are on tofacitinib 10 mg BID for at least 2 consecutive years, and who are in stable remission on tofacitinib 10 mg BID for at least 6 months may have the opportunity to enter Study A3921288 (A Phase 3b/4, Multi-Center, Double-Blind, Randomized, Parallel Group Study of Tofacitinib in Subjects with UC in Stable Remission) if they meet the eligibility criteria. Study A3921288 will evaluate the efficacy and safety of tofacitinib in subjects in stable remission on 10 mg BID who decrease the dose to and remain on 5 mg BID compared to subjects who remain on 10 mg BID.

Subjects from the induction studies A3921094 or A3921095 (ie, non-responders) who fail to demonstrate clinical response at Month 2 of this study will be withdrawn from the study. Clinical response is defined by a decrease from the induction study baseline (A3921094 or A3921095) Mayo score of at least 3 points and at least 30%, with an accompanying decrease in the rectal bleeding subscore of at least 1 point or an absolute rectal bleeding subscore of 0 or 1. The endoscopic subscore based on central reading will be used to assess clinical response.

All subjects who withdraw early or who complete this open-label study, with the exception of those subjects entering Study A3921288, will have a 4-week safety follow-up evaluation after the last dose of study medication.

Subjects will be required to remain on stable doses of their concomitant medications for UC during the study period, with the exception of oral 5-ASA or sulfasalazine and oral corticosteroids described in Section 5.5. Subjects who enter this study on corticosteroids (eg, subjects who withdraw from Study A3921096 due to treatment failure or non-responders at the end of Study A3921094 or A3921095) will need to continue the steroid tapering regimen described in Study A3921096 (see Section 5.5). If a subject requires rescue therapy (see Section 5.7) or undergoes surgery for UC, the subject should be withdrawn from the study and appropriate agents should be given at the discretion of the investigator. If a subject discontinues the use of background oral 5-ASA or sulfasalazine during the study and/or has the therapy re-initiated, this will not constitute rescue therapy, and the subject will be permitted to remain in the study.

Study Treatments:

Subjects will be assigned to one of two dose groups depending on their remission status at baseline of Study A3921139:

- Tofacitinib 5 mg BID (subjects in remission).
- Tofacitinib 10 mg BID (all other subjects).

Statistical Methods:

Sample Size Determination

Approximately 900 subjects are expected to become eligible for the study. Approximately 460 subjects are expected to enroll from the maintenance Study A3921096 assuming a 78% rollover rate from the maintenance study. Approximately 440 subjects are expected to enroll from the induction Study A3921094 or A3921095 assuming that 38% of subjects enrolled in those studies will not achieve clinical response and will not have improving endoscopic subscores after completing induction Study A3921094 or A3921095.

Efficacy Analysis

The primary analysis population will be the Full Analysis Set (FAS) defined as all subjects who receive at least 1 dose of study medication.

The primary objective is to assess the safety and tolerability of long-term tofacitinib therapy. There will be no primary efficacy endpoint.

Due to the design of the study, there will be no formal hypothesis testing. Descriptive summary statistics such as number, percentage for categorical endpoints and mean, standard deviation, median for continuous endpoints will be summarized by the following four subgroups of subjects based on the status at baseline of Study A3921139: 1) in remission defined by a total Mayo score ≤2 with no individual subscore >1, and rectal bleeding subscore of 0, 2) treatment failure defined by an increase in Mayo score of at least 3 points from baseline value of the maintenance study (A3921096), accompanied by an increase in rectal bleeding subscore by at least 1 point, and an increase of endoscopic subscore of at least 1 point (yielding an absolute endoscopic subscore of ≥2), 3) all other subjects from maintenance study A3921096 neither in remission nor fulfilling the definition of treatment failure, and 4) non-responders from induction studies A3921094 or A3921095.

Safety Analysis

The safety data will be summarized in accordance with Pfizer Data Standards based on the safety analysis set defined as all subjects who receive at least 1 dose of study medication.

SCHEDULE OF ACTIVITIES

The Schedule of Activities table provides an overview of the protocol visits and procedures. Refer to Study Procedures (Section 6) and Assessments (Section 7) for detailed information on each procedure and assessment required for compliance with the protocol.

All study visits during the first year will have a window of ±5 days. The 4-week follow-up evaluation visit and all study visits in subsequent years will have a window of ±7 days.

This study will continue until approximately July 2020. Individual subject duration of participation will vary depending on when the subject was enrolled into the study and the end date of approximately July 2020. Therefore, the duration of participation for an individual subject may range from approximately 4 years to more than 7 years. Annual schedule of activities are identical from year 4 and beyond. For illustration purposes, the Schedule of Activities contains study procedures up to Month 72 (year 6). If the study continues beyond year 6 for an individual subject, the investigator should continue to follow the same visit schedule and study procedures outlined during the study visits of year 4.

Schedule of activities for first year:

Study Procedure	**Baseline**	**Open Label Treatment Period**					
	Day 1[1]	**Month 1 (± 5 days)**	**Month 2 (± 5 days)**	**Month 4 (± 5 days)**	**Month 6 (± 5 days)**	**Month 9 (± 5 days)**	**Month 12 (± 5 days) / ET**[2]
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7 or ET**[2]
Informed Consent	X						
Medical History[3]	IND or MNT[1]						
Complete Physical Examination	IND or MNT						X
Targeted Physical Examination[4]		X	X	X	X	X	
Extra-Intestinal Manifestations	IND or MNT						X
Vital Signs[5]	IND or MNT	X	X	X	X	X	X
12-Lead ECG[5]	IND or MNT						X
Laboratory							
Hematology	IND or MNT	X	X	X	X	X	X
Serum Chemistry	IND or MNT	X	X	X	X	X	X[13]
Urinalysis[6]	IND or MNT	X	X	X	X	X	X
Lipid Profile, Fasting	IND or MNT		X	X	X		X
Urine β-hCG[7]	IND or MNT	X	X	X	X	X	X

Study Procedure	Baseline	Open Label Treatment Period					
	Day 1[1]	Month 1 (± 5 days)	Month 2 (± 5 days)	Month 4 (± 5 days)	Month 6 (± 5 days)	Month 9 (± 5 days)	Month 12 (± 5 days) / ET[2]
TB Testing/Chest Radiograph, if necessary, in Specific Countries[8]							X
Endoscopic Procedure							
Flexible Sigmoidoscopy/ Colonoscopy (if preferred)	IND or MNT		X[9]				X[14]
Eligibility Assessment	X						
Dose Assignment	X						
Study Medication Dispensing	X		X	X	X	X	X
Study Drug Accountability		X	X	X	X	X	X
Ulcerative Colitis Assessments							
Bowel Movement Diary Data[10]	X	X	X	X	X	X	X
Partial Mayo Score	IND or MNT	X		X	X	X	
Mayo Score	IND or MNT		X				X
Health Outcome Assessments[11]							
IBDQ	IND or MNT		X		X		X
CCI							
Adverse Event Assessment	IND or MNT	X	X	X	X	X	X
Concomitant Medication	IND or MNT	X	X	X	X	X	X
CCI							

1. The baseline visit of Study A3921139 is the same visit as either the Week 53 visit for subjects who complete Study A3921096 or early termination visit for subjects who are treatment failures during Study A3921096, OR is the same visit as the Week 9 visit for subjects who complete Study A3921094 or A3921095 and are deemed to be non-responders. All procedures done at Week 52/53 visit or the early termination visit of Study A3921096 or Week 8/9 visit of Study A3921094 or A3921095 for subjects enrolled into this study will be used as the baseline data for Study A3921139. Procedures listed as IND or MNT = Induction Study or Maintenance Study procedures will NOT BE REPEATED at baseline of Study A3921139. Only those procedures marked with a 'X' will be performed at the baseline visit.
2. Subjects who discontinue treatment early from the study will have an early termination (ET) visit and all procedures listed at Month 12/ET will be performed on the last day the subject takes the study medication or as soon as possible. Subjects from the induction studies A3921094 or A3921095 (ie, non-responders) who fail to demonstrate clinical response at Month 2 will be withdrawn from the study and will be required to have a modified ET visit consisting of only the following procedures: complete physical examination, 12-lead ECG, return all study drug and perform study drug accountability. The Month 12/ET visit will also serve as the Evaluation Visit for Entry into

Study A3921288. If, after completion of the evaluation visit for entry into Study A3921288, a subject does not meet eligibility criteria, they should remain in this study (A3921139).

3. Medical history from either the induction studies (A3921094 or A3921095) or the maintenance study (A3921096) will be used for Study A3921139. Resolved AEs occurring in these studies will be captured as part of Baseline Medical History, while ongoing AEs from either A3921094 or A3921095, or A3921096 study will be followed throughout Study A3921139.
4. The targeted physical examination consists of weight, general appearance, and examinations of eyes, mouth, lungs, heart, abdomen, musculoskeletal, extremities, skin and lymph nodes.
5. 12-lead ECG and vital sign measurements should be performed before laboratory blood collection and endoscopic procedure, when possible.
6. Dipstick in all cases; microscopy analysis is indicated if urinalysis is positive for blood, nitrite, leucocyte esterase and/or protein. Urine culture performed if urinalysis is positive for nitrite and/or leucocyte esterase or if clinically indicated.
7. Urine β-hCG to be performed only for women of childbearing potential. Pregnancy testing may be performed more frequently per local regulations.
8. Annual tuberculosis (TB) screening will be conducted using Quantiferon-TB® Gold Plus test (QFT) for subjects in those countries in which TB prevalence has been reported at a rate of >50 cases per 100,000 persons (see Section 7.3.6). TB testing is not required at the ET visit. All subjects with positive results must have chest radiograph performed. Note: QFT should not be performed in subjects who had positive result during prior testing (screening visit in Study A3921094 or A3921095 or prior annual visits) and/or previously received adequate treatment for TB.
9. Flexible sigmoidoscopy/colonoscopy (if preferred) will be performed at Month 2 for all subjects. The Mayo endoscopic subscore at Month 2 was assessed by both central reader and study site investigator prior to implementation of Amendment 8. After implementation of Amendment 8, the Month 2 Mayo endoscopic subscore will only be assessed by site investigator. All other endoscopies performed in this study will only be read by study site investigator. Subjects from the induction studies A3921094 or A3921095 (ie, non-responders) who fail to demonstrate clinical response at Month 2 of this study will be withdrawn from the study.
10. Bowel movement (BM) diary data will be collected through a phone-based IVRS tool. Subjects will be instructed in its use at the Baseline visit. Automatic reminders will be generated prior to scheduled visits to remind subjects to start completing the BM diary daily approximately 7 days prior to their next scheduled visit. Study site staff will also contact the subjects 7 days prior to the scheduled visit to ensure compliance. In addition, subjects should be instructed to start completing the BM diary whenever he/she experiences any worsening of UC symptoms anytime during the study.
11. Subjects should complete the self-administered IBDQ, [redacted] prior to any clinical assessments at the scheduled times noted above. A member of the site staff should be available if a subject requires further instruction and to review the questionnaires for completeness prior to leaving the clinic visit. [redacted]

13. For subjects being evaluated for entry into Study A3921288, the serum chemistry panel will include addition of hs-CRP.
14. For subjects being evaluated for entry into Study A3921288, endoscopy (ie, flexible sigmoidoscopy or colonoscopy) will only be performed in subjects who have not had an endoscopy performed within the previous 6 months prior to baseline visit of A3921288. Endoscopic assessment will only be done by local site read.

Schedule of activities for Years 2 and 3:

Study Procedure	Open Label Treatment Period							
	Month 15 (±7 days)	Month 18 (±7 days)	Month 21 (±7 days)	Month 24 (±7 days)	Month 27 (±7 days)	Month 30 (±7 days)	Month 33 (±7 days)	Month 36 (±7 days)
Visit Number	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
Complete Physical Examination				X				X
Targeted Physical Examination[4]	X	X	X		X	X	X	
Extra-Intestinal Manifestations				X				X
Vital Signs[5]	X	X	X	X	X	X	X	X
12-Lead ECG[5]				X				X
Laboratory								
Hematology	X	X	X	X	X	X	X	X
Serum Chemistry	X	X	X	X	X	X	X	X
Urinalysis[6]	X	X	X	X	X	X	X	X
Lipid Profile, Fasting		X		X		X		X
Urine β-hCG[7]	X	X	X	X	X	X	X	X
TB Testing/Chest Radiograph, if necessary, in Specific Countries[8]				X				X
Endoscopic Procedure								
Flexible Sigmoidoscopy/ Colonoscopy (if preferred)				X				X
Study Medication Dispensing	X	X	X	X	X	X	X	X
Study Drug Accountability	X	X	X	X	X	X	X	X
Ulcerative Colitis Assessments								
Bowel Movement Diary Data[10]	X	X	X	X	X	X	X	X
Partial Mayo Score	X	X	X		X	X	X	
Mayo Score				X				X
Health Outcome Assessments[11]								
IBDQ		X		X		X		X
CCI								
Adverse Event Assessment	X	X	X	X	X	X	X	X
Concomitant Medication	X	X	X	X	X	X	X	X

Study Procedure	Open Label Treatment Period							
	Month 15 (±7 days)	Month 18 (±7 days)	Month 21 (±7 days)	Month 24 (±7 days)	Month 27 (±7 days)	Month 30 (±7 days)	Month 33 (±7 days)	Month 36 (±7 days)
CCI [redacted]								

4. The targeted physical examination consists of weight, general appearance, and examinations of eyes, mouth, lungs, heart, abdomen, musculoskeletal, extremities, skin and lymph nodes.
5. 12-lead ECG and vital sign measurements should be performed before laboratory blood collection and endoscopic procedure, when possible.
6. Dipstick in all cases; microscopy analysis is indicated if urinalysis is positive for blood, nitrite, leucocyte esterase and/or protein. Urine culture performed if urinalysis is positive for nitrite and/or leucocyte esterase or if clinically indicated.
7. Urine β-hCG to be performed only for women of childbearing potential. Pregnancy testing may be performed more frequently per local regulations.
8. Annual TB screening will be conducted using Quantiferon-TB® Gold Plus test (QFT) for subjects in those countries in which TB prevalence has been reported at a rate of >50 cases per 100,000 persons (see Section 7.3.6). TB testing is not required at the ET visit. All subjects with positive results must have chest radiograph performed. Note: QFT should not be performed in subjects who had positive result during prior testing (screening visit in Study A3921094 or A3921095 or prior annual visits) and/or previously received adequate treatment for TB.
10. Bowel movement (BM) diary data will be collected through a phone-based IVRS tool. Automatic reminders will be generated prior to scheduled visits to remind subjects to start completing the BM diary daily approximately 7 days prior to their next scheduled visit. Study site staff will also contact the subjects 7 days prior to the scheduled visit to ensure compliance. In addition, subjects should be instructed to start completing the BM diary whenever he/she experiences any worsening of UC symptoms anytime during the study.
11. Subjects should complete the self-administered IBDQ, CCI [redacted] prior to any clinical assessments at the scheduled times noted above. A member of the site staff should be available if a subject requires further instruction and to review the questionnaires for completeness prior to leaving the clinic visit. CCI [redacted]

CCI [redacted]

Schedule of Activities for Year 4:

Study Procedure	Open-Label Treatment Period			
	Month 39 (±7 days)	Month 42 (±7 days)	Month 45 (±7 days)	Month 48 (±7 days)
Visit Number	**16**	**17**	**18**	**19**
Complete Physical Examination				X
Extra-Intestinal Manifestations				X
Vital Signs[5]	X	X	X	X
Laboratory				
Hematology	X	X	X	X
Serum Chemistry	X	X	X	X
Lipid Profile, Fasting		X		X
Urine β-hCG[7]	X	X	X	X
TB Testing/Chest Radiograph, if necessary, in Specific Countries[8]				X
Ulcerative Colitis Assessments				
Bowel Movement Diary Data[10]	X	X	X	X
Partial Mayo Score	X	X	X	X
Health Outcome Assessments[11]				
IBDQ				X
CCI				
Study Medication Dispensing	X	X	X	X
Study Drug Accountability	X	X	X	X
Adverse Event Assessment	X	X	X	X
Concomitant Medication	X	X	X	X
Risk Factor Check for Pulmonary Embolism[12]	X	X	X	X
CCI				

Schedule of Activities for Year 5:

Study Procedure	Open-Label Treatment Period			
	Month 51 (±7 days)	Month 54 (±7 days)	Month 57 (±7 days)	Month 60 (±7 days)
Visit Number	**20**	**21**	**22**	**23**
Complete Physical Examination				X
Extra-Intestinal Manifestations				X
Vital Signs[5]	X	X	X	X
Laboratory				
Hematology	X	X	X	X
Serum Chemistry	X	X	X	X
Lipid Profile, Fasting		X		X
Urine β-hCG[7]	X	X	X	X
TB Testing/Chest Radiograph if necessary, in Specific Countries[8]				X
Ulcerative Colitis Assessments				
Bowel Movement Diary Data[10]	X	X	X	X
Partial Mayo Score	X	X	X	X
Health Outcome Assessments[11]				
IBDQ				X
CCI				
Study Medication Dispensing	X	X	X	X
Study Drug Accountability	X	X	X	X
Adverse Event Assessment	X	X	X	X
Concomitant Medication	X	X	X	X
Risk Factor Check for Pulmonary Embolism[12]	X	X	X	X
CCI				

Schedule of Activities for Year 6:

Study Procedure	Open-Label Treatment Period				Follow-Up Visit
	Month 63 (±7 days)	Month 66 (±7 days)	Month 69 (±7 days)	Month 72* (±7 days)	4 weeks after last dose[14] (±7 days)
Visit Number	**24**	**25**	**26**	**27**	**28**
Complete Physical Examination				X	
Extra-Intestinal Manifestations				X	
Vital Signs[5]	X	X	X	X	X
Laboratory					
Hematology	X	X	X	X	X
Serum Chemistry	X	X	X	X	X
Lipid Profile, Fasting		X		X	
Urine β-hCG[7]	X	X	X	X	X
TB Testing/Chest Radiograph, if necessary, in Specific Countries[8]				X	
Ulcerative Colitis Assessments					
Bowel Movement Diary Data[10]	X	X	X	X	
Partial Mayo Score	X	X	X	X	
Health Outcome Assessments[11]					
IBDQ				X	
CCI					
Study Medication Dispensing	X	X	X	X	
Study Drug Accountability	X	X	X	X	
Adverse Event Assessment	X	X	X	X	X
Concomitant Medication	X	X	X	X	X
Risk Factor Check for Pulmonary Embolism[12]	X	X	X	X	
CCI					

5. 12-lead ECG and vital sign measurements should be performed before laboratory blood collection and endoscopic procedure, when possible. NOTE: Weight will be recorded along with vital sign measurements during visits where complete or targeted physical examinations are not performed.

7. Urine β-hCG to be performed only for women of childbearing potential. Pregnancy testing may be performed more frequently per local regulations.

8. Annual TB screening will be conducted using Quantiferon-TB® Gold Plus test (QFT) for subjects in those countries in which TB prevalence has been reported at a rate of >50 cases per 100,000 persons (see Section 7.3.6). TB testing is not required at the ET visit. All subjects with positive results must have chest radiograph performed. Note: QFT should not be performed in subjects who had positive result during prior testing (screening visit in Study A3921094 or A3921095 or prior annual visits) and/or previously received adequate treatment for TB.
10. Bowel movement (BM) diary data will be collected through a phone-based IVRS tool. Automatic reminders will be generated prior to scheduled visits to remind subjects to start completing the BM diary daily approximately 7 days prior to their next scheduled visit. Study site staff will also contact the subjects 7 days prior to the scheduled visit to ensure compliance. In addition, subjects should be instructed to start completing the BM diary whenever he/she experiences any worsening of UC symptoms anytime during the study.
11. Subjects should complete the self-administered IBDQ, CCI [redacted] prior to any clinical assessments at the scheduled times noted above. A member of the site staff should be available if a subject requires further instruction and to review the questionnaires for completeness prior to leaving the clinic visit. CCI [redacted].
12. **Per Amendment 11, all subjects will be asked at every study visit if they have any newly-developed risk factors for pulmonary embolism as described in Section 7.3.12. At the time of Amendment 11, all subjects have completed the Month 36 study visit and therefore this procedure is only collected at visits beyond Month 36 as applicable to each subject's individual participation. If a subject has a newly identified risk factor for pulmonary embolism and is receiving tofacitinib 10 mg BID, they must reduce their dose to tofacitinib 5 mg BID.**

CCI [redacted]

14. All subjects are required to have a 4-week follow-up evaluation after the last dose of study medication.

* If the study continues beyond Month 72 for an individual subject, the investigator should continue to follow the same visit schedule and study procedures outlined during the study visits of year 4.

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APPENDICES

1. INTRODUCTION

Ulcerative colitis (UC) is a chronic, relapsing, inflammatory disease of the colon characterized by alternating episodes of remission and spontaneous relapse. The prevalence has been estimated to range from 37 to 246 cases per 100,000 persons in North America and 21 to 243 cases per 100,000 persons in Europe.[1] It is most commonly diagnosed in late adolescence and early adulthood, with the peak incidence occurring between 20-39 years of age.[2]

Although the precise pathogenesis of UC is presently unknown, the prevailing paradigm is dysregulation of the enteric immune response in genetically susceptible individuals.[3] Such defective immune system leads to upregulation of macrophages and Th2 lymphocytes in UC, as a result of inability to appropriately downregulate both innate and adaptive immune responses to endogenous luminal antigens. This produces an excess of cytokines, interleukins and chemokines, all of which can lead to enhanced inflammation and tissue damage. Evidence has shown that upregulation of some of the common gamma-chain cytokines may play a role in the pathogenesis of inflammatory bowel disease (IBD), of which the two main forms are UC and Crohn's disease.

The hallmark clinical presentations for UC include diarrhea, rectal bleeding, passage of mucus, tenesmus, urgency, and abdominal pain. Patients may also experience fatigue, fevers, weight loss, and dehydration, particularly in more severe cases. Mortality is not increased in UC in general, but the disease may present as life-threatening fulminant colitis. Most patients follow a chronic intermittent course with periods of increased disease activity separated by periods of disease remission. After the initial diagnosis, approximately half of patients will have active disease at any single point in time and approximately 90% will have a disease course characterized by intermittent flares.[5]

The disease almost universally involves the rectum, extending proximally to involve a portion of or the entire colon. At the time of initial presentation, approximately 45% of patients have disease limited to the rectum and sigmoid (proctosigmoiditis), approximately 35% have disease extending beyond the sigmoid but not involving the entire colon, and approximately 20% of patients have pancolitis.[5] However, a substantial number of patients will experience disease extension over time.[6,7]

Current therapy for the treatment of UC includes 5-aminosalicylic acid (5-ASA), systemic and/or topical steroids, immunosuppressants such as azathioprine/6-mercaptopurine and cyclosporine, and tumor-necrosis factor alpha (TNF alpha) blockers.[4] However, despite these treatment options, a significant proportion of UC patients still require colectomy for refractory or severe fulminant disease, or in some cases for cancer prevention.[5] Although patients with UC are often considered to be cured by restorative proctocolectomy, the quality of life may be poor and the surgery can be associated with short-term and long-term complications, including a decreased female fecundity and the development of pouchitis.[11,8] At present, no current pharmacological therapy is able to provide a cure for UC. The primary treatment goal is to induce remission and then to maintain this state. Therefore, identification of new effective therapies is an important area of research.

This study is designed to evaluate the long term safety and tolerability of tofacitinib in patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy.

1.1. Indication

Tofacitinib, also known as tofacitinib citrate or CP-690,550, is being developed for the treatment of patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy.

1.2. Background and Rationale

Tofacitinib is a potent, selective inhibitor of the JAK family of kinases with a high degree of selectivity against other kinases in the human genome.[12] In kinase assays, tofacitinib inhibits JAK1, JAK2, JAK3, and to a lesser extent TyK2. In cellular settings where JAK kinases signal in pairs, tofacitinib preferentially inhibits signaling by heterodimers containing JAK3 and/or JAK1 with functional selectivity over JAK2 homodimer signaling.[13] Inhibition of JAK1 and JAK3 by tofacitinib blocks signaling through the common gamma chain containing receptors for several cytokines, including IL-2, -4,-7,-9, -15 and -21. These cytokines are integral to lymphocyte activation, proliferation, and function, and inhibition of their signaling may thus result in modulation of multiple aspects of the immune response. In addition, inhibition of JAK1 will result in attenuation of signaling by additional pro-inflammatory cytokines, such as IL-6 and IFNγ.[14] At higher exposures, inhibition of erythropoietin, prolactin and other hormones could occur via inhibition of JAK2 homodimer signaling.

The broad effects of JAK1/3 inhibition on multiple cytokine pathways provides the rationale for developing tofacitinib as treatment for several diseases in which lymphocyte activation/proliferation plays a pathogenic role. Tofacitinib is being studied as an oral treatment for UC, Crohn's disease, as a disease-modifying anti-rheumatic drug (DMARD) for the treatment of RA, as treatment for plaque psoriasis and for the prevention of renal allograft rejection.

Summary of Efficacy:

Efficacy of tofacitinib in the treatment of UC has been evaluated in one Phase 2 study: A3921063. Efficacy of tofacitinib has also been evaluated in Crohn's disease, rheumatoid arthritis, psoriasis, and renal transplant. Details of the efficacy results in these patient populations can be found in the current version of the tofacitinib Investigator Brochure.

Study A3921063 was a randomized, double-blind, placebo-controlled Phase 2 study evaluating the safety and efficacy of tofacitinib in subjects with moderate to severe UC. In this study, 195 subjects with moderate to severe active UC were randomized at a 1:1:1:2:2 ratio into one of the five treatment groups of tofacitinib 0.5 mg BID, 3 mg BID, 10 mg BID, 15 mg BID, and the matched placebo for treatment duration of 8 weeks.

The study demonstrated dose-dependent improvements with tofacitinib treatment in clinical response (primary endpoint) and clinical remission rates. Based on protocol-predefined full-analysis population, the primary endpoint of clinical response (reduction of Mayo score by at least 3 points or 30% from baseline with an accompanying decrease in the subscore for rectal bleeding of at least 1 point or absolute subscore for rectal bleeding of 0 or 1) at Week 8 was achieved in 47.5%, 29.6%, 51.6%, 63.3%, and 80.0% of subjects in the placebo and tofacitinib 0.5 mg, 3 mg, 10 mg, and 15 mg BID groups, respectively. The proportions of subjects in clinical remission (total Mayo score of 2 or lower with no individual subscore exceeding 1) at Week 8 (secondary endpoint) were 12.2%, 7.4%, 35.5%, 50.0%, and 42.2% in the placebo and tofacitinib 0.5 mg, 3 mg, 10 mg, and 15 mg BID treatment groups, respectively. Based on the dose-response model, both 10 mg BID and 15 mg BID doses met the protocol-predefined criteria for proof of concept for the primary endpoint. These data were further supported by results in other secondary efficacy endpoints including endoscopic endpoints and by data in biomarkers and patient-reported outcomes.

Summary of Safety:

The clinical development program for tofacitinib includes healthy volunteers and patients with rheumatoid arthritis, psoriasis, ulcerative colitis, Crohn's disease, dry eye disease, and renal transplant recipients enrolled in more than 50 Phase 1, 2, and 3 studies. In the completed Phase 2 study in UC (A3921063), 146 patients with UC received at least one dose of tofacitinib (ranging from 0.5 mg BID to 15 mg BID) with 8-week treatment duration. In addition, in the completed Phase 2 study in Crohn's disease (A3921043), 105 patients with Crohn's disease received at least one dose of tofacitinib (ranging from 1 mg BID to 15 mg BID) with 4-week treatment duration. These two studies represent an approximate total of 28 patient-years of exposure in IBD (approximately 20 patient-years in UC and 8 patient-years in Crohn's disease).

Safety information from the 8-week Phase 2 study in UC (A3921063) is summarized below.

Based on the totality of the clinical data generated thus far, safety findings and potential risks that may be associated with the use of tofacitinib include serious and other important infections, including tuberculosis and herpes zoster, potential for malignancies including lymphoma, and potential for gastrointestinal perforations. Based on nonclinical data, there is the potential for tofacitinib to have effects on pregnancy and the fetus.

Laboratory changes observed with the oral use of tofacitinib in humans include decreases in neutrophil and lymphocyte counts and hemoglobin levels, increases in serum creatinine, total cholesterol, HDL cholesterol, LDL cholesterol, transaminases and creatine kinase. Recovery of laboratory changes upon discontinuation of tofacitinib treatment are characteristically observed.

In the Phase 2 UC study (A3921063), the overall incidences of AEs were similar between tofacitinib-treated and placebo-treated subjects. The most frequently reported AEs were colitis ulcerative (worsening of ulcerative colitis) (11.3%) and headache (7.2%). The majority of AEs were mild in severity. Most of the AEs were reported by the investigator as

unrelated to study treatment. There were 9 subjects (range 0-4 per treatment group, with highest incidence in the placebo group) with permanent discontinuation of study drug due to an AE. None of the tofacitinib-treated subjects had a treatment-related discontinuation. SAEs were reported in 10 subjects (range 0-4 per treatment group, with highest incidence in the placebo group). One subject each in the placebo and tofacitinib 0.5 mg and 3 mg groups experienced a treatment-related SAE (UC each in placebo and 0.5 mg groups; general physical health deterioration in 3 mg group).

There were no clinically significant changes from baseline at Week 8 in mean neutrophils, hemoglobin, hematocrit, serum creatinine, AST and ALT across all dose groups. Dose-related increases from baseline at Week 8 in both mean LDL and HDL were observed across all dose groups, with the largest increase occurring in the tofacitinib 15 mg group. In conclusion, tofacitinib up to the doses of 15 mg BID for study duration of 8 weeks was generally well tolerated in subjects with UC, and the overall safety profile was consistent with that observed in rheumatoid arthritis and psoriasis.

Complete information for this compound may be found in the Single Reference Safety Document (SRSD), which for this study is the Investigator's Brochure (IB).

1.3. Clinical Pharmacokinetics

The pharmacokinetics of tofacitinib in humans is characterized by rapid absorption and elimination, with a time to peak concentration (T_{max}) of approximately 0.5 hour and a half-life ($t_{1/2}$) of approximately 3 hours. Steady state pharmacokinetics is predictable from single dose data, with no evidence of accumulation. In general, systemic exposure of tofacitinib increases with dose in a dose-proportional manner without regard to duration or population.

The clearance mechanisms for tofacitinib in humans appear to be both non-renal (hepatic metabolism) and renal excretion of the parent drug, the former accounting for approximately 70% of the total clearance. The metabolism of tofacitinib appears to be primarily mediated by CYP3A4 with minor contribution from CYP2C19 (based on data from poor metabolizers of CYP2C19).

1.4. Rationale of Dose Selection

Study A3921139 is an extension to the Phase 3 placebo-controlled induction studies (A3921094 and A3921095) and the maintenance study (A3921096) to provide subjects long-term open-label therapy, thus the doses included in this study are supported by the dose selection rationale for the maintenance Study A3921096.

The inclusion of 5 mg BID and 10 mg BID in Study A3921096 is based on the dose-response data from the Phase 2 induction Study A3921063, where doses ranging from 0.5 mg BID to 15 mg BID were evaluated. It is expected that the maintenance effect will be achieved at doses not higher than the doses for achieving the induction effect. Based on the observed efficacy profile at 10 mg BID after dosing for 8 weeks in Study A3921063, this dose is expected to be sufficient to provide maintenance of remission for 12 months. Although there are no data available on persistence of efficacy with tofacitinib treatment beyond 8 weeks in

patients with UC, completed randomized-controlled studies in RA ranging from 6 to 24 weeks in duration showed persistence of efficacy up to 24 weeks. In addition as a small molecule, tofacitinib is not expected to have a loss of response due to immunogenicity once efficacy and safety are established in a specific patient. Inclusion of 5 mg BID in Study A3921096 allows evaluation of a maintenance dose lower than 10 mg BID. Importantly, extensive safety data from the RA program support the choices of 10 mg BID and 5 mg BID for this study.

The inclusion of both 5 mg and 10 mg BID in this study will provide long term safety data should 5 mg and/or 10 mg BID prove to be effective maintenance doses in Study A3921096.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

Primary objective:

- To assess the safety and tolerability of long-term tofacitinib therapy in subjects with UC.

Secondary objectives:

- To evaluate the efficacy of long-term tofacitinib therapy in subjects with UC.
- To evaluate the effect of long-term tofacitinib therapy on quality-of-life in subjects with UC.

2.2. Endpoints

Primary efficacy endpoint:

- As this is an open-label extension study, there will be no primary efficacy endpoint.

Secondary efficacy endpoints:

- The proportion of subjects in remission at Month 2, Month 12, Month 24 and Month 36. Remission in this study is defined as a Mayo score ≤2 with no individual subscore >1, and rectal bleeding subscore of 0.
- The proportion of subjects in clinical remission at Month 2, Month 12, Month 24 and Month 36. Clinical remission in this study is defined as a Mayo score ≤2 with no individual subscore >1.
- The proportion of subjects in partial Mayo score (PMS) remission over time. PMS remission in this study is defined as a partial Mayo score ≤2 with no individual subscore >1.

- The proportion of subjects who achieve mucosal healing at Month 2, Month 12, Month 24 and Month 36. Mucosal healing is defined as a Mayo endoscopic subscore of 0 or 1.

- The proportion of subjects with total score in Inflammatory Bowel Disease Questionnaire (IBDQ) ≥170 over time.

Safety endpoints:

- Incidence and severity of adverse events (AEs).

- Incidence of serious infections.

- Incidence and severity of clinical laboratory abnormalities, and change from baseline in clinical laboratory values.

- Incidence of vital sign abnormalities and change from baseline in vital signs.

- Incidence of clinically significant changes in physical examinations from baseline.

- Incidence of electrocardiogram (ECG) abnormalities during treatment.

- Summary of adjudicated safety events (eg, cardiovascular, malignancy, opportunistic infections).

- Proportion of subjects with addition of lipid lowering agents.

CCI [redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

3. STUDY DESIGN

This is a Phase 3, multi-center, open-label study in subjects who have completed or demonstrated treatment failure in the maintenance study A3921096, or who were non-responders after completing induction studies A3921094 or A3921095. Approximately 900 subjects are expected to become eligible for the study. This study will continue up to approximately July 2020. Individual subject duration of participation will vary depending on when the subject was enrolled into the study and the end date of approximately July 2020. Therefore, the duration of participation for an individual subject may range from approximately 4 years to more than 7 years. If the study continues beyond Month 72 for an individual subject, the investigator should continue to follow the same visit schedule and study procedures outlined during the study visits of year 4.

Subjects who completed Study A3921096 or had early withdrawal due to treatment failure as defined in the A3921096 protocol may be eligible to enroll in this study, A3921139. In addition, subjects who complete induction Study A3921094 or A3921095 and are classified as non-responders may be eligible to enroll in this study. The eligibility of a subject for this study will be assessed based on study data collected at Week 8/9 of Study A3921094 or A3921095 (for non-responders) or the Week 52/53 visit (for completers) or early termination visit (early withdrawals due to treatment failure) of Study A3921096. The study data collected at the Week 8/9 visit for Study A3921094 or A3921095 (for non-responders) or the Week 52/53 visit or early termination visit of Study A3921096 will be recorded as the baseline data for Study A3921139.

Eligible subjects will be assigned to either tofacitinib 5 mg BID or 10 mg BID depending on whether the subject is in remission at baseline of Study A3921139. Remission is defined by a total Mayo score ≤2 with no individual subscore >1, and rectal bleeding subscore of 0. Eligible subjects who are in remission at Week 52 of Study A3921096 will be assigned to receive tofacitinib 5 mg BID. For treatment assignment at baseline, the central read assessment of the Mayo endoscopic subscore will be used to determine if a subject is in remission. Subjects who complete Study A3921096 but do not meet the remission definition

or who are early withdrawals due to treatment failure in Study A3921096 are eligible to receive tofacitinib 10 mg BID. Treatment failure is defined by an increase in Mayo score of at least 3 points from baseline value of the maintenance study (A3921096), accompanied by an increase in rectal bleeding subscore by at least 1 point, and an increase of endoscopic subscore of at least 1 point (yielding an absolute endoscopic subscore of ≥2) after a minimum of 8 weeks of treatment in the maintenance study. In the scenario where the endoscopic subscore is a '3', and the maintenance baseline endoscopic subscore is already a '3' (maximum value), then an increase by at least 1 point will not be needed in order to meet treatment failure. However, all other components of the treatment failure criteria will still need to be met. Subjects who complete induction studies A3921094 or A3921095 and are classified as non-responders are also eligible to receive tofacitinib 10 mg BID.

Tofacitinib dose can be adjusted from 5 mg BID to 10 mg BID for efficacy and from 10 mg BID to 5 mg BID after meeting specific laboratory abnormalities or other protocol defined criteria regarding efficacy (see Section 5.8 for dose adjustment guidelines). Dose adjustments can only occur after a subject has received at least 8 weeks of treatment in Study A3921139.

Subjects who enroll into this study who are on tofacitinib 10 mg BID for at least 2 consecutive years, and who are in stable remission on tofacitinib 10 mg BID for at least 6 months may have the opportunity to enter Study A3921288 (A Phase 3b/4, Multi-Center, Double-Blind, Randomized, Parallel Group Study of Tofacitinib in Subjects with UC in Stable Remission) if they meet the eligibility criteria. These subjects must:

- Have received tofacitinib 10 mg BID for a minimum of 2 consecutive years in Study A3921139 (and not have their tofacitinib dose reduced to 5 mg BID due to safety or efficacy.
- Be in stable remission on tofacitinib 10 mg BID for the 6 month period in Study A3921139 up to and including the baseline visit of Study A3921288, defined as meeting all of the following criteria:
  - A partial Mayo score ≤2, with no individual subscore >1 and a rectal bleeding subscore of 0 at each study visit during the 6 month period in Study A3921139 prior to and at baseline of Study A3921288; AND
  - At least one assessment of remission based on Mayo score.
- Not be receiving any corticosteroids to treat their UC for at least 4 weeks prior to the baseline visit of Study A3921288.
- Not have any of the risk factors for pulmonary embolism as described in Section 7.3.12.

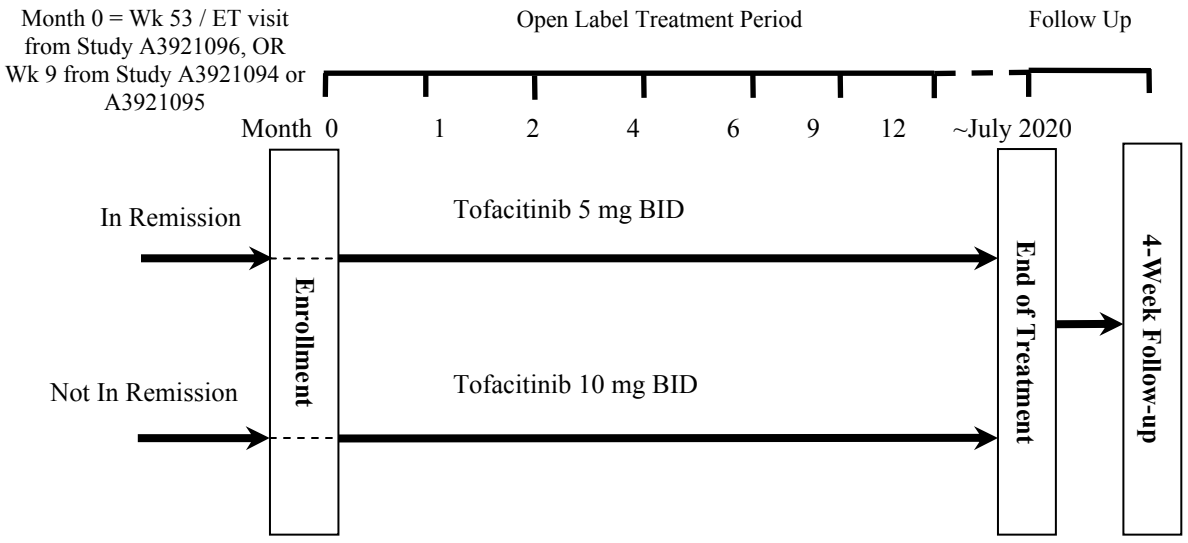
Study A3921288 will evaluate the efficacy and safety of tofacitinib in subjects in stable remission on 10 mg BID who decrease the dose to and remain on 5 mg BID compared to subjects who remain on 10 mg BID.

Subjects from the induction studies A3921094 or A3921095 (ie, non-responders) who fail to demonstrate clinical response at Month 2 of this study will be withdrawn from the study. Clinical response is defined by a decrease from the induction study baseline (A3921094 or A3921095) Mayo score of at least 3 points and at least 30%, with an accompanying decrease in the rectal bleeding subscore of at least 1 point or an absolute rectal bleeding subscore of 0 or 1. The endoscopic subscore based on central reading will be used to assess clinical response.

All subjects who withdraw early or who complete this open-label study, with the exception of those subjects entering Study A3921288, will have a 4-week safety follow-up evaluation after the last dose of study medication.

Subjects will be required to remain on stable doses of their concomitant medications for UC during the study period, with the exception of oral 5-ASA or sulfasalazine and oral corticosteroids described in Section 5.5. Subjects who enter this study on corticosteroids (eg, subjects who withdraw from Study A3921096 due to treatment failure or non-responders at the end of Study A3921094 or A3921095) will need to continue the steroid tapering regimen described in Study A3921096 (see Section 5.5). If a subject requires rescue therapy (see Section 5.7) or undergoes surgery for UC, the subject should be withdrawn from the study and appropriate agents should be given at the discretion of the investigator. If a subject discontinues the use of background oral 5-ASA or sulfasalazine and/or has the therapy re-initiated during the study, this will not constitute rescue therapy, and the subject will be permitted to remain in the study.

Figure 1. Study Design



- Study visits will occur every 3 months after the first year until approximately July 2020.
- All subjects will have a 4-week follow-up evaluation after their last dose of study medication.

Amendment 11

On 17 May 2019, the European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC) issued interim recommendations on the restrictions for prescriptions of tofacitinib. These interim recommendations on the restrictions for prescriptions of tofacitinib state that patients who are at high risk of blood clots in the lungs must not be started on tofacitinib 10 mg BID, and that such patients currently taking tofacitinib 10 mg BID for any condition must be switched to alternative treatments. Updated guidance from PRAC will be provided to patients and their healthcare professionals in the European Union (EU) once PRAC has completed its review of all available data.

In light of the PRAC interim recommendations in the EU, Study A3921139 will be modified globally through protocol Amendment 11, which will involve the following updates:

1. The study investigator or designee will need to review each subject's medical history and study records, including their concomitant medications, to determine whether he/she is at high risk for developing pulmonary embolism. If he/she has any of the risk factors listed below and is receiving tofacitinib 10 mg BID, the subject's tofacitinib dose should be reduced to 5 mg BID (see Section 5.8).

   A subject may be at high risk for pulmonary embolism if he/she:

   - has heart failure;
   - has inherited coagulation disorders;

- has had venous thromboembolism, either deep venous thrombosis or pulmonary embolism;
- is taking combined hormonal contraceptives or hormone replacement therapy;
- has malignancy (association is strongest with cancers other than non-melanoma skin cancers);
- is undergoing major surgery.

If a subject is identified as meeting any of the above criteria, they will be required to adjust their dose from 10 mg BID (administered as 2 x 5 mg tablets in the AM and 2 x 5 mg tablets in the PM) down to 5 mg BID (administered as 1 x 5 mg tablet in the AM and 1 x 5 mg tablet in the PM).

2. If a subject is taking tofacitinib 10 mg BID and does not have any of the risk factors listed above, he/she will remain on tofacitinib 10 mg BID.

3. If a subject is taking tofacitinib 5 mg BID, he/she will remain on tofacitinib 5 mg BID. However, if a subject has any of the risk factors listed above, he/she will not be permitted to increase their dose of tofacitinib to 10 mg BID if he/she experiences a flare of their UC disease (see Section 5.8).

4. The study investigator or designee will be required to ask each subject at each study visit if he/she has any newly-developed risk factors for pulmonary embolism, and if one is identified, the subject will not be permitted to receive tofacitinib 10 mg BID (see Section 7.3.12). At the time of Amendment 11, all subjects have reached the Month 36 study visit, therefore subjects will undergo the risk factor check at visits beyond Month 36 as applicable to their individual participation.

4. SUBJECT SELECTION

This study can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom protocol treatment is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular subject.

4.1. Inclusion Criteria

Subject eligibility should be reviewed and documented by an appropriately qualified member of the investigator's study team before subjects are included in the study.

Subjects must meet either inclusion criterion number 1 or 2, and all of the other following inclusion criteria to be eligible for enrollment into the study:

1. Subjects previously participated in Study A3921096 who either:
   - completed 52-week maintenance treatment in Study A3921096, or

- were early withdrawals from Study A3921096 and met treatment failure criteria defined by an increase in Mayo score of at least 3 points from baseline value of the maintenance study (A3921096), accompanied by an increase in rectal bleeding subscore by at least 1 point, and an increase of endoscopic subscore of at least 1 point (yielding an absolute endoscopic subscore of ≥2), after a minimum of 8 weeks of treatment in the maintenance study. In the scenario where the endoscopic subscore is a '3', and the maintenance baseline endoscopic subscore is already a '3' (maximum value), then an increase by at least 1 point will not be needed in order to meet treatment failure. However, all other components of the treatment failure criteria will still need to be met. Note, endoscopic subscores based on central reading will be used to assess treatment failure.

2. Subjects who previously participated in the induction Study A3921094 or A3921095 who:

   - did not demonstrate clinical response after completing 8 weeks of treatment. Clinical response is defined by a decrease from baseline in Mayo score of at least 3 points and at least 30%, with an accompanying decrease in the rectal bleeding subscore of at least 1 point or an absolute rectal bleeding subscore of 0 or 1, and

   - have an endoscopic subscore at Week 8 that is either the same or higher (worse) than the endoscopic subscore at Week 0 of Study A3921094 or A3921095. Note, endoscopic subscores based on central reading will be used to determine eligibility.

3. Female subjects of childbearing potential must agree to use a highly effective method of contraception throughout the study and for at least 4 weeks after the last dose of assigned treatment. Subjects in Canada who are women of childbearing potential and sexually active must use two contraceptive methods at the same time: one highly effective contraceptive method and one additional effective contraceptive method CCI [redacted].

4. Women of childbearing potential must have a negative pregnancy test prior to study enrollment.

5. Subjects who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, bowel movement diary calls, and other study procedures.

6. Evidence of a personally signed and dated informed consent document indicating that the subject (or a legal representative) has been informed of all pertinent aspects of the study.

4.2. Exclusion Criteria

Subjects presenting with any of the following will not be included in the study:

1. Subjects who had a major protocol violation in Study A3921094, A3921095 or A3921096, as determined by the Sponsor.

2. Presence of indeterminate colitis, microscopic colitis, ischemic colitis, infectious colitis, or clinical findings suggestive of Crohn's disease.

3. Subjects who have had surgery for UC or in the opinion of the investigator, are likely to require surgery for UC during the study period.

4. Subjects who are expected to receive any prohibited medications, including medications that are either moderate to potent CYP3A inducers or inhibitors, during the study period as specified in the protocol (see Appendix 2).

5. Subjects who are expected to receive live or attenuated virus vaccination during study period and for 6 weeks after last dose of study medication.

6. Women who are pregnant or breastfeeding, or planning to become pregnant during the study period.

7. Baseline 12-lead ECG that demonstrates clinically relevant abnormalities which may affect subject safety or interpretation of study results (see Appendix 4).

8. Subjects with evidence of colonic malignancy or any dysplasia (eg, "flat dysplasia"; polyp) identified on endoscopic exam during Study A3921096. Subjects with completely resected adenomatous polyp(s) outside of (proximal to) the extent of colitis may be eligible upon consultation with the sponsor. Note, pathology report must be reviewed prior to subject enrolment.

9. Subjects who, in the opinion of the investigator or Pfizer, will be uncooperative or unable to comply with study procedures.

10. Any other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.

11. Subjects who are investigational site staff members or relatives of those site staff members or subjects who are Pfizer employees directly involved in the conduct of the trial.

12. Subjects who are or interested in participating in other investigational studies during study participation.

4.3. Randomization Criteria

Subjects will not be randomized. Eligible subjects will be assigned to receive either tofacitinib 5 mg BID or 10 mg BID depending on whether the subject is in remission at baseline of Study A3921139. Subjects who are in remission at baseline of Study A3921139 will be assigned to receive tofacitinib 5 mg BID. All other subjects will be assigned to receive tofacitinib 10 mg BID. Subjects will be assigned a subject number in the order of

their acceptance into the study. This identifying number will be retained throughout the study.

4.4. Life Style Guidelines

4.4.1. Tobacco

Smoking can have an influence on the severity of ulcerative colitis symptoms. For that reason, subjects should keep their smoking habits constant throughout the study. Use of nicotine patch should be recorded as a concomitant medication.

4.4.2. Activity

Subjects are encouraged to avoid changing their accustomed exercise levels throughout the study.

4.4.3. Diet and Dietary Supplements

Subjects are encouraged to keep their diet habits constant throughout the study. It is recommended that subjects avoid consumption of grapefruit juice exceeding 8 ounces (~240 mL) total in a day while in the study.

For the purposes of this protocol, dietary supplements, such as vitamins, minerals, purified food substances, and herbals with pharmaceutical properties are considered as concomitant medications. Dietary supplements and herbs are allowed in the study, provided they are taken at stable doses prior to the baseline visit if they are started prior to study entry, and not associated with known effects on CYP3A that may impact on metabolism of the study medication. Starting dietary supplements or herbs during the study as a new medication is permissible as long as they are not listed on the prohibited medication list (see Appendix 2).

4.4.4. Vaccination

Vaccination with live components is prohibited during the study and for 6 weeks after last dose of study medication. Similarly, current routine household contact with individuals who have been vaccinated with live vaccine components should be avoided during treatment and for 6 weeks following completion of study treatment. Following vaccination with live component vaccines, the virus may be shed in bodily fluids, including stool, and there is a potential risk that the virus may be transmitted.

General guidelines suggest that exposure to individuals who have been vaccinated should be avoided for the following time periods:

a. FluMist® (intranasal influenza vaccine) for 1 week following vaccination.

b. Attenuated rotavirus vaccine for 10 days following vaccination.

c. Varicella for 4 weeks following vaccination.

d. Attenuated typhoid fever vaccine for 4 weeks following vaccination.

e. Oral polio vaccine for 6 weeks following vaccination.

4.4.5. Contraception

Based on preclinical data, tofacitinib has a potential risk of teratogenicity and early fetal loss. Due to this potential risk, women of childbearing potential should not be administered tofacitinib until pregnancy is excluded and should use a highly effective method of contraception (failure rate <1% when used consistently and correctly) during therapy with tofacitinib.

For the purposes of this protocol female subjects must be of non-childbearing potential or using adequate contraception, as described below.

4.4.5.1. Females of Non-Childbearing Potential

Female subjects of non-childbearing potential must meet at least one of the following criteria:

- Postmenopausal females are defined as females over the age of 45 years, who have been amenorrheic for at least 12 months with no alternative pathological or physiological cause. Postmenopausal status may be carried forward from Study A3921094, A3921095 or A3921096. If a female has not been confirmed to be postmenopausal during Study A3921094, A3921095 or A3921096, then FSH testing will be required at baseline in this study.

- Females who had a physician-documented hysterectomy and/or bilateral oophorectomy.

- Females who have medically-confirmed ovarian failure.

All other female subjects will be considered to be of childbearing potential.

4.4.5.2. Females of Childbearing Potential

All female subjects who, in the opinion of the investigator, are biologically capable of having children and are sexually active, must agree to use a highly effective method of contraception consistently and correctly for the duration of the active treatment period and through the 4-week follow-up procedures. The investigator, in consultation with the subject, will select the most appropriate method of contraception for the individual subject from the permitted list of contraception methods, and instruct the subject in its consistent and correct use. The investigator, at each study visit, will confirm and document consistent and correct use. In addition, the investigator will instruct the subject to call immediately if the selected birth control method is discontinued or if pregnancy is known or suspected.

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (ie, perfect use) and include:

1. Established use of oral, injected or implanted hormonal methods of contraception.

2. Correctly placed intrauterine device (IUD) or intrauterine system (IUS).
3. Male condom or female condom used WITH a spermicide (ie, foam, gel, film, cream, suppository).
4. Male sterilization with appropriately confirmed absence of sperm in the post-vasectomy ejaculate.
5. Bilateral tubal ligation or bilateral salpingectomy.
6. Absolute sexual abstinence, without a second method, may be considered an acceptable method at the discretion of the investigator.

CCI [redacted]

4.4.5.3. Pregnancy Testing

Female subjects of childbearing potential will be tested for urine β-hCG at baseline and at each study visit (or more frequently if required by local regulations, if a menstrual cycle is missed, or if potential pregnancy is otherwise suspected). Urine β-hCG testing will be performed at the study site using test kits supplied by the central laboratory using methodology with a testing sensitivity at least 25 mIU/mL. If at any point there is a case of a positive urine β-hCG test, the subject will have study drug interrupted and a serum sample will be submitted to the central laboratory for β-hCG testing. If the serum test confirms positive, the subject will be withdrawn from the study and all the necessary follow up will be conducted as per Section 8.9. If the serum test is negative, the subject may resume study drug.

4.4.5.4. Reproductive Status of Male Subjects

No tofacitinib effects on male fertility or offspring of dosed males have been observed in any preclinical studies conducted to date. Therefore, no specific contraceptive measures are required in male subjects during study participation.

4.4.5.5. Surgery

During the course of this study, no elective surgery should be scheduled without first consulting with the Pfizer medical monitor. Investigators should contact the Pfizer medical monitor regarding subjects who undergo non-elective surgery to discuss their suitability to remain in the study.

4.5. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the investigator site file.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, subjects are provided with a contact card. The contact card contains, at a minimum, protocol and investigational compound identifiers, subject study numbers, contact information for the investigational site, and contact details for a contact center in the event that the investigational site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the subject's participation in the study. The contact number can also be used by investigational staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigational site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigational site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the subject directly, and if a subject calls that number, he or she will be directed back to the investigational site.

5. STUDY TREATMENTS

Subjects will be assigned to one of two dose groups depending on their remission status at baseline of Study A3921139:

- Tofacitinib 5 mg BID (subjects in remission).
- Tofacitinib 10 mg BID (all other subjects).

Remission is defined by a total Mayo score ≤2 with no individual subscore >1, and rectal bleeding subscore of 0. Central read assessment of the Mayo endoscopic subscore will be used to determine if a subject is in remission at baseline.

5.1. Allocation to Treatment

Assignment of subject identification number, study medication, and site drug inventory control will be managed by a tele-randomization tool provided by the sponsor. A manual containing complete instructions for web or telephone access and use will be provided to each site prior to study start.

At the baseline visit, provided all inclusion/exclusion criteria have been met, the subject will be assigned to trial medication via the tele-randomization system. The investigative site will contact the tele-randomization system (online or via a telephone call). The site will enroll the subject into the tele-randomization system by indicating minimal information sufficient to distinguish one subject from another (eg, date of birth and initials).

Eligible subjects will be assigned to one of two dose groups by the investigative site, tofacitinib 5 mg BID or tofacitinib 10 mg BID, depending on their remission status at baseline in Study A3921139.

During a successful call, the tele-randomization system will give the investigative site a code which corresponds to study medication that has been previously shipped to the site and is in the site's inventory ready to be dispensed. This code corresponds to study medication of the dose group to which the subject has just been assigned.

As this is an open-label study, the investigator's knowledge of the treatment should not influence the decision to enroll a particular subject or affect the order in which subjects are enrolled.

5.2. Breaking the Blind

This is an open-label study. Assignment to tofacitinib will be open to the investigators, subjects and the Pfizer study team.

5.3. Drug Supplies

5.3.1. Formulation and Packaging

Tofacitinib will be provided as 5 mg tablets by the sponsor for oral administration. Tablets will be supplied in bottles. Sufficient study medication will be dispensed at baseline (Visit 1) and at each subsequent dispensing visit per the Schedule Of Activities to complete dosing until the next scheduled dispensing visit. The number of bottles dispensed will depend on whether the subject is taking 5 mg BID (1 bottle) or 10 mg BID (2 bottles), and the duration between the next dispensing study visit.

5.3.2. Preparation and Dispensing

Subjects will be dispensed tofacitinib 5 mg tablets in bottles as allocated by the tele-randomization system. At each dispensing visit, sufficient study medication of tofacitinib will be dispensed to complete dosing until the next scheduled visit. The amount of study medication dispensed must be recorded. At each study visit the subject must return all tofacitinib containers and any unused medication will be recorded and documented to account for all dispensed study medication.

5.3.3. Administration

Tofacitinib will be self-administered. If a subject is assigned to receive tofacitinib 5 mg BID, they will be instructed to take 1 tablet in the morning and 1 tablet in the evening, approximately 12 hours apart. If a subject is assigned to receive tofacitinib 10 mg BID, they will be instructed to take 2 tablets in the morning and 2 tablets in the evening, approximately 12 hours apart. If a tofacitinib dose is missed and the interval to the next scheduled dose is less than 6 hours, the missed dose of tofacitinib should not be administered. Tofacitinib may be taken with or without food.

Table 1 Study Drug Administration

Treatment Assignment	AM Dosing	PM Dosing
5 mg BID	1 tablet	1 tablet
10 mg BID	2 tablets	2 tablets

Medication errors may result, in this study, from the administration or consumption of the wrong product, by the wrong subject, at the wrong time, or at the wrong dosage strength. Such medication errors occurring to a study participant are to be captured on the medication error CRF, which is a specific version of the adverse event (AE) page, and on the SAE form

when appropriate. In the event of medication dosing error, the sponsor should be notified immediately.

Medication errors are reportable irrespective of the presence of an associated AE/SAE, including:

- Medication errors involving subject exposure to the investigational product.
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is captured on the medication error version of the AE page and, if applicable, any associated AE(s) are captured on an AE CRF page.

5.3.4. Compliance

Investigational product compliance will be assessed by the site at each study visit starting at the visit after the baseline visit (Visit 2) up to the end of treatment. Non-compliance is defined as taking less than 80% or more than 120% of study drug products as directed by the dosing instructions. Subjects are to bring the study drug bottle(s) with any remaining study drug and any empty bottle(s) to each visit for review. The investigator has the discretion to withdraw any subject from the study for reasons of non-compliance with the dosing regimen. Investigators should indicate on the appropriate CRF page noncompliance with study treatment and provide an explanation. Inventory control of all study medications must be rigorously maintained throughout the duration of the study until all medication has been accounted for and/or returned to the sponsor. Any discrepancies noted between drug dispensing records and the drug inventory must be reported to Pfizer.

5.4. Drug Storage and Drug Accountability

Tofacitinib must be stored at room temperature (15-30°C or 59-86°F) in a locked area with restricted access. Storage conditions stated in the SRSD, the IB, may be superseded by the label storage.

Investigators and site staff are reminded to check temperatures daily for business days and ensure that thermometers are working correctly as required for proper storage of investigational products. These include thermometers for both the room storage and refrigerator storage. Any temperature excursions should be reported immediately.

The investigator or appropriate delegate at the site (eg, pharmacist), will ensure that all study drug is stored in a secured area, under recommended storage condition, and in accordance with regulatory requirements.

The investigator must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product. To ensure adequate records, all drug supplies will be accounted for in the drug accountability inventory forms as instructed by Pfizer and will be monitored by counting of unused medications returned by the subject at each visit from Visit 2 to the end of treatment. All bottles used to distribute the drug supplies must be returned to the investigator by the subject and the investigator will return the bottles to Pfizer.

At the end of trial, Pfizer will provide instructions as to the disposition of any unused investigational product. If Pfizer authorizes destruction at the trial site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer. Destruction must be adequately documented.

5.5. Concomitant Medications

All subjects will be questioned about concomitant medication use at each study visit. In addition the following concomitant medications that the subject had been taking from the study they enrolled from (ie, Study A3921096, Study A3921094 or Study A3921095) and will continue to take in this study will be recorded:

Table 2. Concomitant Medications

Treatment Type	Information Recorded	Recording Period
Ulcerative colitis (UC)*	Daily dose, unit, frequency, route, start and stop dates	Treatment period Follow-up period
Oral corticosteroids	Total daily dose, reason for dose change, start and stop dates	Treatment period Follow-up period
Lipid lowering agents	Daily dose, unit, frequency, route, start and stop dates	Treatment period Follow-up period
Anti-hypertension agents	Start and stop dates	Treatment period Follow-up period
Anti-diabetic agents	Start and stop dates	Treatment period Follow-up period
All other treatments+	Indication, start and stop dates	Treatment period Follow-up period

* Concomitant treatment for UC must remain at a stable dose (no increase or decrease) during the study treatment period, with the exception of oral 5-ASA or sulfasalazine and oral corticosteroids as described below.

\+ Includes nonprescription drugs, vitamins, and dietary supplements.

The following therapies for the treatment of UC are allowed providing their doses are not changed (reduced or increased), with the exception of oral 5-ASA or sulfasalazine and oral corticosteroids (see below) during the study treatment period:

- Oral 5-ASA or sulfasalazine dose modifications during the study are permitted.
- Chronic treatment for ulcerative colitis with antibiotics (eg, metronidazole, rifaximin) if continued from the preceding study.

Oral Corticosteroids

- Oral corticosteroids are allowed for subjects entering Study A3921139 on oral corticosteroids (maximum dose of 25 mg/day of oral prednisone or equivalent) and tapering must commence starting the first week of the study.

- The daily dose of oral prednisone or equivalent should be decreased at a rate of 5 mg per week until the dose reaches 20 mg/day, then reduce by 2.5 mg to 5.0 mg weekly until the dose reaches 0 mg.

- *For example only*, if a subject is receiving oral prednisone 25 mg/day at baseline, the subject's corticosteroid tapering regimen could be as follows:

    - Baseline/Day 1: 25 mg/day

    - Week 1 (±2 days): 20 mg/day

    - Week 2 (±2 days): 15 mg/day

    - Week 3 (±2 days): 10 mg/day

    - Week 4 (±2 days): 7.5 mg/day

    - Week 5 (±2 days): 5.0 mg/day

    - Week 6 (±2 days): 2.5 mg/day

    - Week 7 (±2 days): 0 mg/day

- Oral budesonide: the daily dose should be decreased at a rate of 3 mg every 3 weeks until discontinuation.

    - *For example only*, if a subject is receiving oral budesonide 9 mg/day at baseline, the subject's steroid tapering regimen could be as follows:

    - Week 1 – 3 (Day 1 – Day 21): 6 mg/day

    - Week 4 – 6 (Day 22 – Day 42): 3 mg/day

    - Week 7 and beyond (≥ Day 43): 0 mg/day

- If a subject experiences worsening of UC symptoms during the corticosteroid taper or symptoms related to chronic corticosteroid therapy that in the opinion of the investigator are attributable to the corticosteroid taper, then the investigator may instruct the subject to revert back to the preceding dose in the taper schedule (ie, "step up"). The signs or symptoms leading to this change (eg, increased stool frequency, increased rectal bleeding) must be recorded on the CRF. Study subjects with signs or

symptoms attributed to corticosteroid taper are permitted to step up their corticosteroid dosage one time during participation in A3921139 and then resume corticosteroid taper to achieve steroid-free status.

- If a subject cannot tolerate tapering their corticosteroid dose below 10 mg/day, the subject is permitted to remain in the study provided their dose does not exceed 10 mg/day. However, efforts should be made to taper corticosteroids completely off.

- Re-initiation of oral corticosteroid therapy above 10 mg/day of prednisone or equivalent for the treatment of UC, after a subject has achieved steroid-free status during either Study A3921096 or A3921139, will be considered rescue therapy and the subject should be discontinued from the study.

- Initiation of oral corticosteroids during Study A3921139 for the treatment of non-UC indications (eg, allergic reaction, asthma, etc) may be permitted and the sponsor should be notified.

Subjects receiving tofacitinib 10 mg BID and either concomitant combined hormonal contraceptives or hormone replacement therapy must have their tofacitinib dose reduced to 5 mg BID.

5.6. Prohibited Concomitant Medications

The following medications are prohibited throughout the study (see Appendix 2):

- Azathioprine, 6-mercaptopurine and methotrexate;

- Cyclosporine, mycophenolate mofetil/mycophenolic acid and tacrolimus;

- Interferon;

- Anti-TNF alpha therapy (eg, infliximab, adalimumab, golimumab, or certolizumab);

- Intravenous and rectally administered corticosteroids;

- Rectally administered 5-ASA;

- Natalizumab, vedolizumab, or any other anti-adhesion molecule therapy (including investigational agents);

- Other investigational or marketed immunosuppressants or biologics with immunomodulatory properties;

- Leukocyte apheresis including selective lymphocyte, monocyte or granulocyte apheresis (eg, Cellsorba®) or plasma exchange;

- Moderate to potent CYP3A inducers or inhibitors listed in Appendix 2 due to potential for drug interactions or confounding of data interpretation.

5.7. Rescue Therapy

If a subject requires initiation of a new therapy for UC (including re-initiation of oral corticosteroid therapy above 10 mg/day of prednisone or equivalent after a subject has achieved steroid-free status during either Study A3921096 or A3921139), the subject should be withdrawn from the study and appropriate agents should be given at the discretion of the investigator. If a subject discontinues the use of background oral 5-ASA or sulfasalazine during the study and/or has the therapy re-initiated, this will not constitute rescue therapy, and the subject will be permitted to remain in the study.

5.8. Tofacitinib Dose Adjustment Guidelines

The maximum tofacitinib dose allowed in this study is 10 mg BID. Tofacitinib dose adjustments (increase or decrease) can only occur after a subject has received at least 8 weeks of treatment in Study A3921139.

If a subject receiving tofacitinib 5 mg BID experiences loss of response, defined by an increase in partial Mayo score of at least 2 points from baseline in the maintenance study (A3921096) for two consecutive visits (at least 2 weeks apart), accompanied by an increase in rectal bleeding subscore by at least 1 point from baseline of the maintenance study (A3921096), then the subject could be scheduled for endoscopy to determine if the subject is experiencing a flare. Flare is defined by an increase in Mayo score of at least 3 points from baseline value of the maintenance study (A3921096), accompanied by an increase in rectal bleeding subscore by at least 1 point, and an increase of endoscopic subscore of at least 1 point (unless the endoscopic subscore was a '3' at baseline and remains a '3'), after a minimum of 8 weeks of treatment in Study A3921139. Once the subject is confirmed to meet the definition for flare, documented by site read endoscopy, the investigator may increase the tofacitinib dose from 5 mg BID to 10 mg BID provided that the subject does not have any of the risk factors for pulmonary embolism.

Subjects receiving tofacitinib 5 mg BID who develop one or more of the risk factors for pulmonary embolism during the study will not be permitted to increase their dose to tofacitinib 10 mg BID.

Clostridium difficile (C. difficile) toxin testing is recommended for subjects in whom C. difficile infection is suspected (eg, atypical symptoms or features of their usual UC disease course, significantly worsening disease activity assessments from the previous visit, and/or the presence of risk factors such as recent antibiotic use or a recent history of C. difficile infection). A full course of C. difficile treatment, as defined by local practice, must be given to subjects with C. difficile infection to permit their continued participation in the study. Subjects with C. difficile infection that meets serious infection criteria must be withdrawn from the study. Stool testing and treatment for other enteric pathogens is at the discretion of the investigator.

For subjects receiving tofacitinib 10 mg BID, the tofacitinib dose may be adjusted to 5 mg BID if the subject meets any of the following laboratory criteria after they are repeated and confirmed within approximately 7 days:

- Any single hemoglobin value that drops >2 g/dL (>20 g/L) below baseline of Study A3921139.
- Absolute neutrophil count <1.2 x 10^9/L (<1200/mm^3).
- Absolute lymphocyte count <0.75 x 10^9/L (<750/mm^3).
- Platelet count <100 x 10^9/L (<100,000/mm^3).

In addition, for subjects receiving tofacitinib 10 mg BID, the tofacitinib dose may be adjusted to 5 mg BID if the subject is in remission (based on Mayo score) or in PMS remission at Month 24 or any visit beyond Month 24, after discussion with the sponsor. PMS remission is defined as a partial Mayo score ≤2 with no individual subscore >1. If a subject experiences loss of response and flare after the dose reduction from 10 mg BID to 5 mg BID, the dose may be increased back to 10 mg BID. In this situation, loss of response is defined as an increase in partial Mayo score of at least 2 points from the time when the subject was in remission or PMS remission (ie, when the dose was reduced to 5 mg BID) for two consecutive visits (at least 2 weeks apart), accompanied by an increase in rectal bleeding subscore by at least 1 point from when the subject was in remission or PMS remission. If response is lost, endoscopy should be performed to determine if the subject is experiencing a flare. Flare, in this situation, is defined by an increase in Mayo score of at least 3 points from the time when the subject was in remission or PMS remission, accompanied by an increase in rectal bleeding subscore by at least 1 point, and an increase of endoscopic subscore of at least 1 point (unless the endoscopic subscore was a '3' and remains a '3').

Lastly, subjects receiving tofacitinib 10 mg BID and who are identified to have one or more of the risk factors for pulmonary embolism will need to reduce their tofacitinib dose to 5 mg BID.

Tofacitinib dose adjustments should be implemented at a scheduled study visit, unplanned study visit, or upon verification of laboratory abnormalities upon repeat testing. Subjects who meet the laboratory discontinuation criteria described in Appendix 3 will be withdrawn from the study.

5.9. Tofacitinib Temporary Withholding

If the investigator deems it necessary to withhold tofacitinib to treat a non-serious infection or other medical condition, temporary withholding is permitted for up to 5 days. If study drug interruption exceeding 5 days is required for a medical reason, the investigator must contact the sponsor for approval.

Temporary withholding of tofacitinib, as described above, is permitted once during the study without obtaining prior approval from the sponsor. Any additional request(s) for temporary withholding of study drug require documented approval by the sponsor.

6. STUDY PROCEDURES

6.1. Study Period

6.1.1. Baseline (Visit 1)

The baseline visit will occur on the same day as either the Week 9 visit for those subjects enrolling from Study A3921094 or A3921095, or the same day as the Week 53 visit or the early termination visit for those subjects enrolling from Study A3921096.

Subject's eligibility into the study will be evaluated at Baseline of Study A3921139 based on remission status, AEs, physical examination, ECG (read by study site), and all inclusion/exclusion criteria.

For eligible subjects from Study A3921096, all relevant study information recorded on CRFs at Week 52/53 or the early termination visit of Study A3921096 will be used as baseline data for Study A3921139. For eligible subjects from Study A3921094 or Study A3921095, all relevant study information recorded on CRFs at Week 8/9 of Study A3921094 or A3921095 will be used as baseline data for Study A3921139.

To prepare for study participation, subjects will be instructed to continue to follow the Life Style Guidelines (see Section 4.4) and Concomitant Medications (see Section 5.5) as they did in their previous study.

The study investigator or appropriate delegate at the site will discuss with each subject the nature of the study, its requirements, risks and its restrictions. Written informed consent must be obtained prior to performing any protocol-specific procedures.

The following procedures will be recorded:

- Informed consent.
- Complete medical history. Medical history from either the induction studies (A3921094 or A3921095) or the maintenance study (A3921096) will be used as baseline for Study A3921139. Resolved AEs occurring in these studies will be captured as part of Baseline Medical History, while ongoing AEs from either Study A3921094 or A3921095, or A3921096 will be followed throughout Study A3921139.

The following procedures will be recorded from either Week 8/9 of Study A3921094 or A3921095 or from Week 52/53 or early termination visit of Study A3921096:

- UC Assessments (review of Bowel Movement Diary Data, calculation of Mayo score and partial Mayo score).

- Health Outcome (HO) Assessments (IBDQ, [redacted].
- Complete physical examination (including weight).
- Vital signs including temperature.
- 12-lead electrocardiography (ECG). ECG reading from the study sites will be used to determine eligibility. Central reading will be used for data analysis. See Section 7.3.11.
- Extra-intestinal manifestations.
- Laboratory blood tests including:
  - Serum chemistry.
  - Hematology.
  - Lipid profile (fasting).
  - [redacted]
- Urinalysis.
- Urine β-hCG for women of childbearing potential.

Eligibility Assessment

- Review study data collected from Week 8/9 of Study A3921094 or A3921095 to assess if a subject is eligible for Study A3921139. Similarly, review study data collected from either Week 52/53 or the early termination visit of Study A3921096 to assess eligibility into Study A3921139. This includes an assessment of all inclusion/exclusion criteria.

Entry into Study A3921139

- Dose assignment based on subject's remission status (see Section 4.3).
- Subjects will be reminded of instructions for using the phone-based IVRS tool (Bowel Movement Diary).
- Study medication dispensing.

Assessments to be used from Study A3921094, A3921095 or A3921096

- Adverse event monitoring from either Week 8/9 of the induction studies (A3921094 or A3921095) or Week 52/53 or early termination visit of the maintenance study (A3921096) will be used in Study A3921139. Resolved AEs occurring in these studies will be captured as part of Baseline Medical History, while ongoing AEs from either Study A3921094 or A3921095, or A3921096 will be followed throughout Study A3921139.

- Concomitant medication assessment of current and prior medications including a complete history of all drugs (including nonprescription drugs, vitamins, and dietary supplements), taken during Study A3921094, A3921095 or A3921096. Prior medications recorded in the study the subject enrolls from will be used for Study A3921139.

6.1.2. Month 1 (±5 days, Visit 2)

The following procedures will be performed:

- [redacted]

- UC Assessments (review Bowel Movement Diary Data and calculate partial Mayo score, see Section 7.1).

- Targeted physical examination (including weight, general appearance, and examinations of eyes, mouth, lungs, heart, abdomen, musculoskeletal, extremities, skin and lymph nodes, see Section 7.3.2).

- Vital signs including temperature (see Section 7.3.1).

- Laboratory blood tests (see Section 7.3.5):

  - Hematology.

  - Serum chemistry.

- Urinalysis (see Section 7.3.5).

- Urine β-hCG for women of childbearing potential (see Section 7.3.7).

- Study medication accountability.

- Adverse event monitoring.

- Concomitant medication assessment.

6.1.3. Months 2, 4 and 6 (±5 days, Visits 3, 4 and 5)

Visit procedures are identical for all visits, except where noted.

Subjects are required to fast (no food or drink except water) for at least 9 hours prior to these visits, as required for fasting lipid profile and fasting glucose sample collection.

The following procedures will be performed:

- HO Assessments [IBDQ **(Months 2 and 6 only)**, CCI [redacted].
- UC Assessments (review Bowel Movement Diary Data at all visits, **calculate partial Mayo score (Months 4 and 6 only)**).
- Targeted physical examination (including weight).
- Vital signs including temperature.
- Laboratory blood tests:
  - Hematology.
  - Serum chemistry.
  - Lipid profile (fasting).
  - CCI [redacted]
- Urinalysis.
- Urine β-hCG for women of childbearing potential.
- Flexible sigmoidoscopy/colonoscopy (if preferred) **(Month 2 only)**.
- Calculate Mayo score **(Month 2 only)**.
- Study medication dispensing and accountability.
- Adverse event monitoring.
- Concomitant medication assessment.

6.1.4. Month 9 (±5 days, Visit 6)

The following procedures will be performed:

- [redacted]
- UC Assessments (review Bowel Movement Diary Data and calculate partial Mayo score).
- Targeted physical examination (including weight).
- Vital signs including temperature.
- Laboratory blood tests:
  - Hematology.
  - Serum chemistry.
  - [redacted]
- Urinalysis.
- Urine β-hCG for women of childbearing potential.
- Study medication dispensing and accountability.
- Adverse event monitoring.
- Concomitant medication assessment.

6.1.5. Month 12, Early Termination (ET) or Evaluation Visit for Entry into Study A3921288 (±5 days, Visit 7 or ET)

Subjects are required to fast (no food or drink except water) for at least 9 hours prior to this visit, as required for fasting lipid profile and fasting glucose sample collection.

Subjects who discontinue treatment early from the study will have an early termination (ET) visit and all procedures listed at Month 12/ET will be performed on the last day the subject takes the study medication or as soon as possible.

Subjects undergoing evaluation for entry into Study A3921288 will have all procedures listed at Month 12/ET. Please refer to Section 3, Study Design for eligibility criteria for Study A3921288. If, after completion of the evaluation visit for entry into Study A3921288, a subject does not meet eligibility criteria, they should remain in this study (A3921139).

- HO Assessments (IBDQ, [redacted].
- UC Assessments (review Bowel Movement Diary Data).
- Complete physical examination (including weight).
- Assessment of extra-intestinal manifestations (see Section 7.3.3).
- Vital signs including temperature.
- 12-lead ECG.
- Laboratory blood tests:
  - Hematology.
  - Serum chemistry. **For subjects being evaluated for entry into Study A3921288, the serum chemistry panel will include addition of high sensitivity C reactive protein (hs-CRP).**
  - Lipid profile (fasting).
  - [redacted]
  - Tuberculosis (TB) testing (QFT) for subjects in specific countries (see Section 7.3.6). All subjects with a positive result must have a chest radiograph performed. (NOTE: TB testing is not required at the ET visit).
- Urinalysis.
- Urine β-hCG for women of childbearing potential.
- Flexible sigmoidoscopy/colonoscopy (if preferred). **For subjects being evaluated for entry into Study A3921288, endoscopy (ie., flexible sigmoidoscopy or colonoscopy) will only be performed for subjects who have not had an endoscopy performed within the previous 6 months prior to baseline visit of Study A3921288. Endoscopic assessment will only be done by local site read.**
- Calculate Mayo score.
- Study medication dispensing and accountability.
- Adverse event monitoring.
- Concomitant medication assessment.

Subjects who enroll from induction studies A3921094 or A3921095 (ie, non-responders) who fail to demonstrate clinical response at Month 2 will be withdrawn from the study and will be required to have a modified ET visit consisting of only the following procedures:

- Complete physical examination (including weight).
- 12-lead ECG.
- Return study medication and perform study medication accountability.

6.1.6. Months 15, 21, 27, and 33 (±7 days, Visits 8, 10, 12, and 14)

Visit procedures are identical for all visits.

The following procedures will be performed:

- [redacted]
- UC Assessments (review Bowel Movement Diary Data and calculate partial Mayo score).
- Targeted physical examination (including weight).
- Vital signs including temperature.
- Laboratory blood tests:
  - Hematology.
  - Serum chemistry.
  - [redacted]
- Urinalysis.
- Urine β-hCG for women of childbearing potential.
- Study medication dispensing and accountability.
- Adverse event monitoring.
- Concomitant medication assessment.

6.1.7. Months 18, 24, 30 and 36 (±7 days, Visits 9, 11, 13, and 15)

Visit procedures are identical for all visits, except where noted.

Subjects are required to fast (no food or drink except water) for at least 9 hours prior to these visits, as required for fasting lipid profile and fasting glucose sample collection.

The following procedures will be performed:

- HO Assessments (IBDQ, CCI [redacted].
- UC Assessments (review Bowel Movement Diary Data at all visits, **calculate partial Mayo score (Months 18 and 30 only)**).
- Targeted physical examination, including weight **(Months 18 and 30 only)**.
- Complete physical examination, including weight **(Months 24 and 36 only)**.
- Assessment of extra-intestinal manifestations **(Months 24 and 36 only).**
- Vital signs including temperature.
- 12-lead ECG **(Months 24 and 36 only)**.
- Laboratory blood tests:
  - Hematology.
  - Serum chemistry.
  - Lipid profile (fasting).
  - C [redacted]
  - TB testing (QFT) for subjects in specific countries. All subjects with a positive result must have a chest radiograph performed **(Months 24 and 36 only)**.
- Urinalysis.
- Urine β-hCG for women of childbearing potential.
- Flexible sigmoidoscopy/colonoscopy (if preferred) **(Months 24 and 36 only)**.
- Calculate Mayo score **(Months 24 and 36 only)**.
- Study medication dispensing and accountability.
- Adverse event monitoring.

- Concomitant medication assessment.

6.1.8. Months 39, 42, 45, 51, 54, 57, 63, 66, and 69 (±7 days, Visits 16, 17, 18, 20, 21, 22, 24, 25 and 26)

Visit procedures are identical for all visits, except where noted.

Subjects are required to fast (no food or drink except water) for at least 9 hours prior to the visits indicated below, as required for fasting lipid profile and fasting glucose sample collection.

The following procedures will be performed:

- [redacted]
- UC Assessments (review Bowel Movement Diary Data and calculate partial Mayo score).
- Vital signs including temperature **and weight**.
- Laboratory blood tests:
  - Hematology.
  - Serum chemistry.
  - Lipid profile (fasting) **(Months 42, 54, and 66 only).**
- Urine β-hCG for women of childbearing potential.
- Study medication dispensing and accountability.
- Adverse event monitoring.
- Concomitant medication assessment.
- Risk factor check for pulmonary embolism (see Section 7.3.12).

6.1.9. Months 48, 60, and 72 (±7 days, Visits 19, 23 and 27)

Visit procedures are identical for all visits.

Subjects are required to fast (no food or drink except water) for at least 9 hours prior to these visits, as required for fasting lipid profile and fasting glucose sample collection.

The following procedures will be performed:

- HO Assessments (IBDQ, [redacted].

- UC Assessments (review Bowel Movement Diary Data and calculate partial Mayo score).
- Complete physical examination, including weight.
- Assessment of extra-intestinal manifestations.
- Vital signs including temperature.
- Laboratory blood tests:
  - Hematology.
  - Serum chemistry.
  - Lipid profile (fasting).
  - [redacted]
  - TB testing (QFT) for subjects in specific countries. All subjects with a positive result must have a chest radiograph performed.
- Urine β-hCG for women of childbearing potential.
- Study medication dispensing and accountability (study medication will be dispensed at Month 72 for those subjects who participate beyond Month 72).
- Adverse event monitoring.
- Concomitant medication assessment.
- Risk factor check for pulmonary embolism (see Section 7.3.12).

6.2. Follow-up Visit (±7 days, Visit 28)

This follow-up visit is to occur 4 weeks (±7 days) after the last dose of study medication is administered.

The following procedures will be performed:

- Vital signs including temperature **and weight**.
- Laboratory blood tests:
  - Hematology.
  - Serum chemistry.

- Urine β-hCG for women of childbearing potential.
- Adverse event monitoring.
- Concomitant medication assessment.

6.3. Subject Withdrawal

Should a subject withdraw from active treatment, the subject should complete the procedures listed at the Month 12/ET Visit. After completing the procedures for the early withdrawal visit, the subject should return for a safety evaluation to occur approximately 4 weeks after discontinuing study medication as per the follow-up visit.

Subjects will be withdrawn from the study if any of the following occurs during the study treatment period:

- If a subject who enrolled from the induction studies A3921094 or A3921095 (ie, non-responders) fails to demonstrate clinical response at Month 2. Clinical response is defined by a decrease from the induction study baseline (A3921094 or A3921095) Mayo score of at least 3 points and at least 30%, with an accompanying decrease in the rectal bleeding subscore of at least 1 point or an absolute rectal bleeding subscore of 0 or 1. The endoscopic subscore based on central reading will be used to assess clinical response.
- If rescue therapy is initiated for UC with the exception of oral 5-ASA or sulfasalazine. Rescue therapy includes re-initiation of oral corticosteroid therapy above 10 mg/day of prednisone or equivalent after a subject has achieved steroid-free status during either Study A3921096 or A3921139.
- If a subject undergoes surgery for UC.
- If a subject remains on oral corticosteroids exceeding 15 mg/day of prednisone or equivalent after Month 3.

A subject may be withdrawn from the study for any of the safety concerns as listed in Appendix 3.

Subjects who develop a serious infection during the study, defined as any infection (viral, bacterial, and fungal) requiring hospitalization or parenteral antimicrobials or being classified as a serious adverse event should be withdrawn from the study (see Section 7.3.10).

All abnormal laboratory events of clinical significance should be followed until the laboratory values have returned to normal or baseline levels (see Appendix 3). Subjects who meet the discontinuation criteria described in Appendix 3 will be withdrawn from the study.

If a subject has any clinically significant, study-related abnormalities at the conclusion of the study, the Pfizer medical monitor (or designated representative) should be notified and every effort should be made to arrange follow-up evaluations at appropriate intervals to document the course of the abnormalities.

The reason for a subject discontinuing from the study will be recorded in the Case Report Form (CRF). A discontinuation occurs when a subject ceases participation in the study, regardless of the circumstances, prior to completion of the protocol. The investigator must determine the primary reason for discontinuation. Withdrawal due to adverse event should be distinguished from withdrawal due to insufficient response. The early withdrawal evaluation required by the protocol (see Month 12/ET visit procedures) will be performed at the time of study discontinuation, or as soon as possible thereafter. The investigator will record the reason for study discontinuation, provide or arrange for appropriate follow-up (if required) for each such subject, and document the course of the subject's condition.

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety or behavioral reasons, or the inability of the subject to comply with the protocol required schedule of study visits or procedures at a given study site. If a subject does not return for a scheduled visit, every effort should be made to contact the subject. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request the subject to return all unused investigational product(s), request the subject to return for a final visit, if applicable, and follow-up with the subject regarding any unresolved adverse events (AEs).

In accordance with due diligence requirements, if a subject fails to return for scheduled visit(s), the site shall record information concerning attempts to contact the subject in the subject source documents, including method of contact (eg, letter, phone call) and date of each attempted contact. It is recommended that the investigational site makes two phone calls to the subject who missed the visit, documenting each call in the source documents. A third contact attempt is a certified letter to the subject, and this letter and the response received become part of the source documents. When a site has made at least 3 attempts to contact the subject, the subject is considered lost to follow up (LTFU). Subject's status shall be designated LTFU in the CRF and in the study monitoring report.

If the subject withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

7. ASSESSMENTS

Every effort should be made to ensure that the protocol required tests and procedures are completed as described. However it is anticipated that from time to time there may be circumstances, outside of the control of the investigator, that may make it unfeasible to perform the test. In these cases the investigator will take all steps necessary to ensure the safety and well-being of the subject. When a protocol required test cannot be performed the

investigator will document the reason for this and any corrective and preventive actions which he/she has taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely fashion.

7.1. Ulcerative Colitis Assessments

7.1.1. Subject Bowel Movement Diary

Subjects will use a phone-based interactive voice recording system (IVRS) tool to record their bowel movement data throughout the study. Subjects will be instructed in its use at the Baseline visit. This information should be entered daily approximately 7 days prior to their study visit AND any time during the study that the subject experiences a worsening of UC symptoms. Automatic reminders will be sent to the subject before their scheduled visit to remind them to record their bowel movement data. Also, as an additional reminder the site personnel will call the subject 7 days before their next scheduled visit to prompt them to complete their stool data in the phone-based tool.

The phone-based IVRS tool will be provided at baseline for subjects to record the following information during the study:

- 'Normal' number of stools per day (when not having a flare and will only be asked at baseline of induction study).
- Number of toilet visits for bowel movements (per day).
- Presence of blood in the stools (if any).
- Description of blood in the stools (if any).

7.1.2. Partial Mayo Score

A partial Mayo score (PMS) is an instrument designed to measure disease activity of ulcerative colitis without endoscopy. Partial Mayo score ranges from 0 to 9 points. It consists of 3 subscores, each graded from 0 to 3 with higher scores indicating more severe disease.

- stool frequency (0-3);
- rectal bleeding (0-3);
- physician global assessment (PGA) (0-3).

The partial Mayo score (PMS) will be assessed prior to the administration of study medication at each specified study visit (see Schedule Of Activities). Partial Mayo score of 2 or less with no individual subscore >1, is defined as PMS remission, and reduction of PMS of 2 or greater from baseline is defined as PMS response.

The PMS will be calculated based on the subject's diary data recorded over the 3 prior consecutive days. The physician's global assessment (PGA) acknowledges the three other criteria, the patient's recollection of abdominal discomfort and general sense of wellbeing, and other observations, such as physical findings and the patient's performance status.

7.1.3. Mayo Score

The Mayo score is an instrument designed to measure disease activity of ulcerative colitis. Mayo score ranges from 0 to 12 points. It consists of 4 subscores, each graded from 0 to 3 with higher scores indicating more severe disease (see Appendix 1).

- Stool frequency (0-3).
- Rectal bleeding (0-3).
- Findings of flexible sigmoidoscopy (0-3).
- Physician global assessment (PGA) (0-3).

Mayo score is assessed at Month 2, at the following annual study visits (Months 12, 24 and 36), and at the early withdrawal/early termination visit per the Schedule Of Activities.

The endoscopic finding at Month 2 will be read by both central reader and site investigators prior to Amendment 8. The endoscopic subscore read by central reader will be used to calculate the Mayo score at Month 2 and determine clinical response until implementation of Amendment 8. After implementation of Amendment 8, Month 2 endoscopic subscore will be locally read by study site investigator. The endoscopic subscore at all other applicable visits will be read by study site investigator before and after Amendment 8.

Calculation of the Mayo score requires an assessment of the subject's stool frequency and quantification of the amount of blood in the stool. The subject will use the phone-based IVRS tool to record this information. Mayo score will be calculated based on the subject's BM diary data recorded over the 3 prior consecutive days.

The mucosal appearance during the sigmoidoscopic portion of endoscopic examination will be assessed for the Mayo endoscopic subscore, based on the scoring system provided in the protocol (see Appendix 1).

The PGA acknowledges the three other criteria, the patient's recollection of abdominal discomfort and general sense of wellbeing, and other observations, such as physical findings and the patient's performance status. The endoscopic subscore and the PGA must be performed by a physician qualified to perform endoscopy, and it is recommended that the same physician performs all such assessments for a particular subject throughout the study, when possible.

7.2. Patient Reported Outcomes

Paper diary will be used to record various patient reported outcomes (PRO) assessments during the study. PRO assessments collected during the study will be presented in separate tables, figures, and data listings, and will be reviewed in the final study report.

It is important to note that the PRO measurements are collected and evaluated in a different manner than the observed or volunteered adverse events. Given these differences, no attempt will be made to resolve any apparent discrepancies between observed or volunteered adverse events and PRO data collected from subjects. Adverse event incidence rates will not be calculated from these solicited data but rather from the information recorded on the AE pages on the CRF.

CCI [redacted]

[redacted]

To be completed during study visits:

The following PROs will be completed as specified in the Schedule Of Activities. Subjects should be encouraged to complete the PROs at the clinic at the beginning of the study visit prior to any clinical assessments. A member of the staff should be available if a subject requires further instruction and to review the PRO questionnaires for completeness prior to leaving the clinic.

- Inflammatory Bowel Disease Questionnaire (IBDQ) (see Appendix 9).

CCI [redacted]

7.2.1. Inflammatory Bowel Disease Questionnaire (IBDQ)

IBDQ Questionnaire is a psychometrically validated PRO instrument for measuring the disease-specific quality of life in subjects with Inflammatory Bowel Disease, including ulcerative colitis. The IBDQ comprises 32-items, which are grouped into 4 dimensions: bowel function, emotional status, systemic symptoms and social function.[10] The 4 domains are scored as follows:

- Bowel symptoms: 10 to 70.

- Systemic symptoms: 5 to 35.
- Emotional function: 12 to 84.
- Social function: 5 to 35.

The total IBDQ score ranges from 32 to 224. For the total score and each domain, a higher score indicates better quality of life. A score of ≥170 corresponds to clinical remission and an increase of at least 16 points is considered to indicate a clinically meaningful improvement.

CCI

CCI

[redacted]

7.3. Safety

Safety will be assessed by vital signs, physical examinations, ECGs, clinical laboratory tests and the spontaneous reporting of AEs, in all subjects who received at least 1 dose of study medication. Unscheduled safety assessments may be performed at any time during the study to assess any perceived safety concerns. Investigators and Pfizer Clinicians will review individual subject data throughout the conduct of the study to ensure subjects' well-being. Subject safety monitoring and discontinuation guidelines are provided in Appendix 3.

7.3.1. Vital Signs

As a guideline, blood pressure should be measured in the subject's dominant arm and recorded to the nearest mmHg. The same arm should be used throughout the study, when possible. All blood pressure in this study should be measured with the subject in the sitting position after resting for at least 5 minutes, when possible.

The use of automated devices for measuring blood pressure and pulse rate are acceptable, although, when done manually, pulse rate will be measured in the brachial/radial artery for at least 30 seconds. When the timing of these measurements coincides with a blood collection, blood pressure and pulse rate should be obtained first.

Temperature will be collected as either oral, axillary or tympanic temperature, but the same method should be used throughout the study.

7.3.2. Physical Examinations

A complete physical examination will be performed at each specified visit according to the Schedule Of Activities. The following parameters and body systems will be examined and any abnormalities described: weight, general appearance, head, ears, eyes, nose, mouth, throat, thyroid, skin (presence of rash), lungs (auscultation), heart (auscultation for presence of murmurs, gallops, rubs, peripheral edema), abdominal (palpation and auscultation), perianal, musculoskeletal, extremities, neurologic (mental status, gait, reflexes, motor and sensory function, coordination) and lymph nodes.

Targeted physical examination will be performed at each specified visit according to the Schedule Of Activities. The following will be assessed: weight, general appearance, eyes, mouth, lungs, heart, abdomen, musculoskeletal, extremities, skin and lymph nodes.

Recommendations for evaluation of emergent lymphadenopathy or other findings suggestive of lymphoproliferative disorder are provided in Appendix 6.

7.3.3. Extra-Intestinal Manifestations

Assessment of the following extra-intestinal manifestations will be obtained on all subjects at specified visits according to the Schedule Of Activities: peripheral arthritis, sacroiliitis, ankylosing spondylitis, myopathy, pyoderma gangrenosum, erythema nodosum, scleritis, episcleritis, uveitis, iritis, oral ulcer/stomatitis, and thromboembolic disorder.

7.3.4. Electrocardiogram

Twelve (12) lead ECGs will be obtained on all subjects at specified visits according to the Schedule Of Activities. All scheduled ECGs should be performed after the subject has rested quietly for at least 10 minutes in a supine position, when possible.

The ECG results from Week 8 of Study A3921094 or A3921095, or from Week 52 or the early termination visit of Study A3921096 will be used to evaluate subject's eligibility for Study A3921139 and serve as the baseline for Study A3921139. The ECG results should be maintained in the subject's source documentation. ECG data will be submitted to a central laboratory for measurement through Month 36 and at early termination. Any clinically significant changes from the baseline ECG should be recorded as AEs and evaluated further, as clinically warranted.

The list of ECG values of potential clinical concern is listed in Appendix 4.

7.3.5. Clinical Laboratory Tests

Blood and urine samples will be collected at each specified visit according to the Schedule Of Activities. Unscheduled clinical labs may be obtained at any time during the study to assess any perceived safety concerns or in accordance with the guidelines for subject safety monitoring and discontinuation (see Appendix 3). Clinically significant abnormal findings should be recorded as AEs per Section 8.4.

The following laboratory tests will be performed during the study:

Table 3. Laboratory Test Parameters

Hematology	Serum Chemistry	Urinalysis	Others
Hemoglobin	Blood urea nitrogen	Specific gravity	Follicle stimulating hormone (FSH)[2]
Hematocrit	Creatinine	pH	β-hCG urine pregnancy test[1]
Reticulocyte	Glucose (fasting)[4]	Color	Lipid profile (fasting)[2]
Platelet count	Glucose (non-fasting)[5]	Glucose	Total cholesterol
White blood cell (WBC) count	Calcium	Nitrite	Low density lipoprotein cholesterol (LDL-C)[3]
Neutrophils (abs, %)	Sodium	Blood	High density lipoprotein cholesterol (HDL-C)
Eosinophils (abs, %)	Potassium	Leucocyte esterase	Triglycerides[3]
Monocytes (abs, %)	Chloride	Protein	[redacted]
Basophils (abs, %)	Total carbon dioxide (CO_2) or bicarbonate	Microscopy[1]	CCI [redacted]
Lymphocytes (abs, %)	Aspartate aminotransferase (AST)		hs-CRP
Red blood cell (RBC) count	Alanine aminotransferase (ALT)		
Mean corpuscular volume (MCV)	Total bilirubin		
Mean corpuscular hemoglobin (MCH)	Direct bilirubin		
Red cell distribution width (RDW)	Indirect bilirubin		
	Alkaline phosphatase		
	Gamma-glutamine transferase (GGT)		
	Total protein		
	Albumin		
	Lactate dehydrogenase (LDH)		
	Uric acid		
	Creatine kinase (CK)/ creatine phosphokinase (CPK)		

1. Dipstick in all cases; microscopy analysis is indicated if urinalysis is positive for blood, nitrite, leucocyte esterase and/or protein; Urine culture performed if urinalysis is positive for nitrite and/or leucocyte esterase or if clinically indicated.
2. Follicle stimulating hormone (FSH) to confirm postmenopausal status at baseline visit only if postmenopausal status has not been confirmed in Studies A3921094, A3921095 or A3921096.
1. Urine testing performed with a sensitivity of at least 25 mIU/mL at the study site using test kits supplied by the central laboratory at baseline and at all study visits for females of childbearing potential.
2. Fasting lipid profile will be obtained according to the Schedule Of Activities.
3. If triglycerides >400 mg/dl, LDL-C will be determined by direct measurement.
4. Fasting glucose will be measured at study visits when fasting lipid profile is obtained according to the Schedule Of Activities.
5. Non-fasting glucose will be measured at all other study visits according to the Schedule Of Activities.

C [redacted]

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[redacted]

10. Serum chemistry panel will include addition of hs-CRP only for those subjects being evaluated for entry into Study A3921288.

Clinically significant abnormal findings should be recorded as AEs if they meet any of the following criteria:

- Test result is associated with accompanying symptom, and/or
- Test result requires additional diagnostic testing or medical/surgical intervention, and/or
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or
- Test result is considered to be an adverse event by the Investigator or sponsor.

Abnormal test results determined to be caused from laboratory error should not be reported as AEs. Clinically significant laboratory findings at the final assessment should be followed to resolution or until determined by the Investigator to be stabilized. Repeat tests may be indicated.

7.3.6. Annual Tuberculosis Testing

Annual tuberculosis (TB) testing will be conducted using Quantiferon-TB® Gold Plus test (QFT) for subjects in those countries in which TB prevalence has been reported at a rate of >50 cases per 100,000 persons (eg, Brazil, Latvia, Romania, Russia, Ukraine, South Africa, and South Korea, based on World Health Organization, 2015 http://www.who.int/tb/country/data/profiles/en/index.html). All subjects with positive results must have a chest radiograph performed and the radiograph must be negative for active TB infection for the subject to continue study participation. Subjects identified as having latent TB (positive QFT and negative chest radiograph for active TB) should be treated appropriately; for subjects remaining on study during their treatment, the only acceptable regimen is 9 months of isoniazid. Subjects can continue to take tofacitinib without interruption while receiving treatment for latent TB. Note: QFT should not be performed in subjects who had a positive result during prior testing (screening visit in Study A3921094 or A3921095 or prior annual visits) and/or previously received adequate treatment for TB.

7.3.7. Pregnancy Testing

For female subjects of childbearing potential, a urine β-hCG pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed at baseline (Visit 1), before investigational product administration. A negative urine β-hCG test result is required before the subject may receive the investigational product. Urine β-hCG tests will also be done whenever one menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected), repeated at all study visits and at the end of the study to confirm the subject has

not become pregnant during the study. Pregnancy tests may also be repeated as per request of IRB/IECs or if required by local regulations.

If at any point there is a case of a positive urine β-hCG test, the subject will have study drug interrupted and a serum sample submitted to the central laboratory for β-hCG testing. If the serum test confirms positive, the subject will be withdrawn from the study and all the necessary follow up will be conducted as per Section 8.9. If the serum test is negative, the subject may resume study drug. It is essential to make sure that female study subjects use acceptable birth control (see Section 4.4.5.2 and CCI [redacted]) from the time of the first dose of study medication until completion of follow-up procedures.

In Austria, if the interval between study visits exceeds one month, female subjects of childbearing potential should have a pregnancy test performed each month between study visits and results reported to the investigational site to be entered into the subject's study record.

7.3.8. Serum Lipids

Total cholesterol, LDL-cholesterol, direct HDL-cholesterol and triglycerides will be measured during the study at specific study visits according to the Schedule Of Activities requiring subjects to fast at least 9 hours prior to sample collection. See Appendix 8 for recommended clinical management of cholesterol.

7.3.9. Creatinine Clearance

A commonly used surrogate marker for actual creatinine clearance is the Cockcroft-Gault formula (see Appendix 5), which employs creatinine measurements and a subject's weight to calculate the clearance. Cockcroft-Gault GFR calculation will be done as part of clinical laboratory tests from baseline (Visit 1) through follow-up.

7.3.10. Infections

Subjects will be monitored for development of infection. Infections will be classified as either treated or non-treated infections. All treated infections occurring during the study should be cultured if feasible and the results (eg, any identified organisms or absence of growth) recorded in the CRF.

Treated infections are infections that:

- Require antimicrobial therapy by any route of administration or;
- Require any surgical intervention (eg, incision and drainage).

Treated infections will be further classified as serious or non-serious. Serious infections are treated infections that:

- Require parenteral antimicrobial therapy or;
- Require hospitalization for treatment or;

- Meet other criteria that require the infection to be classified as a serious adverse event (SAE).

A subject who experiences a serious infection should be discontinued from the study. A serious infection should be reported as a SAE and should be listed as the reason for discontinuation in the CRF. All serious infections occurring during the study should undergo appropriate laboratory investigations, including culture, and the results (eg, any identified organisms or absence of growth) recorded in the CRF.

Subjects who experience non-serious infections that require treatment may have their study drug temporarily discontinued during treatment (see Section 5.9). Temporary discontinuation of study drug should be recorded in the CRF.

Clostridium difficile (C. difficile) toxin testing is recommended for subjects in whom C. difficile infection is suspected (eg, atypical symptoms or features of their usual UC disease course, significantly worsening disease activity assessments from the previous visit, and/or the presence of risk factors such as recent antibiotic use or a recent history of C. difficile infection). A full course of C. difficile treatment, as defined by local practice, must be given to subjects with C. difficile infection to permit their continued participation in the study. Subjects with C. difficile infection that meets serious infection criteria must be withdrawn from the study. Stool testing and treatment for other enteric pathogens is at the discretion of the investigator.

7.3.11. Cardiovascular, and Malignancy, and Other Safety Events of Interest

The identification of a cardiovascular, malignancy, or other safety events of interest can be identified by the study site and communicated to Pfizer or designee. These safety events may also be identified by the Pfizer Study Team or designee during the review of subject data listings or by site monitors during routine monitoring of subject study records.

Criteria for defining specific cardiovascular, cerebrovascular and peripheral vascular events will be provided to investigators in a separate study manual. The Pfizer Study Team or designee will provide a listing of specific documents needed to support cardiovascular event adjudication by the Cardiovascular Event Adjudication Committee (CV-EAC; see Section 9.7). Cardiovascular event documentation will include, but is not limited to any of the following: hospital discharge summaries, operative reports, clinic notes, ECGs, diagnostic enzymes, results of other diagnostic tests, autopsy reports and death certificate information.

When there is a decision to biopsy a potentially malignant tumour, lymph node, or other tissue, the investigator and/or consultant(s) should contact Pfizer or designee to discuss the issue and any decisions as soon as possible. For all biopsies of potentially malignant tumours, suspicious lymphadenopathy, or possible extranodal lymphoproliferative disorder (LPD), the study site will request the pathologist to send the original slides used to make the definitive diagnosis, ancillary study reports, and the pathologist's report to the central laboratory for a blinded review by a central pathologist. See Appendix 6 for the steps to take in the event of potentially malignant tumours, lymphadenopathy or possible extra-nodal LPD

which might arise in the course of this study. See Appendix 7 for the steps to take when gastrointestinal tract biopsies are obtained.

7.3.12. Risk Factor Check for Pulmonary Embolism

All subjects will undergo a risk factor check at each study visit to check for newly-developed risk factors for pulmonary embolism. This information is to be captured in the subject's source file and on the relevant case report form.

A subject may be at high risk for pulmonary embolism if he/she:

- has heart failure;
- has inherited coagulation disorders;
- has had venous thromboembolism, either deep venous thrombosis or pulmonary embolism;
- is taking combined hormonal contraceptives or hormone replacement therapy;
- has malignancy (association is strongest with cancers other than non-melanoma skin cancers);
- is undergoing major surgery.

If a subject has any of the risk factors listed above and is receiving tofacitinib 10 mg BID, the subject's tofacitinib dose should be reduced to 5 mg BID. If a subject has any newly-developed risk factors for pulmonary embolism identified during the study, they will not be permitted to receive tofacitinib 10 mg BID.

Lastly, if a subject has any of the risk factors listed above, the subject will not be eligible to enroll in Study A3921288.

8. ADVERSE EVENT REPORTING

8.1. Adverse Events

All observed or volunteered AEs regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following sections.

For all AEs, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as an SAE requiring immediate notification to Pfizer or its designated representative. For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE. The investigator is required to assess causality. Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

As part of ongoing safety reviews conducted by the Sponsor, any non-serious adverse event that is determined by the Sponsor to be serious will be reported by the Sponsor as an SAE. To assist in the determination of case seriousness further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

8.2. Reporting Period

For SAEs, the active reporting period to Pfizer or its designated representative begins from the time that the subject provides informed consent, which is obtained prior to the subject's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 28 calendar days after the last administration of the investigational product. SAEs occurring to a subject after the active reporting period has ended should be reported to the sponsor if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product are to be reported to the sponsor.

- AEs (serious and non-serious) should be recorded on the CRF from the time the subject has taken at least 1 dose of investigational product through the subject's last visit.

8.3. Definition of an Adverse Event

An AE is any untoward medical occurrence in a clinical investigation subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include but are not limited to:

- Abnormal test findings;
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease;
- Drug abuse;
- Drug dependency.

Additionally, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;

- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure.

8.4. Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms, and/or
- Test result requires additional diagnostic testing or medical/surgical intervention, and/or
- Test result leads to a change in study dosing, outside of those permitted by the protocol, or discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or
- Test result is considered to be an AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

8.5. Serious Adverse Events

A serious adverse event is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

8.5.1. Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported by the investigator as described in previous sections, and will be handled as SAEs in the safety database (see the section on Serious Adverse Event Reporting Requirements).

8.5.2. Potential Cases of Drug-Induced Liver Injury

Abnormal values in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) levels concurrent with abnormal elevations in total bilirubin level that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy's law cases) and should always be considered important medical events.

The threshold of laboratory abnormalities for a potential case of drug-induced liver injury depends on the subject's individual baseline values and underlying conditions. Subjects who present with the following laboratory abnormalities should be evaluated further to definitively determine the etiology of the abnormal laboratory values:

- Subjects with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT values ≥3 times the upper limit of normal (× ULN) concurrent with a total bilirubin ≥2 × ULN with no evidence of hemolysis and an alkaline phosphatase ≤2 × ULN or not available.

- For subjects with preexisting ALT **OR** AST **OR** total bilirubin values above the upper limit of normal, the following threshold values should be used in the definition mentioned above:

    - For subjects with pre-existing AST or ALT baseline values above the normal range: AST or ALT values ≥2 times the baseline values and ≥3 × ULN, or ≥8 × ULN (whichever is smaller).

Concurrent with

- For subjects with pre-existing values of total bilirubin above the normal range: Total bilirubin level increased from baseline by an amount of at least 1 time the upper limit of normal **or** if the value reaches ≥3 times the upper limit of normal (whichever is smaller).

The subject should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history and physical assessment.

In addition to repeating measurements AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/international normalized ratio (INR), and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (eg, biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for liver function tests (LFT) abnormalities identified at the time should be considered potential Hy's law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's law cases should be reported as SAEs.

8.6. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit should be assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;

- Same day surgeries (as outpatient/same day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for work-up of persistent pre-treatment laboratory abnormality);
- Social admission (eg, subject has no place to sleep);
- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Pre-planned treatments or surgical procedures should be noted in the baseline documentation for the entire protocol and/or for the individual subject.

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE, and the resulting appendectomy should be recorded as treatment of the AE.

8.7. Severity Assessment

If required on the AE case report forms (CRFs), the investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:	
MILD	Does not interfere with subject's usual function.
MODERATE	Interferes to some extent with subject's usual function.
SEVERE	Interferes significantly with subject's usual function.

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with the subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

8.8. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the serious adverse reporting requirements if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the Sponsor (see the Section on Reporting Requirements). If the investigator's causality assessment is "unknown but not related to investigational product", this should be clearly documented on study records.

In addition, if the investigator determines an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

8.9. Exposure During Pregnancy

For both unapproved/unlicensed products and for marketed products, an exposure during pregnancy occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the investigational product;

   An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

2. A male has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a study subject or study subject's partner becomes or is found to be pregnant during the study subject's treatment with the investigational product, the investigator must submit this information to the Pfizer drug safety unit on an SAE report form and an EDP supplemental form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer of the outcome as a follow up to the initial EDP supplemental form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetile demise, neonatal death, or congenital anomaly [in a live born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to investigational product.

Additional information regarding the EDP may be requested by the investigator. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the study subject with the Pregnant Partner Release of Information Form to deliver to his partner. The Investigator must document in the source documents that the subject was given the Pregnant Partner Release of Information Form to provide to his partner.

8.10. Occupational Exposure

An occupational exposure occurs when, during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an AE.

An occupational exposure is reported to the drug safety unit within 24 hours of the investigator's awareness, using the SAE report form, regardless of whether there is an associated AE/SAE. Since the information does not pertain to a subject enrolled in the study, the information is not reported on a CRF; however, a copy of the completed SAE report form is maintained in the investigator site file.

8.11. Withdrawal Due to Adverse Events (See Also the Section on Subject Withdrawal)

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of AE noted earlier, and recorded on the appropriate AE CRF page.

When a subject withdraws because of an SAE, the SAE must be reported in accordance with the reporting requirements defined below.

8.12. Eliciting Adverse Event Information

The investigator is to report all directly observed AEs and all AEs spontaneously reported by the study subject. In addition, each study subject will be questioned about AEs.

8.13. Reporting Requirements

Each AE is to be assessed to determine if it meets the criteria for SAEs. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

8.13.1. Serious Adverse Event Reporting Requirements

If an SAE occurs, Pfizer is to be notified within 24 hours of investigator awareness of the event. In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available AE information. This timeframe also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of EDP, exposure via breastfeeding, and occupational exposure cases.

In the rare event that the investigator does not become aware of the occurrence of an SAE immediately (eg, if an outpatient study subject initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his/her first awareness of the AE.

For all SAEs, the investigator is obligated to pursue and provide information to Pfizer in accordance with the timeframes for reporting specified above. In addition, an investigator may be requested by Pfizer to obtain specific additional follow-up information in an expedited fashion. This information collected for SAEs is more detailed than that captured on the AE CRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications, vaccines, and/or illnesses must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

8.13.2. Non-Serious Adverse Event Reporting Requirements

All AEs will be reported on the AE page(s) of the CRF. It should be noted that the form for collection of SAE information is not the same as the AE CRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used on both forms. AEs should be reported using concise medical terminology on the CRFs as well as on the form for collection of SAE information.

8.13.3. Sponsor's Reporting Requirements to Regulatory Authorities

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

9. DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan, which will be maintained by the sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

9.1. Sample Size Determination

Approximately 900 subjects are expected to become eligible for the study. Approximately 460 subjects are expected to enroll from the maintenance Study A3921096 assuming a 78% rollover rate from the maintenance study. Approximately 440 subjects are expected to enroll from the induction Study A3921094 or A3921095 assuming that 38% of subjects enrolled in those studies will not achieve clinical response and will not have improving endoscopic subscores after completing induction Study A3921094 or A3921095.

9.2. Efficacy Analysis

The primary analysis population will be the Full Analysis Set (FAS) defined as all subjects who receive at least 1 dose of study medication.

9.2.1. Analysis of Primary Endpoint

The primary objective is to assess the safety and tolerability of long-term tofacitinib therapy. There will be no primary efficacy endpoint.

9.2.2. Analysis of Secondary Endpoints

Due to the design of the study, there will be no formal hypothesis testing. Descriptive summary statistics such as number, percentage for categorical endpoints and mean, standard deviation, median for continuous endpoints will be summarized by the following four subgroups of subjects based on the status at baseline of Study A3921139: 1) in remission defined by a total Mayo score ≤2 with no individual subscore >1, and rectal bleeding subscore of 0, 2) treatment failure defined by an increase in Mayo score of at least 3 points from baseline value of the maintenance study (A3921096), accompanied by an increase in rectal bleeding subscore by at least 1 point, and an increase of endoscopic subscore of at least 1 point (yielding an absolute endoscopic subscore of ≥2), 3) all other subjects from maintenance study A3921096 neither in remission nor fulfilling the definition of treatment failure, and 4) non-responders from induction studies A3921094 or A3921095.

9.3. Analysis of Health Outcome Assessments

These endpoints will be analyzed using the same approach as the secondary endpoints.

9.4. Safety Analysis

The safety data will be summarized in accordance with Pfizer Data Standards based on the safety analysis set defined as all subjects who receive at least 1 dose of study medication.

9.5. Interim Analysis

As this is an open-label and uncontrolled study, interim analyses may be performed for study monitoring for internal decision making, application for approval or due to regulatory requests. There are no issues of protecting the Type I error rate as no hypothesis testing will be conducted.

9.6. Data Monitoring Committee

An independent Data Safety Monitoring Board (DSMB), a group of experts external to Pfizer, will review accumulating safety data from this study on an ongoing basis. Review of efficacy data may occur as part of any risk-benefit assessment deemed the responsibility of this committee. Based on these reviews, the DSMB will have the capacity to make recommendations to Pfizer that might impact the future conduct of the trial. The DSMB will have access to unblinded treatment information during the clinical trial. The management and process of this committee will be in accordance with Pfizer's Standard Operating Procedures and will be documented in the DSMB Charter. The DSMB members will all be individuals who are independent of Pfizer.

A DSMB Liaison will be appointed; this is an individual who represents Pfizer to coordinate communications and facilitates access to Pfizer's resources, but is not involved in the study design, study management, site management, data accrual, or study analysis. Records of DSMB meetings, interactions with Pfizer contacts, assessments and recommendations and materials reviewed will be maintained and kept proprietary and confidential by the DSMB. Further information about the DSMB can be found in the DSMB Charter, which outlines the operating procedures of the committee, including specific description of the scope of their responsibilities, including a plan where communication timelines are defined.

The DSMB will be responsible for ongoing monitoring of the efficacy and safety of subjects in the study according to the Charter. The recommendations made by the DSMB to alter the conduct of the study will be forwarded to Pfizer for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data which are not endpoints, to regulatory authorities, as appropriate.

9.7. Safety Event Adjudication Committees

To help assess specific safety events in this and other studies for the tofacitinib program, adjudication committees have been established to harmonize and standardize selected safety event assessment. Members of these safety event adjudication committees will be blinded to treatment assignment in order to allow for unbiased assessments. These committees include a Cardiovascular Endpoint Adjudication Committee (CV EAC), Malignancy Adjudication Committee (MAC), Opportunistic Infection Review Committee (OIRC), Hepatic Event Review Committee (HERC) and Gastrointestinal Perforation Review Committee (GIPRC). Further information about these committees can be found in the respective charters, including specific descriptions of the scope of their responsibilities, and the processes and definitions used to review and assess specific safety events.

In addition to the event adjudication or review committees described above, all biopsies of potentially malignant tumors, suspicious lymphadenopathy, or possible extranodal lymphoproliferative disorder, and all bowel biopsies containing dysplasia or malignancy, should be submitted to the central laboratory for review by central laboratory pathologists. In some instances, additional expert pathology review of submitted samples may be performed. Description of the scope of review and the processes used to obtain and assess biopsies is described in the Histopathology Review for Potential Malignancy charter.

In addition to these external committees, an internal committee of medically qualified Pfizer personnel with expertise in the assessment and diagnosis of respiratory disease will review and categorize potential events of interstitial lung disease (Interstitial Lung Disease Review Committee, ILDRC).

Additional safety event adjudication or review committees may be established to harmonize and standardize selected safety event assessments. As described above, individual committee charters will provide specific descriptions of the scope of responsibilities and the processes and definitions used to review and assess specific safety events.

10. QUALITY CONTROL AND QUALITY ASSURANCE

During study conduct, Pfizer or its agent will conduct periodic monitoring visits to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs is accurate. The investigator and institution will allow Pfizer monitors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification.

The study site may be subject to review by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC), and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included subject. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic / original, attributable, complete,

consistent, legible, timely (contemporaneous), enduring and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs is true. Any corrections to entries made in the CRFs, source documents must be dated, initialed and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital's or the physician's subject chart. In these cases data collected on the CRFs must match the data in those charts.

In some cases, the CRF, or part of the CRF, may also serve as source documents. In these cases, a document should be available at the investigator's site as well as at Pfizer and clearly identify those data that will be recorded in the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

To enable evaluations and/or audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, telephone calls reports). The records should be retained by the investigator according to International Conference on Harmonisation (ICH), local regulations, or as specified in the Clinical Study Agreement (CSA), whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer.

Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

12. ETHICS

12.1. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/IEC. All correspondence with the IRB/IEC should be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/IEC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/IEC and Pfizer in writing immediately after the implementation.

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for GCP (ICH 1996), and the Declaration of Helsinki (World Medical Association 1996, 2008).

In addition, the study will be conducted in accordance with the protocol, the International Conference on Harmonization guideline on Good Clinical Practice, and applicable local regulatory requirements and laws.

12.3. Subject Information and Consent

All parties will ensure protection of subject personal data and will not include subject names on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws.

Subject names, address, birth date and other identifiable data will be replaced by a numerical code consisting of a numbering system provided by Pfizer in order to de-identify the trial subject. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subject personal data.

The informed consent document must be in compliance with ICH GCP, local regulatory requirements, and legal requirements.

The informed consent document used in this study, and any changes made during the course of the study, must be prospectively approved by both the IRB/IEC and Pfizer before use.

The investigator must ensure that each study subject, or his/her legal representative, is fully informed about the nature and objectives of the study and possible.

The investigator, or a person designated by the investigator, will obtain written informed consent from each subject or the subject's legal representative before any study-specific activity is performed. The investigator will retain the original of each subject's signed consent document.

12.4. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable Competent Authority in any area of the World, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in a Member State

End of Trial in a Member State of the European Union is defined as the time at which it is deemed that sufficient subjects have been recruited and completed the study as stated in the regulatory application (ie, Clinical Trial Application (CTA)) and ethics application in the Member State. Poor recruitment (recruiting less than the anticipated number in the CTA) by a Member State is not a reason for premature termination but is considered a normal conclusion to the study in that Member State.

13.2. End of Trial in all Participating Countries

End of Trial in all participating countries is defined as last subject last visit.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, drug safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of tofacitinib at any time.

If a study is prematurely terminated or discontinued, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating subjects and the hospital pharmacy (if applicable) within 1 week. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

Pfizer fulfills its commitment to publicly disclose clinical trial results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial US Basic Results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies conducted in patients that evaluate the safety and/or efficacy of a Pfizer product, regardless of the geographical location in which the study is conducted. US Basic Results are submitted for posting within 1 year of the primary completion date for studies in

adult populations or within 6 months of the primary completion date for studies in pediatric populations.

Primary completion date is defined as the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the prespecified protocol or was terminated.

EudraCT

Pfizer posts EU Basic Results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

www.pfizer.com

Pfizer posts Public Disclosure Synopses (clinical study report synopses in which any data that could be used to identify individual patients has been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

15.2. Publications by Investigators

Pfizer supports the exercise of academic freedom and has no objection to publication by principal investigator of the results of the study based on information collected or generated by principal investigator, whether or not the results are favorable to the Pfizer product. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, the investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure of the results of the study (collectively, "Publication") before it is submitted or otherwise disclosed.

The investigator will provide any publication to Pfizer at least 30 days before they are submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The investigator will, on request, remove any previously undisclosed confidential information before disclosure except for any study- or Pfizer product-related information necessary to the appropriate scientific presentation or understanding of the study results.

If the study is part of a multi-centre study, the investigator agrees that the first publication is to be a joint publication covering all study sites, and that any subsequent publications by the principal investigator will reference that primary publication. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, the investigator is free to publish separately, subject to the other requirements of this section.

For all publications relating to the study, the institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the CSA between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the CSA.

If there is any conflict between the CSA and any Attachments to it, the terms of the CSA control. If there is any conflict between this protocol and the CSA, this protocol will control as to any issue regarding treatment of study subjects, and the CSA will control as to all other issues.

16. REFERENCES

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Appendix 1. Mayo Scoring System*

Stool frequency†:

0 = Normal no. of stools for this patient
1 = 1 to 2 stools more than normal
2 = 3 to 4 stools more than normal
3 = 5 or more stools more than normal
Subscore, 0 to 3

Rectal bleeding‡:

0 = No blood seen
1 = Streaks of blood with stool less than half the time
2 = Obvious blood with stool most of the time
3 = Blood alone passes
Subscore, 0 to 3

Findings on endoscopy:

0 = Normal or inactive disease
1 = Mild disease (erythema, decreased vascular pattern)
2 = Moderate disease (marked erythema, absent vascular pattern, any friability, erosions)
3 = Severe disease (spontaneous bleeding, ulceration)
Subscore, 0 to 3

Physician's global assessment§:

0 = Normal
1 = Mild disease
2 = Moderate disease
3 = Severe disease
Subscore, 0 to 3

* The Mayo score ranges from 0 to 12, with higher scores indicating more severe disease.[9]

† Each patient serves as his or her own control to establish the degree of abnormality of the stool frequency. Normal number of bowel movements represents the number of bowel movements when not having a flare.

‡ The daily bleeding score represents the most severe bleeding of the day.

§ The physician's global assessment acknowledges the three other criteria, the patient's recollection of abdominal discomfort and general sense of wellbeing, and other observations, such as physical findings and the patient's performance status.

Appendix 2. Prohibited Concomitant Medications

This is not an all inclusive list. Study personnel should stay current and consult with their pharmacy to exclude all concomitant medications that are either moderate to potent CYP3A inhibitors or inducers.

Moderate to Potent CYP3A Inhibitors	Moderate to Potent CYP3A Inducers	Other Prohibited Medications
Amprenavir	Avasimibe#	Azathioprine
Amiodarone	Bosentan	6-Mercaptopurine
Aprepitant	Barbiturates	Methotrexate
Atazanavir	Carbamazepine#	Cyclosporine
Boceprevir	Efavirenz	Mycophenolate mofetil /mycophenolic acid
Casopitant	Etravirine	Tacrolimus
Cimetidine	Mitotane#	Interferon
Ciprofloxacin	Modafinil	Infliximab
Clarithromycin#	Nafcillin	Adalimumab
		Certolizumab
Cobicistat#	Phenobarbital#	Golimumab
Conivaptan#	Phenytoin#	Corticosteroids IV or PR
Darunavir	Rifabutin#	5-ASA PR
	Rifampin#	Natalizumab, vedolizumab, and other anti-adhesion molecule therapy (including investigational agents)
Diethyldithiocarbamate	St. John's Wort#	Leukocyte apheresis including selective lymphocyte, monocyte or granulocyte apheresis (eg, Cellsorba®) or plasma exchange
Diltiazem		Other immunosuppressants
Dronedarone	Talviraline	Other biologics with immunomodulatory properties
Elvitegravir#		
Erythromycin		
Fluconazole		
Fluvoxamine		
Imatinib		
Indinavir#		
Itraconazole#		
Ketoconazole#		
Lopinavir#		
Mibefradil#		
Mifepristone (RU486)		
Nefazodone#		
Nelfinavir#		
Norfloxacin		
Posaconazole#		
Ritonavir#		
Saquinavir#		
Schisandra sphenanthera		

Telaprevir		
Telithromycin#		
Tipranavir#		
Tofisopam		
Troleandomycin#		
Verapamil		
Voriconazole#		

 # Notated as potent inhibitors or inducers

It is recommended that subjects avoid consumption of grapefruit juice exceeding 8 ounces (~240 mL) total in a day while in the study.

In a situation where appropriate medical care of a subject requires the use of a prohibited CYP3A inhibitor or inducer: Potent inhibitors and inducers of CYP3A are not permitted in the study **EXCEPT** in emergency situations requiring no more than one day of administration. *Note: Mitotane (half-life of 18-159 days) is not permitted for any duration due to its long half-life.* Subjects may be initiated on moderate inhibitors (except amiodarone) and moderate inducers (shown above), as required, if the total duration of treatment lasts less than or equal to 7 days. If a subject requires multiple courses of treatment with a prohibited medication as described above, the investigator should contact the sponsor to discuss the suitability of the subject to remain in the study. Topical (including skin or mucous membranes) application of antibacterial and antifungal medications is permitted.

Appendix 3. Guidelines for Monitoring and Discontinuations

The following laboratory abnormalities require monitoring and re-testing ideally within 3-5 days:

- Absolute neutrophil count <1.2 x 10^9/L (<1200/mm^3).
- Absolute lymphocyte count <0.5 x 10^9/L (<500/mm^3).
- Any single hemoglobin value <8.0 g/dL, or any decrease in hemoglobin >2.0 g/dL from baseline.
- Platelet count <100 x 10^9/L (<100,000/mm^3).
- An increase in serum creatinine of >50% from the baseline value; OR an absolute increase in serum creatinine >0.5 mg/dL (>44.2 umol/L) from baseline value.
- Any single AST and/or ALT elevation ≥3 times the upper limit of normal (repeat laboratory testing should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, GGT, PT [prothrombin time] with INR [international normalized ratio], and alkaline phosphatase), regardless of the total bilirubin. (Please note that 3 times the upper limit of normal increases in ALT, AST need confirmation on separate blood draw before undertaking thorough evaluation for liver injury).
- Any creatine kinase (CK) >10 times the upper limit of normal (repeat laboratory testing should also include cardiac troponin).
- For women of child-bearing potential with any positive urine β-hCG test, the subject will have study drug interrupted and a serum sample submitted to the central laboratory for β-hCG testing.

Additional individual subject safety monitoring in addition to these guidelines is at the discretion of the investigator and dependent on any perceived safety concerns. Unscheduled laboratory testing through the central laboratory may be obtained at any time during the study to assess such concerns, and a subject may be withdrawn at any time at the discretion of the investigator.

Treatment with tofacitinib will be discontinued and the subject withdrawn from this study for:

- Serious infections defined as any infection (viral, bacterial, and fungal) requiring parenteral antimicrobial therapy, hospitalization for treatment, or meeting other criteria that require the infection to be classified as serious adverse event.
- [redacted]
- Two sequential absolute neutrophil counts <0.75 x 10^9/L (<750/mm^3).

- Two sequential absolute lymphocyte counts <0.5 x 10^9/L (<500/mm^3).
- Two sequential hemoglobin <8.0 g/dL or a decrease of >30% from baseline.
- Two sequential platelet counts <75 x 10^9/L (<75,000/ mm^3).
- Two sequential increases in serum creatinine >50% over the baseline value AND an absolute increase in serum creatinine >0.5 mg/dL (>44.2 umol/L).
- Two sequential AST or ALT elevation ≥3 times the upper limit of normal with at least one total bilirubin value ≥2 times the upper limit of normal.[a]
- Two sequential AST or ALT elevation ≥3 times the upper limit of normal accompanied by signs or symptoms consistent with hepatic injury.[a]
- Two sequential AST or ALT elevation ≥5 times the upper limit of normal, regardless of total bilirubin or accompanying signs or symptoms.[a]
- Two sequential CK elevations >10 times the upper limit of normal, unless the causality is known not to be medically serious (eg, exercise induced).
- Female subjects found to be pregnant during the study.
- Initiation of a new treatment for UC.
- Surgery for UC.
- Other serious or severe AEs, after consultation with the Pfizer medical monitor or designee.

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[redacted]

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

Appendix 4. ECG Values of Potential Clinical Concerns

Rhythms/Patterns of Potential Clinical Concern (Adverse Effects)

- Marked Sinus Bradycardia (rate <35 bpm) lasting >10 minutes.
- New PR interval prolongation >280 ms.
- New prolongation of QRS duration to >120 ms or by >40 ms or by ≥50% when baseline ≤100 ms.
- New prolongation of QTcF (Fridericia correction) to >480 ms or by ≥60 ms.
- New Onset Atrial Flutter or Fibrillation, with controlled ventricular response rate: ie, rate <120 bpm.
- New Onset Type I Second Degree (Wenckebach) AV Block of >30 seconds duration.
- Frequent Premature Ventricular Complexes (PVCs), Ventricular Bigeminy, Triplets or short intervals (<30 seconds) of consecutive ventricular complexes.

Adverse Experiences

- QTcF (Fridericia correction) prolongation >500 ms.
- New ST-T changes suggestive of myocardial ischaemia.
- New Onset Left Bundle Branch Block (QRS>120 ms).
- Symptomatic Marked Sinus Bradycardia (rate <40 bpm).
- Sinus Pause >3 seconds without an escape beat.
- Atrial Flutter or Fibrillation, with rapid ventricular response rate: rapid = rate >120 bpm.
- Sustained Supraventricular Tachycardia (rate >120 bpm) ('sustained' = short duration with relevant symptoms or lasting >1 minute).
- Ventricular Rhythms >30 seconds duration, including idioventricular rhythm (rate <40 bpm), accelerated idioventricular rhythm (40< x<100) and monomorphic/polymorphic ventricular tachycardia >100 bpm (such as Torsades de pointes).
- Type II Second Degree (Mobitz) AV Block.
- Complete (third degree) Heart Block.

Serious Adverse Experiences

- Change in pattern suggestive of new or indeterminate age myocardial infarction.
- Sustained Ventricular Tachyarrhythmias (>30 seconds duration).
- Second or third degree AV block requiring pacemaker placement.
- Sinus pauses requiring pacemaker placement.
- Atrial flutter or fibrillation with rapid ventricular response requiring cardioversion.
- Ventricular Fibrillation/Flutter.
- At the discretion of the investigator, any arrhythmia classified as an adverse experience.

Appendix 5. Cockcroft-Gault GFR Calculation

Cockcroft-Gault GFR = ([M] or [F]) x (140 – Age) x BW / (72 x Creatinine)

			Units or Value
GFR	=	Glomerular Filtration Rate	mL/min
M	=	Male	1
F	=	Female	0.85
Age	=	Age	Years
BW	=	Body Weight	Kg
Creatinine	=	Serum Creatinine	mg/dL

When serum creatinine is expressed as μmol/L the appropriate formula is:
Cockcroft-Gault GFR = ([M] or [F]) x (140 – Age) x BW / (0.814 x Creatinine)

Appendix 6. Evaluation of Potentially Malignant Tumors, Suspicious Lymphadenopathy or Possible Extranodal Lymphoproliferative Disorder (LPD)

The following steps should be taken in the event of suspicious lymphadenopathy or possible extranodal lymphoproliferative disorder (LPD) which might arise in the course of this or other studies of Pfizer's experimental immunosuppressive drugs.

Any new cases or worsening cases of existing lymphadenopathy need to be discussed with Pfizer study team first. In addition, when there is a decision to biopsy a suspicious lymph node, the investigator and/or consultants should discuss the issue and any decisions as soon as possible with Pfizer study team. It is recommended that specialists with experience in the evaluation of immunosuppressed patients be consulted.

If a biopsy for lymphadenopathy or lymphoma is to be performed, the investigator or consultant should refer to the study biopsy procedures instructions and review the following points with the surgeon and pathologist:

- Fine needle aspiration and core needle biopsy are strongly discouraged; excisional biopsy is required for accurate diagnosis;
- Tissue must be sent fresh to the pathology laboratory; the pathologist must be consulted before the procedure;
- Archive multiple frozen tissue samples, if possible;
- Include flow cytometry and cytogenetics as part of the pathologic evaluation;
- Culture for mycobacterium and fungi, if indicated;
- Collect and snap freeze peripheral blood lymphocytes for germ line evaluation (DNA);
- Archive multiple aliquots of serum samples.

For <u>all biopsies</u> of potentially malignant tumors, suspicious lymphadenopathy, or possible extranodal lymphoproliferative disorder (LPD), request the pathologist to send the original slides used to make the definitive diagnosis, ancillary study reports, and the pathologist's report to the central laboratory for a blinded review by a central pathologist. Should the central pathologist make a diagnosis that is not essentially similar to the local pathologist's diagnosis, the site will be notified and provided with an opportunity to consult with the central pathologist. Translation during this consultation, if needed, will be provided by the staff of the Pfizer Clinical Country Office (CCO) or designee.

Appendix 7. Evaluation of Gastrointestinal Tract Biopsies

For gastrointestinal tract biopsies, obtained from any gastrointestinal endoscopic procedure performed during the study because of a clinical suspicion of malignancy (even if the local pathologist reading is negative for dysplasia or malignancy) OR gastrointestinal tract biopsies obtained during the study for any reason that show the findings or suspicion of dysplasia or malignancy, the original slides will need to be sent for central pathologist over read in addition to the local pathologist's diagnosis.

Appendix 8. Recommended Clinical Management of Cholesterol

Safety monitoring of a subject's lipid panel results is recommended to include an assessment of individual subject risk for cardiovascular disease. Management of lipid levels should be determined on an individual subject level due to the individualized nature of cholesterol treatment recommendations. The Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP III, National Cholesterol Education Program 2002) provides guiding principles for the intensity of lipid lowering therapy based on an individual's absolute risk for coronary heart disease (CHD). ATP III guidelines and/or other relevant local practices and guidelines should be used to determine if any lipid lowering intervention is required for a subject. Such assessments should occur throughout the study, in light of the observed increases in lipid levels in previous clinical trials with tofacitinib. As appropriate, lipid management decisions may be considered in collaboration with the subject's primary care physician or general practitioner.

A copy of the complete ATP III guidelines will be provided to each study site for reference.

Appendix 9. Quality of Life in Inflammatory Bowel Disease Questionnaire (IBDQ)

This questionnaire is designed to find out how you have been feeling during the last 2 weeks.

You will be asked about symptoms you have been having as a result of your inflammatory bowel disease, the way you have been feeling in general, and how your mood has been.

1. How frequent have your bowel movements been during the last two weeks? Please indicate how frequent your bowel movements have been during the last 2 weeks by picking one of the options from:

    1. BOWEL MOVEMENTS AS OR MORE FREQUENT THAN THEY HAVE EVER BEEN
    2. EXTREMELY FREQUENT
    3. VERY FREQUENT
    4. MODERATE INCREASE IN FREQUENCY OF BOWEL MOVEMENTS
    5. SOME INCREASE IN FREQUENCY OF BOWEL MOVEMENTS
    6. SLIGHT INCREASE IN FREQUENCY OF BOWEL MOVEMENTS
    7. NORMAL, NO INCREASE IN FREQUENCY OF BOWEL MOVEMENTS

2. How often has the feeling of fatigue or of being tired and worn out been a problem for you during the last 2 weeks? Please indicate how often the feeling of fatigue or tiredness has been a problem for you during the last 2 weeks by picking one of the options from:

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

3. How often during the last 2 weeks have you felt frustrated, impatient, or restless? Please choose an option from:

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

4. How often during the last 2 weeks have you been unable to attend school or do your work because of your bowel problem? Please choose an option from:

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

5. How much of the time during the last 2 weeks have your bowel movements been loose? Please choose an option from:

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

6. How much energy have you had during the last 2 weeks? Please choose an option from:

    1. NO ENERGY AT ALL
    2. VERY LITTLE ENERGY
    3. A LITTLE ENERGY
    4. SOME ENERGY
    5. A MODERATE AMOUNT OF ENERGY
    6. A LOT OF ENERGY
    7. FULL OF ENERGY

7. How often during the last 2 weeks did you feel worried about the possibility of needing to have surgery because of your bowel problem? Please choose an option from:

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

8. How often during the last 2 weeks have you had to delay or cancel a social engagement because of your bowel problem? Please choose an option from:

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

9. How often during the last 2 weeks have you been troubled by cramps in your abdomen? Please choose an option from:
    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME
10. How often during the last 2 weeks have you felt generally unwell? Please choose an option from:
    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME
11. How often during the last 2 weeks have you been troubled because of fear of not finding a washroom? Please choose an option from:
    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

12. How much difficulty have you had, as a result of your bowel problems, doing leisure or sports activities you would have liked to have done during the last 2 weeks? Please choose an option from:

    1. A GREAT DEAL OF DIFFICULTY; ACTIVITIES MADE IMPOSSIBLE
    2. A LOT OF DIFFICULTY
    3. A FAIR BIT OF DIFFICULTY
    4. SOME DIFFICULTY
    5. A LITTLE DIFFICULTY
    6. HARDLY ANY DIFFICULTY
    7. NO DIFFICULTY; THE BOWEL PROBLEMS DID NOT LIMIT SPORTS OR LEISURE ACTIVITIES

13. How often during the last 2 weeks have you been troubled by pain in the abdomen? Please choose an option from:

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

14. How often during the last 2 weeks have you had problems getting a good night's sleep, or been troubled by waking up during the night? Please choose an option from:

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

15. How often during the last 2 weeks have you felt depressed or discouraged? Please choose an option from:

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

16. How often during the last 2 weeks have you had to avoid attending events where there was no washroom close at hand? Please choose an option from:

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

17. Overall, in the last 2 weeks, how much of a problem have you had with passing large amounts of gas? Please choose an option from:

    1. A MAJOR PROBLEM
    2. A BIG PROBLEM
    3. A SIGNIFICANT PROBLEM
    4. SOME TROUBLE
    5. A LITTLE TROUBLE
    6. HARDLY ANY TROUBLE
    7. NO TROUBLE

18. Overall, in the last 2 weeks, how much a problem have you had maintaining or getting to, the weight you would like to be at? Please choose an option from:

    1. A MAJOR PROBLEM
    2. A BIG PROBLEM
    3. A SIGNIFICANT PROBLEM
    4. SOME TROUBLE
    5. A LITTLE TROUBLE
    6. HARDLY ANY TROUBLE
    7. NO TROUBLE

19. Many patients with bowel problems often have worries and anxieties related to their illness. These include worries about getting cancer, worries about never feeling any better, and worries about having a relapse. In general, how often during the last 2 weeks have you felt worried or anxious? Please choose an option from:

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

20. How much of the time during the last 2 weeks have you been troubled by a feeling of abdominal bloating? Please choose an option from:

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

21. How often during the last 2 weeks have you felt relaxed and free of tension? Please choose an option from:

    1. NONE OF THE TIME
    2. A LITTLE OF THE TIME
    3. SOME OF THE TIME
    4. A GOOD BIT OF THE TIME
    5. MOST OF THE TIME
    6. ALMOST ALL OF THE TIME
    7. ALL OF THE TIME

22. How much of the time during the last 2 weeks have you had a problem with rectal bleeding with your bowel movements? Please choose an option from:

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

23. How much of the time during the last 2 weeks have you felt embarrassed as a result of your bowel problem? Please choose an option from:

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

24. How much of the time during the last 2 weeks have you been troubled by a feeling of having to go to the bathroom even though your bowels were empty? Please choose an option from

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

25. How much of the time during the last 2 weeks have you felt tearful or upset? Please choose an option from:

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

26. How much of the time during the last 2 weeks have you been troubled by accidental soiling of your underpants? Please choose an option from:

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

27. How much of the time during the last 2 weeks have you felt angry as a result of your bowel problem? Please choose an option from:

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

28. To what extent has your bowel problem limited sexual activity during the last 2 weeks? Please choose an option from:

    1. NO SEX AS A RESULT OF BOWEL DISEASE
    2. MAJOR LIMITATION AS A RESULT OF BOWEL DISEASE
    3. MODERATE LIMITATION AS A RESULT OF BOWEL DISEASE
    4. SOME LIMITATION AS A RESULT OF BOWEL DISEASE
    5. A LITTLE LIMITATION AS A RESULT OF BOWEL DISEASE
    6. HARDLY ANY LIMITATION AS A RESULT OF BOWEL DISEASE
    7. NO LIMITATION AS A RESULT OF BOWEL DISEASE

29. How much of the time during the last 2 weeks have you been troubled by nausea or feeling sick to your stomach? Please choose an option from:

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

30. How much of the time during the last 2 weeks have you felt irritable? Please choose an option from:

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

31. How often during the past 2 weeks have you felt a lack of understanding from others? Please choose an option from:

    1. ALL OF THE TIME
    2. MOST OF THE TIME
    3. A GOOD BIT OF THE TIME
    4. SOME OF THE TIME
    5. A LITTLE OF THE TIME
    6. HARDLY ANY OF THE TIME
    7. NONE OF THE TIME

32. How satisfied, happy, or pleased have you been with your personal life during the past 2 weeks? Please choose one of the following options from:

    1. VERY DISSATISFIED, UNHAPPY MOST OF THE TIME
    2. GENERALLY DISSATISFIED, UNHAPPY
    3. SOMEWHAT DISSATISFIED, UNHAPPY
    4. GENERALLY SATISFIED, PLEASED
    5. SATISFIED MOST OF THE TIME, HAPPY
    6. VERY SATISFIED MOST OF THE TIME, HAPPY
    7. EXTREMELY SATISFIED, COULD NOT HAVE BEEN MORE HAPPY OR PLEASED

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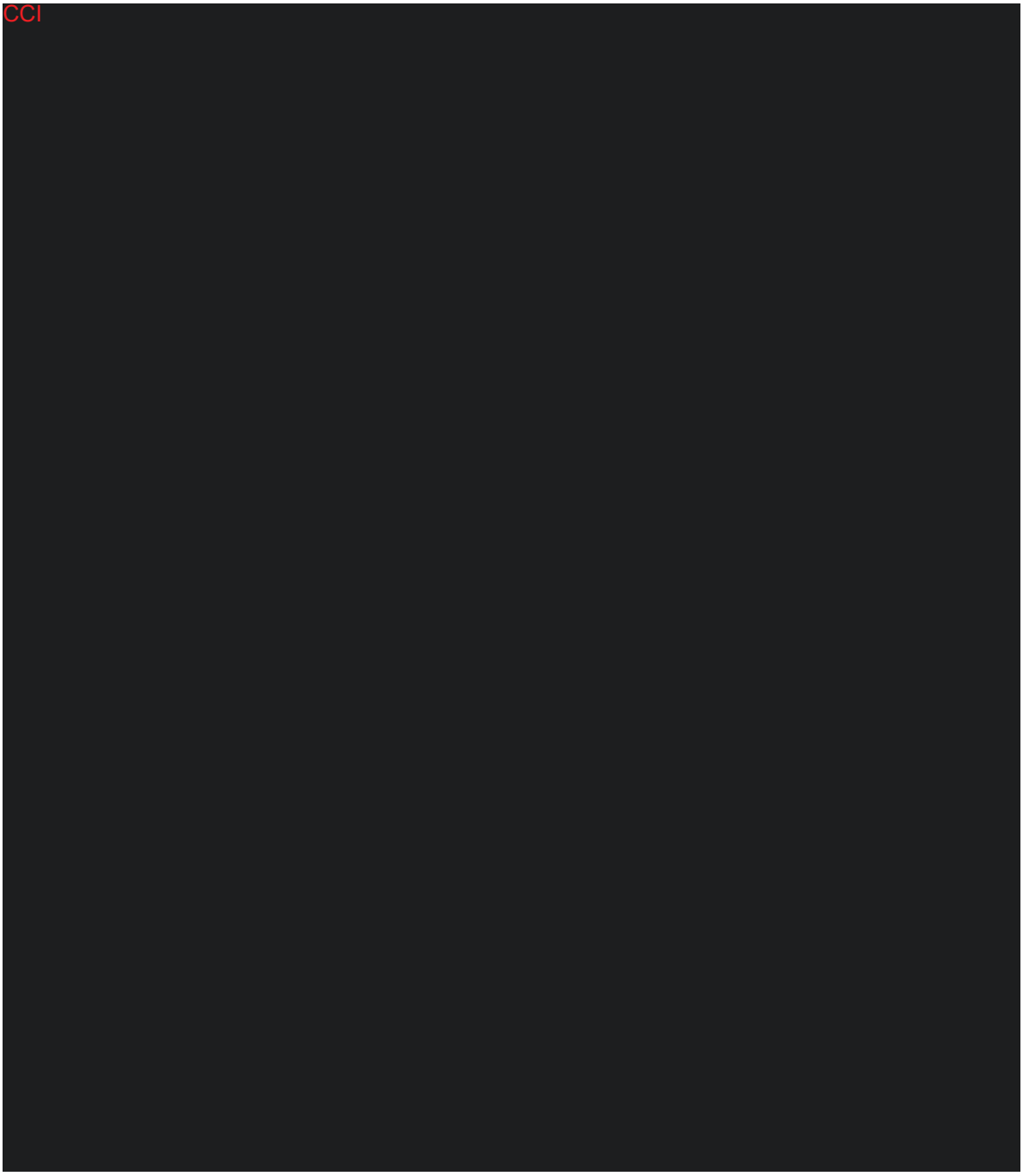

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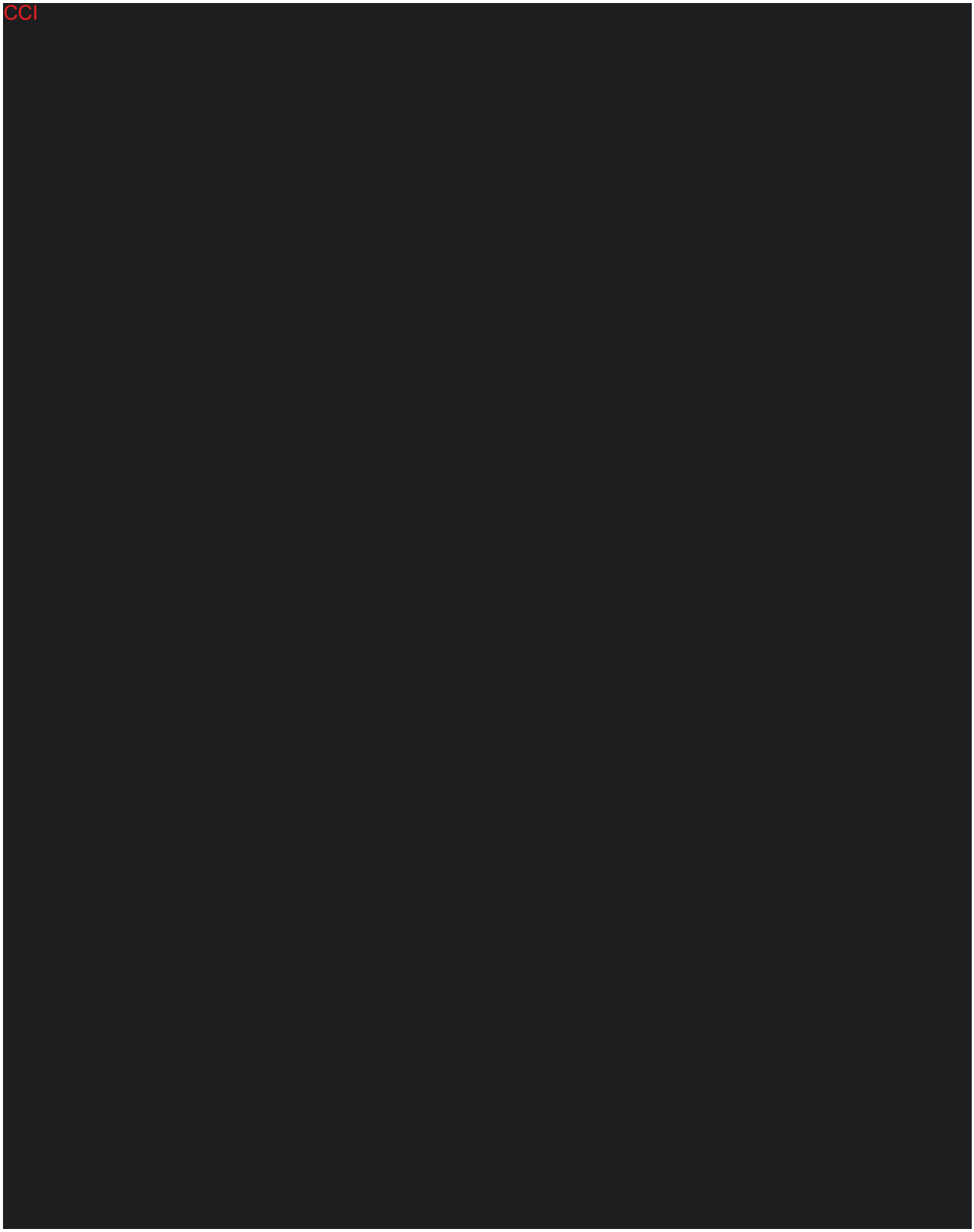


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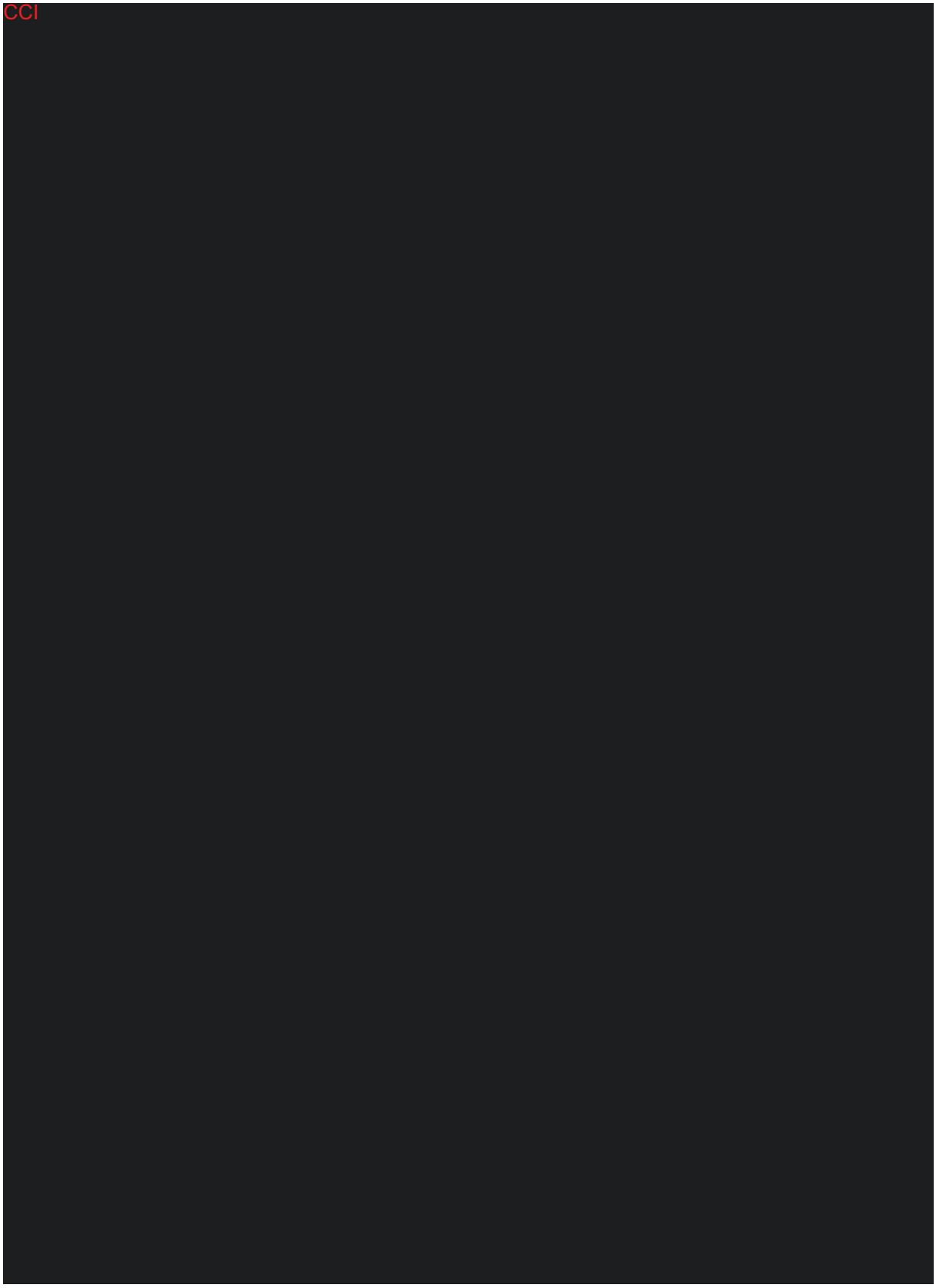

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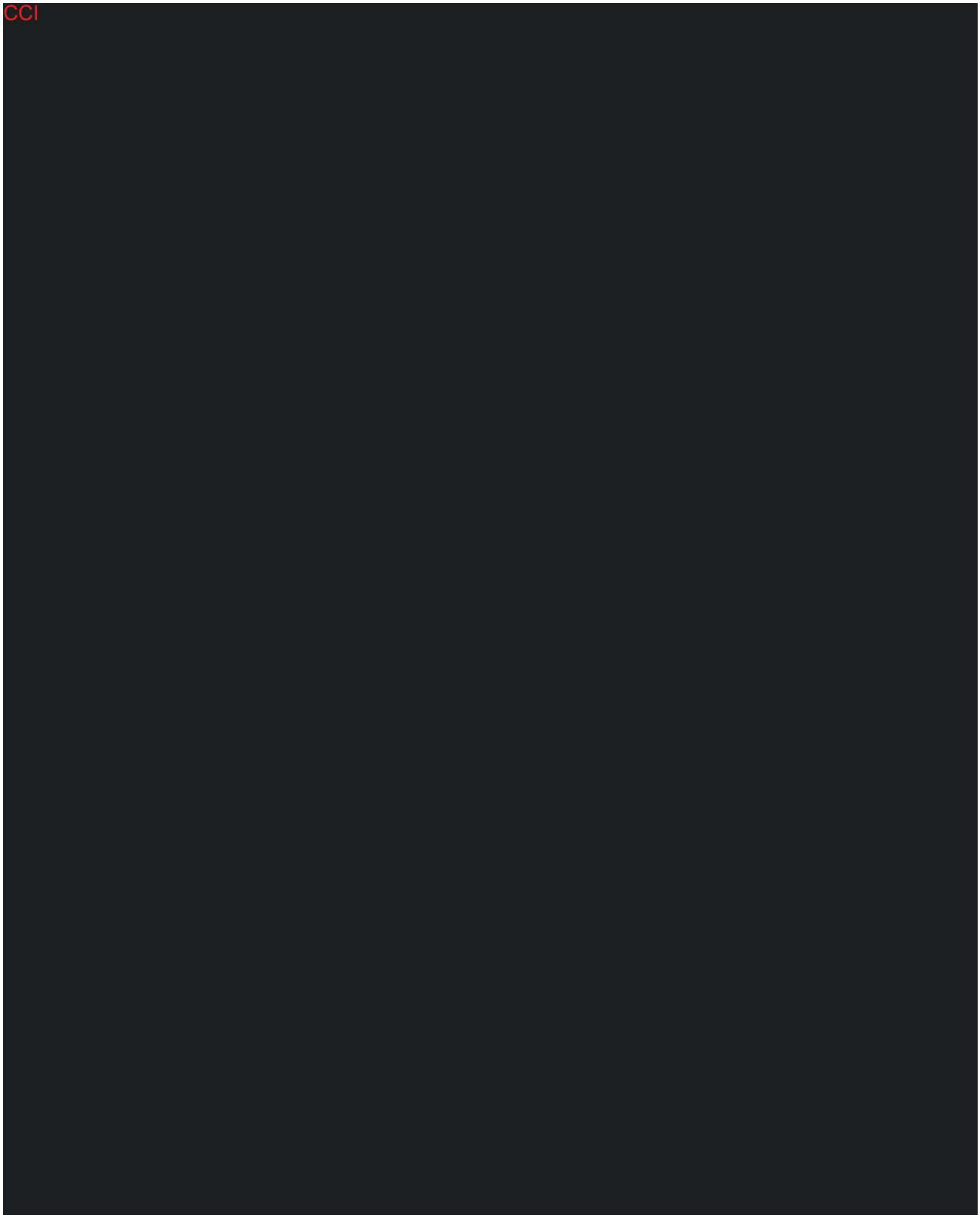

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Appendix 15. Abbreviations

Abbreviation	Term
AE	adverse event
AV	atrialventricular
5-ASA	5- aminosalicylic acid
ALT	alanine aminotransferase
AST	aspartate aminotransferase
β-hCG	beta human chorionic gonadotropin
BID	twice a day
bpm	beats per minute
BUN	blood urea nitrogen
BW	body weight
CD	cluster determinant
CHD	coronary heart disease
CK	creatine kinase
CO_2	carbon dioxide
CP-690,550	compound 690,550
CPK	creatine phosphokinase
CRF	case report form
CSA	Clinical Study Agreement
CT	computerized tomography
CYP3A	cytochrome P450, family 3, subfamily A
CV-SEAC	Cardiovascular Safety Endpoint Adjudication Committee
DMARD	disease modifying anti-rheumatic drug
DNA	Deoxyribonucleic acid
DSMB	Data Safety Monitoring Committee
ECG	electrocardiogram
EDP	exposure during pregnancy
ET	early termination
EudraCT	European Clinical Trials Database
FMA	First Market Approval
PRO	Patient Reported Outcomes
CCI	
EU	European Union
FAS	full analysis set
GCP	good clinical practice
GGT	gamma-glutamyl transferase
g/dL	grams per deciliter
GFR	glomerular filtration rate
HDL-C	high density lipoprotein cholesterol
HO	health outcomes
hs-CRP	high sensitivity C reactive protein
IBD	inflammatory bowel disease
IBDQ	Inflammatory Bowel Disease Questionnaire
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IFN γ	interferon γ (gamma)
IL-6	Interleukin 6
INR	international normalized ratio
IRB	Institutional Review Board
IUD	intrauterine device

Abbreviation	Term
IV	intravenous
IVRS	Interactive Voice Recording System
JAK	janus kinase
kg	kilograms
LDH	lactate dehydrogenase
LDL-C	low density lipoprotein cholesterol
LFT	liver function test
LPD	lymphoproliferative disorder
LTFU	lost to follow up
6-MP	6-mercaptopurine
MCV	mean corpuscular volume
MCH	mean corpuscular hemoglobin
MRI	magnetic resonance image
mL	milliliters
mg	milligrams
NK	natural killer
µmol	micromoles
pH	potential of hydrogen
PhRMA	Pharmaceutical Research and Manufactures of America
PMS	partial Mayo score
PR	per rectum
PRAC	Pharmacovigilance Risk Assessment Committee
PT	prothrombin time
PVCs	premature ventricular complexes
QTc	corrected QT interval
RA	rheumatoid arthritis
RBC	red blood cell
RDW	red cell distribution
SAE	serious adverse event
CCI	
SRSD	Single Reference Safety Document
t½	half-life
TB	tuberculosis
Tmax	time to maximum plasma concentration
TNF alpha	tumor necrosis factor alpha
UC	ulcerative colitis
CCI	
CCI	
ULN	upper limit of normal
US	United States
WBC	white blood cell
CCI	