



**A PHASE 3B/4, MULTI-CENTER, DOUBLE-BLIND, RANDOMIZED, PARALLEL
GROUP STUDY OF TOFACITINIB (CP-690,550) IN SUBJECTS WITH
ULCERATIVE COLITIS IN STABLE REMISSION**

Investigational Product Number:	CP-690,550
Investigational Product Name:	Tofacitinib
United States (US) Investigational New Drug (IND) Number:	CCI [REDACTED]
European Clinical Trials Database (EudraCT) Number:	2017-002274-39
Protocol Number:	A3921288
Phase*:	3b/4

*Designation of Phase 3b is for countries where approval of tofacitinib for ulcerative colitis has not yet been granted; Phase 4 designation is for countries where approval of tofacitinib for ulcerative colitis has been granted.

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Document History

Document	Version Date	Summary of Changes and Rationale
Amendment 3	11 May 2020	<p>This global amendment incorporates monitoring and discontinuation guidelines for venous thromboembolism.</p> <p>Pfizer has determined that venous thromboembolism is an important identified risk/dose dependent adverse drug reaction for tofacitinib.</p> <p>The following sections have been updated to reflect these changes:</p> <p>Schedule of Activities, Section 3 (Study Design), Section 4.2 (Exclusion Criteria), Section 5 (Study Treatments), Section 5.5 (Administration) Section 5.11 (Tofacitinib Dose Adjustment Guidelines), Section 5.12 (Tofacitinib Temporary Withholding), Section 6 (Study Procedures), Section 6.4 (Subject Withdrawal), Section 7.3.3 (Clinical Laboratory Tests), Section 7.3.6 (Risk Factor Check for Venous Thromboembolism), Section 16 (References), Appendix 1 and Appendix 4.</p> <p>Protocol Administrative Clarification Letter dated 19 August 2019 have been incorporated.</p> <p>Lastly, the changes described in the Protocol Administrative Clarification Letter for Amendment 2 due to COVID-19 have been incorporated in newly added Appendix 9.</p>
Amendment 2	19 June 2019	<p>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 (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) in the European Union.</p> <p>Subjects who are identified as having one or more of the contraindicated risk factors for pulmonary embolism as described by PRAC will have their tofacitinib dose adjusted to open-label 5 mg BID.</p>

		<p>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.</p> <p>A risk factor check for pulmonary embolism is added for all study visits. At the time of Amendment 2, 138 subjects have been enrolled in the study and have each completed various durations of participation. Therefore, this new procedure will only be collected at visits applicable to each subject’s individual participation.</p> <p>Lastly, the changes described in the Protocol Administrative Clarification Letter for Amendment 1 have been incorporated; namely the addition of an ‘X’ in the Schedule of Activities at Month 18 for the procedure of Investigational Product Dispensing and the corresponding correction in Section 6.2.8, Month 18 Visit.</p> <p>The following sections have been updated in this protocol amendment:</p> <ul style="list-style-type: none"> • Protocol Summary Study Design, Schedule of Activities, Section 3 (Study Design), Section 4.2 (Exclusion Criteria), Section 5 (Study Treatments), Section 5.5 (Administration), Section 5.8 (Concomitant Medications), Section 5.11 (Tofacitinib Dose Adjustment Guidelines), Section 6 (Study Visit Procedures), newly added Section 7.3.6 (Risk Factor Check for Pulmonary Embolism), Section 9.1 (Sample Size Determination), and Appendix 1 (Abbreviations).
Amendment 1	30 November 2018	<ul style="list-style-type: none"> • Protocol Summary and Section 3, Study Design revised to change treatment duration from 18 months to 42 months. The increased treatment duration includes 8 additional visits to the study site at Months 21, 24, 27, 30, 33, 36, 39 and 42. <p>Rationale: This protocol is being amended to extend subject participation an additional 2 years, from 18 months to 42 months. The</p>

		<p>study is being extended from 18 to 42 months to gather additional long term safety data. In addition, the increase in duration provides a longer time horizon to observe any potential divergence of efficacy between the two dose groups.</p> <ul style="list-style-type: none"> • Protocol Summary, Section 3, Study Design and Section 9.1, Sample Size Determination have been revised to clarify that the final sample size may exceed 130 subjects. <p>Rationale: These revisions were made to optimize recruitment of potentially eligible subjects from Study A3921139.</p> <ul style="list-style-type: none"> • Collection of demography information at Baseline has been added to the Schedule of Activities and Section 6.2.1, Baseline (Visit 1). <p>Rationale: Collection of demography information at Baseline is included as an administrative change that was communicated via a Protocol Administrative Clarification Letter dated 20 September 2017.</p> <ul style="list-style-type: none"> • Schedule of Activities for Months 21 through 42 included. Assessments will be the same as those done during Month 1 through Month 18; no new assessments are introduced. Sections 6.2.9, 6.2.10, 6.2.11 and 6.2.12 have been added to describe study procedures during Months 21 through 42. <p>Rationale: The Schedule of Activities and subsequent Procedures sections are updated to reflect the increased treatment duration of the study to 42 months.</p> <ul style="list-style-type: none"> • Schedule of Activities, Sections 6 and 7.3.3.2 have been revised to reflect the change in tuberculosis test name from QuantiFERON® TB Gold In-Tube test to QuantiFERON® TB Gold Plus test. <p>Rationale: The name of the tuberculosis assay utilized by the central laboratory has changed.</p>
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		<ul style="list-style-type: none">Removed all references to legally acceptable representative throughout the protocol. Subjects must be able to provide their own consent to participate in this study. Rationale: All references to legally authorized representative have been removed throughout the protocol as all subjects recruited into this study are only those subjects who are already participated in Study A3921139 and provided their own consent to participate.Section 4, Subject Eligibility Criteria revised Inclusion criterion #1 and removed Exclusion criterion #1 to allow subjects who have received tofacitinib 10 mg BID for a minimum of 2 consecutive years in Study A3921139 to be eligible for this study. Rationale: Revising the Eligibility Criteria will enable more patients to be considered for study entry that are aligned with clinical practice.Section 4.4.4, Contraception revised to clearly state that male condom or female condom used WITH a separate spermicide product (ie, foam, gel, film, cream, or suppository) is not appropriate or accepted in the European Union (EU); an alternate form of contraception must be selected. Rationale: Contraception section is revised in response to a request from the Voluntary Harmonization Process to align with Heads of Medicines Agencies (HMA) guidance and clearly note within the protocol that male condom or female condom used with a spermicide is not an appropriate method in the whole EU.Section 7.3.3.2, Tuberculosis Testing revised to reflect additional testing done at Months 24 and 36 in high TB prevalence countries. Rationale: The additional TB testing is updated to reflect the increased treatment duration of the study to 42 months while still ensuring annual
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		<p>testing in high TB prevalence countries.</p> <ul style="list-style-type: none"> Section 7.3.4, Infections revised to clarify that if high-risk behaviour(s) or environmental exposures are identified, subjects may be tested to provide evidence that pre-specified infections (eg, HIV, HCV, HBV) are not present. <p>Rationale: Section 7.3.4 is revised in response to competent authority feedback for continued subject safety.</p> <ul style="list-style-type: none"> Appendix 4, Guidelines for Monitoring and Discontinuation revised to clarify references to changes from baseline. <p>Rationale: Revisions to the guidelines and monitoring criteria are made to clarify which study baseline is used for comparison.</p> <ul style="list-style-type: none"> Appendix 8, France Appendix included satisfying the requirements of Contrat Unique in France. <p>Editorial and administrative changes throughout.</p>
Original protocol	13 July 2017	Not applicable (N/A)

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ECs.

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PROTOCOL SUMMARY

Background and Rationale

The tofacitinib Phase 3 ulcerative colitis (UC) program evaluated the efficacy and safety of tofacitinib in patients with moderately to severely active UC who had prior failure or intolerance to corticosteroids, azathioprine/6-mercaptopurine (AZA/6-MP), and/or tumor necrosis factor inhibitor (TNFi) agents. The program consists of 2 completed, identically designed 8-week induction studies (A3921094 and A3921095) with tofacitinib 10 mg twice daily (BID) or placebo, 1 completed 52-week maintenance study (A3921096) with tofacitinib 5 mg BID, tofacitinib 10 mg BID or placebo, and 1 ongoing open-label long-term extension (LTE) study (A3921139) with tofacitinib 5 mg BID and tofacitinib 10 mg BID.

This study is designed to evaluate (1) the efficacy and safety of tofacitinib in subjects in stable remission on 10 mg BID who decrease the dose to 5 mg BID compared to subjects remaining on 10 mg BID; (2) the efficacy and safety of tofacitinib in subjects in stable remission on 10 mg BID who decrease the dose to 5 mg BID with option for dose escalation for flare (“flexible dosing regimen”) compared to subjects staying on 10 mg BID; and (3) the efficacy and safety of the subset of subjects who have flare on maintenance tofacitinib 5 mg BID and are re-treated with 10 mg BID.

Objectives

Primary Objective

- To 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 (“5 mg BID dose group”) compared to subjects remaining on 10 mg BID.

Secondary Objectives

- To evaluate the efficacy and safety of tofacitinib in subjects in stable remission on 10 mg BID who decrease the dose to 5 mg BID with option for dose escalation for flare (“flexible dosing regimen”) compared to subjects staying on 10 mg BID.
- To evaluate the efficacy and safety of the subset of subjects in stable remission on 10 mg BID who have flare after dose decrease to tofacitinib 5 mg BID and are re-treated with 10 mg BID.

Endpoints

Primary Efficacy Endpoint

- Remission based on modified Mayo score at Month 6.

Secondary Efficacy Endpoints

- Time to loss of remission based on modified Mayo score.

- Remission at all applicable scheduled visits based on the following: modified Mayo score (excluding Month 6), modified partial Mayo score, total Mayo score, and partial Mayo score.
- Change from baseline (of Study A3921288) at all applicable scheduled visits in the following: modified Mayo score, modified partial Mayo score, total Mayo score, and partial Mayo score.
- Mucosal healing at all applicable scheduled visits.
- Clinical response based on Mayo score at all applicable scheduled visits.
- Change from baseline at all applicable scheduled visits in fecal calprotectin and hs-CRP levels.

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.
- Adjudicated safety events (eg, opportunistic infections, malignancy, gastrointestinal perforation, and cardiovascular events).

STUDY DESIGN

This is a Phase 3b/4, multi-center, randomized double-blind study. Designation of Phase 3b is for countries where approval of tofacitinib for UC has not yet been granted; Phase 4 designation is for countries where approval of tofacitinib for UC has been granted. This study will enroll subjects from currently enrolled subjects in Study A3921139 who are in stable remission on tofacitinib 10 mg BID for at least 6 months prior to enrollment. Subjects must have received tofacitinib 10 mg BID for a minimum of 2 consecutive years in Study A3921139, and not be receiving any corticosteroids to treat their UC for at least 4 weeks prior to baseline in order to be eligible for this study. Subjects enrolling under Amendment 2 must not have any risk factors for pulmonary embolism as described in [Section 4.2](#), exclusion criterion #12.

Although approximately 130 subjects are estimated to be enrolled into this study (based on availability of eligible subjects from Study A3921139 and based on the conservative assumptions of the attrition rate of 50% -60% in Study A3921139), the final sample size may exceed 130 subjects. The Sponsor will continue to engage with investigative sites participating in Study A3921139 to assess the ability to enroll additional eligible subjects.

This study will have a total of 42 months of treatment duration. The primary analysis will be conducted after the last subject enrolled reaches their Month 6 study visit. This study will remain double-blinded to the site and the subject to the initial treatment assignment at baseline.

Study visits will occur at baseline (enrollment), and at Months 1, 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39 and 42. All subjects, who withdraw early or who complete this study, will have a 4-week safety follow-up evaluation after the last dose of investigational product.

If during the course of the study, a subject experiences an increase in clinical symptoms, such as an increase in rectal bleeding or an increase in stool frequency, then an endoscopy should be performed to assess if the subject is experiencing flare. Flare must be confirmed prior to performing any dose adjustments. In addition, subjects who experience atypical symptoms or features of their usual UC disease course or have significantly worsening disease activity assessments from the previous visit, or have the presence of risk factors such as recent antibiotic use or a recent history of *C. difficile* infection should have *Clostridium difficile* (*C. difficile*) toxin testing performed before assessing for flare and performing any dose adjustments.

Please refer to [Section 5.11](#) for tofacitinib dose adjustment guidelines and definition of flare.

STUDY TREATMENTS

Subjects will be randomized to one of two dosing groups at baseline of Study A3921288:

- Tofacitinib 5 mg BID.
- Tofacitinib 10 mg BID.

STATISTICAL METHODS

Sample Size Determination

Although approximately 130 subjects are estimated to be enrolled into this study (based on availability of eligible subjects from the open label Study A3921139 and based on the conservative assumptions of the attrition rate of 50% - 60% in Study A3921139). The final sample size may exceed 130 subjects and may equal up to 200 subjects if the actual attrition rate is lower than the assumed one. The Sponsor will continue to engage with investigative sites participating in Study A3921139 to assess the ability to enroll additional eligible subjects.

With 130 (65 per group) subjects, the estimated half width of the 95% confidence for treatment difference between tofacitinib 10 mg BID and 5 mg BID in proportion of remission at Month 6 based on the modified Mayo score is about 16%, assuming the remission rates are greater than 70% in both groups.

Efficacy Analysis

Analysis Population

The primary analysis population will be the Full Analysis Set (FAS) defined as all subjects who are randomized into the study and receive at least 1 dose of investigational product.

Primary Analysis

The primary endpoint is remission based on the modified Mayo score at Month 6. The primary analysis will be performed at Month 6 based on the FAS for the estimation of treatment difference between the following two dose groups:

- Tofacitinib 10 mg BID Dose Group: subjects who are initially assigned to tofacitinib 10 mg BID at randomization.
- Tofacitinib 5 mg BID Dose Group: subjects who are initially assigned to tofacitinib 5 mg BID at randomization, regardless of whether the dose is escalated back to tofacitinib 10 mg BID or not.

The stratified estimation of the treatment difference between tofacitinib 10 mg BID and 5 mg BID in the proportion of subjects with remission at Month 6 will be presented along with its 95% confidence interval (CI). The Cochran-Mantel-Haenszel (CMH) weight method will be used for the stratified estimation of the treatment difference. The stratified CI will be constructed using the NewCombe method. Subjects with dose escalation prior to Month 6 or with missing values at Month 6 will be treated as non-responders at Month 6. Sensitivity analyses for handling with missing data will be performed and further details will be provided in the statistical analysis plan.

Secondary Analysis

Dose comparison between tofacitinib 5 mg BID and 10 mg BID

For the primary objective, the treatment difference for the binary secondary efficacy endpoints will also be estimated based on the FAS, using the same approach as described above for the primary endpoint. For continuous endpoints, the change from baseline will be analyzed using linear mixed-effects model with baseline value, dose group, the endoscopic subscore at baseline (0 versus 1), visit, and dose group by visit interaction all as fixed effects, and subject as a random effect. The adjusted estimations and associated 95% CI for the overall difference between the two dose groups will be computed. Kaplan-Meier estimates at the scheduled visits will be computed for time to event endpoint. The log-rank test stratified

by endoscopic subscore at baseline (0 versus 1) will also be performed for the comparison between dose groups.

If a subject has a dose escalation back to tofacitinib 10 mg BID, then

- For binary efficacy endpoints, the subject will be considered as a non-responder for any visit after the dose escalation visit.
- For continuous efficacy endpoints, the data collected for any visit after the dose escalation visit will be considered as missing.
- For time to loss of remission, the subject will be considered as having an event at the visit with a dose escalation if the event criteria are met or having a censor time at the visit with a dose escalation if the event criteria are not met.

For continuous endpoints that are measured repeatedly over time, the missing values will be handled in a linear mixed-effects model where the *mechanism of missingness* is assumed to be missing at random.

Regimen comparison between flexible dosing and fixed dosing

For the first secondary objective, analyses will be performed based on the FAS for comparisons of the following two dose regimens:

- Tofacitinib fixed 10 mg BID Dose Regimen: subjects who are initially assigned to tofacitinib 10 mg BID at randomization and stay on tofacitinib 10 mg BID until completion or discontinuation.
- Tofacitinib flexible 5 mg/10 mg BID Dose Regimen: subjects who are initially assigned to tofacitinib 5 mg BID at randomization, staying on tofacitinib 5 mg BID or having dose escalation from tofacitinib 5 mg BID to 10 mg BID.

Analysis methods are the same as the ones described above for comparison between dose groups except that data from subjects with dose escalation back to tofacitinib 10 mg BID will be treated as it is. Only the visits with missing data will be treated as non-responders.

For the second secondary objective, summary descriptive statistics will be reported for the sub-group of subjects who are initially assigned to tofacitinib 5 mg BID and later are retreated with tofacitinib 10 mg BID. Missing data will not be imputed.

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 investigational product.

Summaries will be performed by dose group and dose regimens as defined in the efficacy sub-section.

SCHEDULE OF ACTIVITIES (BASELINE THROUGH MONTH 18)

The schedule of activities table provides an overview of the protocol visits and procedures. Refer to the [STUDY PROCEDURES](#) and [ASSESSMENTS](#) sections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities table, in order to conduct evaluations or assessments required to protect the well-being of the subject.

All study visits after Baseline will have a visit window of ± 7 days.

Refer to [Appendix 9](#) for permitted alternative measures for certain study procedures in response to the ongoing global COVID-19 pandemic.

Study Procedure	Baseline	Treatment Period						
	Day 1 ¹	Month 1 (± 7 days)	Month 3 (± 7 days)	Month 6 (± 7 days)	Month 9 (± 7 days)	Month 12 (± 7 days)	Month 15 (± 7 days)	Month 18 (± 7 days)
Visit Number	1	2	3	4	5	6	7	8
Informed Consent	X							
Medical History ²	X							
Demography ¹⁰	X							
Targeted Physical Examination ³	OLE	X	X	X	X	X	X	X
Vital Signs, Including Temperature	OLE	X	X	X	X	X	X	X
Laboratory								
Hematology	OLE	X	X	X	X	X	X	X
Serum Chemistry	OLE	X	X	X	X	X	X	X
Lipid Profile, Fasting	OLE			X		X		X
Urine β -hCG ⁴	OLE	X	X	X	X	X	X	X
Dispense Stool Sample Collection Kit	X	X	X	X	X	X	X	X
Collect Stool Sample for Fecal Calprotectin ⁵	X	X	X	X	X	X	X	X
High-Sensitivity CRP	OLE	X	X	X	X	X	X	X
Tuberculosis Testing/Chest Radiograph, if necessary in Specific Countries ⁶						X		

Study Procedure	Baseline	Treatment Period						
	Day 1 ¹	Month 1 (±7 days)	Month 3 (±7 days)	Month 6 (±7 days)	Month 9 (±7 days)	Month 12 (±7 days)	Month 15 (±7 days)	Month 18 (±7 days)
HBV DNA Testing (Japan Only) ⁷	OLE	X	X	X	X	X	X	X
Endoscopic Procedure								
Flexible Sigmoidoscopy/ Colonoscopy (if preferred) ⁸	OLE			X				X
Eligibility Assessment	X							
Randomization	X							
Investigational Product Dispensing	X		X	X	X	X	X	X
Investigational Product Accountability		X	X	X	X	X	X	X
Ulcerative Colitis Assessments								
Bowel Movement Diary Data ⁹	X	X	X	X	X	X	X	X
Partial Mayo Score		X	X		X	X	X	
Mayo Score	OLE			X				X
Contraception Check For Females of Childbearing Potential	X	X	X	X	X	X	X	X
Adverse Event Monitoring	X	X	X	X	X	X	X	X
Concomitant Medication Review	X	X	X	X	X	X	X	X
Risk Factor Check for Venous Thromboembolism ¹¹	X	X	X	X	X	X	X	X

Abbreviations: ET = early termination; β -hCG = beta-human chorionic gonadotropin; OLE = open-label extension study (A3921139).

1. The baseline visit of Study A3921288 is the same visit as the last visit in Study A3921139. All procedures done at the last visit in A3921139 for subjects enrolled into Study A3921288 will be used as the baseline data for Study A3921288. Procedures listed as OLE procedures will NOT BE REPEATED at baseline of Study A3921288. Only those procedures marked with an 'X' will be performed at the baseline visit of Study A3921288.
2. Medical history from Study A3921139, including resolved adverse events (AEs) will be used for Study A3921288. Ongoing AEs from Study A3921139 will be followed throughout Study A3921288.
3. The targeted physical examination consists of weight, general appearance, and examinations of eyes, mouth, lungs, heart, abdomen, musculoskeletal, extremities, skin and lymph nodes.
4. Urine β -hCG to be performed only for females of childbearing potential. Pregnancy testing may be performed more frequently per local regulations.
5. Stool samples will be collected at baseline and at each scheduled study visit to measure fecal calprotectin (see [Section 7.3.3.1](#)). In addition, stool samples should be obtained at the time of worsening disease and/or flare when possible.

6. Tuberculosis (TB) screening will be conducted at Month 12 using Quantiferon-TB[®] Gold Plus test (QFT) only for subjects in those countries in which TB prevalence has been reported at a rate of >50 cases per 100,000 persons (see [Section 7.3.3.2](#)). 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 Induction Study A3921094 or A3921095 or prior annual visits in Study A3921139) and/or previously received adequate treatment for TB.
7. Safety monitoring for a subset of subjects in Japan only. See [Appendix 4](#) for details.
8. Flexible sigmoidoscopy/colonoscopy (if preferred) will be performed at Month 6, Month 18 and at ET for all subjects. In order for a subject to be eligible for Study A3921288, they must have an endoscopy performed in Study A3921139 ≤6 months prior to baseline of Study A3921288 with an endoscopic subscore of 0 or 1. Mayo endoscopic subscore will only be assessed by local site read.
9. Bowel movement (BM) diary data will be collected through a phone-based interactive voice recording system (IVRS) tool. Subjects will be instructed in its use at the Baseline visit. Subjects should start completing the BM diary daily approximately 7 days prior to their next scheduled visit. Study site staff should 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.
10. Demography, including birth date, sex/gender, ethnicity and race will be collected at the Baseline/Day 1 visit and provided in the case report form as allowed by local regulations.
11. **Per Amendment 2, all subjects will be asked at every study visit if they have any newly-developed risk factors for pulmonary embolism as described in [Section 7.3.6](#). At the time of Amendment 2, 138 subjects have been enrolled in the study and have each completed various durations of participation. Per Amendment 3, all subjects will be asked at each applicable visit if they have any newly developed risk factors for venous thromboembolism as described in [Section 7.3.6](#). At the time of Amendment 3, all subjects were enrolled and completed the Month 6 study visit. Therefore, this procedure will only be collected at visits applicable to each subject's individual participation. If a subject has a newly identified risk factor for venous thromboembolism, the subject's tofacitinib dose will be adjusted to open-label 5 mg BID.**

SCHEDULE OF ACTIVITIES (MONTH 21 THROUGH MONTH 42)

Study Procedure	Treatment Period								Follow-Up
	Month 21 (±7 days)	Month 24 (±7 days)	Month 27 (±7 days)	Month 30 (±7 days)	Month 33 (±7 days)	Month 36 (±7 days)	Month 39 (±7 days)	Month 42/ET ¹ (±7 days)	4-weeks after last dose (±7 days)
Visit Number	9	10	11	12	13	14	15	16	17
Targeted Physical Examination ²	X	X	X	X	X	X	X	X	X
Vital Signs, Including Temperature	X	X	X	X	X	X	X	X	X
Laboratory									
Hematology	X	X	X	X	X	X	X	X	X
Serum Chemistry	X	X	X	X	X	X	X	X	X
Lipid Profile, Fasting		X		X		X		X	X
Urine β-hCG ³	X	X	X	X	X	X	X	X	X
Dispense Stool Sample Collection Kit	X	X	X	X	X	X	X		
Collect Stool Sample for Fecal Calprotectin ⁴	X	X	X	X	X	X	X	X	
High-Sensitivity CRP	X	X	X	X	X	X	X	X	
Tuberculosis Testing/Chest Radiograph, if necessary in Specific Countries ⁵		X				X			
HBV DNA Testing (Japan Only) ⁶	X	X	X	X	X	X	X	X	X
Endoscopic Procedure									
Flexible Sigmoidoscopy/ Colonoscopy (if preferred) ⁷				X				X	
Investigational Product Dispensing	X	X	X	X	X	X	X		
Investigational Product Accountability	X	X	X	X	X	X	X	X	
Ulcerative Colitis Assessments									
Bowel Movement Diary Data ⁸	X	X	X	X	X	X	X	X	
Partial Mayo Score	X	X	X		X	X	X		
Mayo Score				X				X	
Contraception Check For Females of Childbearing Potential	X	X	X	X	X	X	X	X	X
Adverse Event Monitoring	X	X	X	X	X	X	X	X	X
Concomitant Medication Review	X	X	X	X	X	X	X	X	X

Study Procedure	Treatment Period								Follow-Up
	Month 21 (±7 days)	Month 24 (±7 days)	Month 27 (±7 days)	Month 30 (±7 days)	Month 33 (±7 days)	Month 36 (±7 days)	Month 39 (±7 days)	Month 42/ET ¹ (±7 days)	
Risk Factor Check for Venous Thromboembolism ⁹	X	X	X	X	X	X	X	X	4-weeks after last dose (±7 days)

Abbreviations: β-hCG = beta-human chorionic gonadotropin.

- Subjects who discontinue treatment early from the study will have an early termination (ET) visit and all procedures listed at Month 42/ET will be performed on the last day the subject takes the investigational product or as soon as possible thereafter.
- The targeted physical examination consists of weight, general appearance, and examinations of eyes, mouth, lungs, heart, abdomen, musculoskeletal, extremities, skin and lymph nodes.
- Urine β-hCG to be performed only for females of childbearing potential. Pregnancy testing may be performed more frequently per local regulations.
- Stool samples will be collected at baseline and at each scheduled study visit to measure fecal calprotectin (see [Section 7.3.3.1](#)). In addition, stool samples should be obtained at the time of worsening disease and/or flare when possible.
- Tuberculosis (TB) screening will be conducted at Month 24 and 36 using Quantiferon-TB[®] Gold Plus test (QFT) only for subjects in those countries in which TB prevalence has been reported at a rate of >50 cases per 100,000 persons (see [Section 7.3.3.2](#)). 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 Induction Study A3921094 or A3921095 or prior annual visits in Study A3921139) and/or previously received adequate treatment for TB.
- Safety monitoring for a subset of subjects in Japan only. See [Appendix 4](#) for details.
- Flexible sigmoidoscopy/colonoscopy (if preferred) will be performed at Month 30, Month 42 and at ET for all subjects. Mayo endoscopic subscore will only be assessed by local site read.
- Bowel movement (BM) diary data will be collected through a phone-based interactive voice recording system (IVRS) tool. Subjects will be instructed in its use at the Baseline visit. Subjects should start completing the BM diary daily approximately 7 days prior to their next scheduled visit. Study site staff should 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.
- Per Amendment 2, all subjects will be asked at every study visit if they have any newly-developed risk factors for pulmonary embolism as described in [Section 7.3.6](#). At the time of Amendment 2, 138 subjects have been enrolled in the study and have each completed various durations of participation. Per Amendment 3, all subjects will be asked at each applicable visit if they have any newly developed risk factors for venous thromboembolism as described in [Section 7.3.6](#). At the time of Amendment 3, all subjects were enrolled and completed the Month 6 study visit. Therefore, this procedure will only be collected at visits applicable to each subject’s individual participation. If a subject has a newly identified risk factor for venous thromboembolism, the subject’s tofacitinib dose will be adjusted to open-label 5 mg BID.**

1. INTRODUCTION

Ulcerative colitis (UC) is a chronic, inflammatory disease of the colon characterized clinically by intermittent flares interposed between variable periods of remission and pathologically by inflammation confined to the mucosa. Patients with moderately to severely active UC are challenged with few treatment options for a life-long chronic condition with high disease burden, reduced quality-of-life, and associated comorbidities.

1.1. Mechanism of Action/Indication

Tofacitinib is a potent, selective inhibitor of the Janus kinase (JAK) family of kinases with a high degree of selectivity against other kinases.¹ In kinase assays, tofacitinib inhibits JAK1, JAK2, JAK3, and to a lesser extent tyrosine kinase 2 (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.² Inhibition of JAK1 and JAK3 by tofacitinib blocks signaling through the common gamma chain containing receptors for several cytokines, including interleukin (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 interferon gamma (IFN γ).³ 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, including UC, in which lymphocyte activation/proliferation plays a pathogenic role.

Tofacitinib is currently being studied as an oral treatment for UC, rheumatoid arthritis (RA) and Psoriatic Arthritis (PsA).

1.2. Background and Rationale

The tofacitinib Phase 3 UC program evaluated the efficacy and safety of tofacitinib in patients with moderately to severely active UC who had prior failure or intolerance to corticosteroids, azathioprine/6-mercaptopurine (AZA/6-MP), and/or tumor necrosis factor inhibitor (TNFi) agents. The program consists of 2 completed, identically designed 8-week induction studies (A3921094 and A3921095) with tofacitinib 10 mg twice daily (BID) or placebo, 1 completed 52-week maintenance study (A3921096) with tofacitinib 5 mg BID, tofacitinib 10 mg BID or placebo, and 1 ongoing open-label long-term extension (LTE) study (A3921139) with tofacitinib 5 mg BID and tofacitinib 10 mg BID.

In both induction studies (A3921094 and A3921095), statistically significantly higher proportions of subjects in the tofacitinib 10 mg BID group achieved the primary endpoint of remission as well as the key secondary endpoint of mucosal healing at Week 8 compared with placebo based on the centrally read endoscopy data. The tofacitinib 10 mg BID group also had statistically significantly higher proportions of subjects with the secondary endpoints of clinical response and endoscopic remission at Week 8 as compared with

placebo. These results were supported by all other secondary and exploratory efficacy endpoints, biomarkers, and patient-reported outcomes (PROs). The observed treatment effects were consistent regardless of prior TNFi treatment.

In addition, tofacitinib 10 mg BID showed significantly greater improvement from baseline in partial Mayo score compared with placebo by Week 2, which was the first post-baseline timepoint assessed and these improvements continued to increase at Week 4 and Week 8. In these 8-week induction studies, the tofacitinib 10 mg BID dose appeared to be well tolerated. Most adverse events (AEs) were mild or moderate in severity, and the most frequent treatment-emergent adverse events (TEAEs) were headache and nasopharyngitis, with similar rates between the tofacitinib and placebo group.

In the maintenance study (A3921096), both tofacitinib 5 mg BID and 10 mg BID demonstrated statistically significantly greater treatment effects versus placebo for remission at Week 52 (primary endpoint), mucosal healing at Week 52, and sustained corticosteroid free remission among subjects in remission at baseline (key secondary endpoints). Tofacitinib 5 mg BID and 10 mg BID also demonstrated statistically significantly higher proportions of subjects with clinical response compared with placebo. Time to treatment failure was statistically significantly different in the tofacitinib 5 mg BID and 10 mg BID treatment groups compared with placebo, with earlier and more frequent events in the placebo group. The efficacy of tofacitinib 5 mg BID and 10 mg BID was supported by all other secondary and exploratory efficacy endpoints and PROs.

The observed treatment effect was higher in the tofacitinib 10 mg BID group than the tofacitinib 5 mg BID group in the overall population for primary and key secondary endpoints, and was generally consistent across subgroups.

In the 52-week maintenance study, both the tofacitinib 5 mg BID and 10 mg BID doses appeared to be well tolerated. Most AEs were mild or moderate in severity, and the most frequent TEAEs were colitis ulcerative (higher incidence in the placebo group) and nasopharyngitis (higher incidence in the tofacitinib groups). Discontinuation from the study due to AEs occurred more frequently in the placebo group compared with the tofacitinib 5 mg BID and 10 mg BID groups, with the most frequent AE leading to discontinuation being colitis ulcerative (worsening of UC). Serious adverse event (SAEs) occurred at similar frequencies across treatment groups. More subjects in the tofacitinib treatment groups experienced infection AEs compared with placebo, though serious infections occurred at similar rates across treatment groups. The most frequent infection AE in all treatment groups was nasopharyngitis. There was a dose-dependent increase in the rate of herpes zoster (HZ).

The safety profile of tofacitinib in UC has been well characterized based on a substantial safety database in UC as well as an extensive safety database from other indications, mostly RA. The safety data from the overall UC clinical program showed that the safety profile of tofacitinib treatment in the UC population was consistent with that of the RA population. There was evidence of dose effect for HZ, consistent with other indications. Overall, rates of events of special interest were similar to the rates in RA and psoriasis, except for a higher incidence rate of HZ. The overall safety profile of tofacitinib was also similar to that of

TNFi agents except for a higher rate of HZ. The majority of HZ events were cutaneous zoster involving 1 or 2 adjacent dermatomes. The totality of data supports an overall acceptable safety profile for both tofacitinib 5 mg BID and 10 mg BID maintenance therapy in moderately to severely active UC patients.

Additional information for this compound may be found in the single reference safety document (SRSD), which for this study is the Investigator's Brochure (IB).

The open-label LTE study (A3921139) is ongoing and the main objective of the study is to collect long term safety data for both tofacitinib 5 mg BID and 10 mg BID doses. Subjects who completed the induction studies but did not achieve clinical response were eligible to enter into the open-label LTE study. Subjects who either completed the maintenance study treatment period or who withdrew early from the maintenance study by meeting prespecified protocol defined criteria for treatment failure were also potentially eligible to enter the open-label LTE study. Subjects completing maintenance Study A3921096 in remission who enrolled into open-label LTE study were assigned to receive tofacitinib 5 mg BID at baseline. All other subjects were assigned to tofacitinib 10 mg BID at baseline. Among those subjects entering the open-label LTE Study A3921139 in remission who received tofacitinib 10 mg BID during maintenance treatment, 72.7% of these subjects remained in remission and 81.8% had mucosal healing after 12 months of open-label treatment with tofacitinib 5 mg BID.

Based on the Phase 3 data, the observed treatment effect was higher with tofacitinib 10 mg BID than tofacitinib 5 mg BID maintenance therapy and a dose-dependent response observed in the rate of herpes zoster. While the data from the uncontrolled open-label LTE study suggest maintenance of efficacy with dose reduction to 5 mg BID for subjects who are in remission after 52 weeks of receiving tofacitinib 10 mg BID, this double-blind, randomized study may help to further evaluate the benefits of dosing flexibility with tofacitinib, and provide additional data for selecting the most appropriate regimen for an individual subject.

This study is designed to evaluate (1) the efficacy and safety of tofacitinib in subjects in stable remission on 10 mg BID who decrease the dose to 5 mg BID compared to subjects remaining on 10 mg BID; (2) the efficacy and safety of tofacitinib in subjects in stable remission on 10 mg BID who decrease the dose to 5 mg BID with option for dose escalation for flare ("flexible dosing regimen") compared to subjects staying on 10 mg BID; and (3) the efficacy and safety of the subset of subjects who have flare on maintenance tofacitinib 5 mg BID and are re-treated with 10 mg BID.

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 minimal accumulation with twice daily dosing. In general, systemic exposure of tofacitinib increases with dose in a dose-proportional manner.

The clearance mechanisms for tofacitinib in humans include 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

In the UC Phase 3 program, tofacitinib 10 mg BID was evaluated for 8 weeks of induction therapy, followed by 5 mg or 10 mg BID for 52 weeks for maintenance therapy in patients with moderate to severe UC. These studies showed tofacitinib 10 mg BID as an induction therapy and both tofacitinib 5 mg BID and 10 mg BID as a maintenance therapy were efficacious, relative to placebo, and had an acceptable safety and tolerability profile. Based on exposure response modeling of the maintenance data, there was a significant trend for increase in efficacy response, as well as a trend for increase in some AE rates, with increasing tofacitinib dose and exposure. Patients enrolled in the ongoing open label LTE Study A3921139 have continued to demonstrate efficacy and acceptable safety and tolerability at both 5 mg BID and 10 mg BID doses. Therefore, the doses selected for this study are consistent with the primary study objective of evaluating whether UC patients in stable remission on tofacitinib 10 mg BID are able to maintain efficacy when switched to tofacitinib 5 mg BID.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

Primary Objective

- To 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 (“5 mg BID dose group”) compared to subjects remaining on 10 mg BID.

Secondary Objectives

- To evaluate the efficacy and safety of tofacitinib in subjects in stable remission on 10 mg BID who decrease the dose to 5 mg BID with option for dose escalation for flare (“flexible dosing regimen”) compared to subjects staying on 10 mg BID.
- To evaluate the efficacy and safety of the subset of subjects in stable remission on 10 mg BID who have flare after dose decrease to tofacitinib 5 mg BID and are re-treated with 10 mg BID.

2.2. Endpoints

Primary Efficacy Endpoint

- Remission based on modified Mayo score at Month 6.

Secondary Efficacy Endpoints

- Time to loss of remission based on modified Mayo score.
- Remission at all applicable scheduled visits based on the following: modified Mayo score (excluding Month 6), modified partial Mayo score, total Mayo score, and partial Mayo score.
- Change from baseline (of Study A3921288) at all applicable scheduled visits in the following: modified Mayo score, modified partial Mayo score, total Mayo score, and partial Mayo score.
- Mucosal healing at all applicable scheduled visits.
- Clinical response based on Mayo score at all applicable scheduled visits.
- Change from baseline at all applicable scheduled visits in fecal calprotectin and hs-CRP levels.

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.
- Adjudicated safety events (eg, opportunistic infections, malignancy, gastrointestinal perforation, and cardiovascular events).

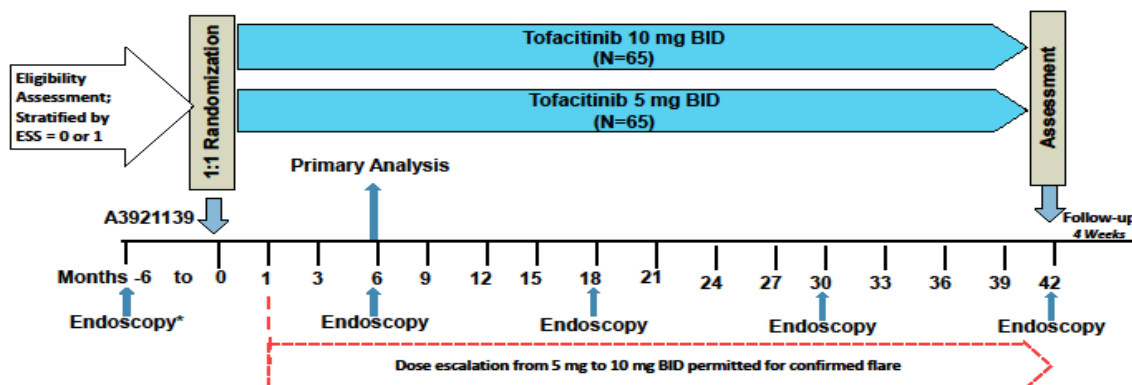
3. STUDY DESIGN

This is a Phase 3b/4, multi-center, randomized double-blind study. Designation of Phase 3b is for countries where approval of tofacitinib for UC has not yet been granted; Phase 4 designation is for countries where approval of tofacitinib for UC has been granted. This study will enroll subjects from currently enrolled subjects in Study A3921139 who are in stable remission on tofacitinib 10 mg BID for at least 6 months prior to enrollment. Subjects must have received tofacitinib 10 mg BID for a minimum of 2 consecutive years in Study A3921139, not be receiving any corticosteroids to treat their UC for at least 4 weeks prior to baseline in order to be eligible for this study. Subjects enrolling under Amendment 2 must not have any risk factors for pulmonary embolism as described in [Section 4.2](#), exclusion criterion #12.

Although approximately 130 subjects are estimated to be enrolled into this study (based on availability of eligible subjects from Study A3921139 and based on the conservative assumptions of the attrition rate of 50% - 60% in Study A3921139), the final sample size may exceed 130 subjects. The Sponsor will continue to engage with investigative sites participating in Study A3921139 to assess the ability to enroll additional eligible subjects.

This study will have a total of 42 months of treatment duration. The primary analysis will be conducted after the last subject enrolled reaches their Month 6 study visit. This study will remain double-blinded to the site and the subject to the initial treatment assignment at baseline.

Study visits will occur at Baseline (Day 1, enrollment), and at Months 1, 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39 and 42. All subjects, who withdraw early or who complete this study, will have a 4-week safety follow-up evaluation after the last dose of investigational product.



* All subjects must have an endoscopy performed in Study A3921139 ≤6 months prior to baseline of Study A3921288 with an endoscopic subscore of 0 or 1, in order to be eligible for enrollment. Local site read of endoscopy only.

If during the course of the study, a subject experiences an increase in clinical symptoms, such as an increase in rectal bleeding or an increase in stool frequency, then an endoscopy should be performed to assess if the subject is experiencing flare. Flare must be confirmed prior to performing any dose adjustments. In addition, subjects who experience atypical symptoms or features of their usual UC disease course or have significantly worsening disease activity assessments from the previous visit, or have the presence of risk factors such as recent antibiotic use or a recent history of *C. difficile* infection should have *Clostridium difficile* (*C. difficile*) toxin testing performed before assessing for flare and performing any dose adjustments.

Please refer to [Section 5.11](#) for tofacitinib dose adjustment guidelines and definition of flare.

Amendment 2

On 17 May 2019, the European Medicines Agency's (EMA) 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 A3921288 will be modified globally through protocol Amendment 2, 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, the subject's tofacitinib dose should be adjusted to open-label 5 mg BID (see [Section 5.11](#)).

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.

1. If a subject is identified as meeting any of the above criteria, the subject's tofacitinib dose will be adjusted to open-label 5 mg BID. The subject's initial treatment assignment at baseline (5 mg BID or 10 mg BID) will remain blinded in this process. The subject should return to the study site as soon as possible to receive new study medication (1 bottle of 5 mg tablets) and they should be instructed to take 1 x 5 mg tablet in the AM and 1 x 5 mg tablet in the PM.
2. If a subject does not have any of the risk factors listed above, he/she will remain on their current assigned tofacitinib dose.
3. 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 5.11](#)).
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 need to have their tofacitinib dose adjusted to open-label 5 mg BID if they are taking open label 10 mg BID or are receiving blinded study medication (5 mg BID or 10 mg BID); see [Section 7.3.6](#). At the time of Amendment 2, 138 subjects have been enrolled in the study and have each completed various durations of participation. Therefore, this new procedure will only be collected at visits applicable to each subject's individual participation.

Amendment 3

Per Amendment 3, in addition to the risk factors already listed above under Amendment 2 for pulmonary embolism, all subjects in the study will be evaluated for risk factors for venous thromboembolism.⁵

Two additional risk factors for venous thromboembolism to be added to the list of pulmonary embolism risk factors above include:

- Prior myocardial infarction within the past 3 months; and
- Being immobilized.

If a subject has one or more of the risk factors for venous thromboembolism listed above under Amendment 2 and 3, the subject's tofacitinib dose will be adjusted to open-label 5 mg BID. The subject's initial treatment assignment at baseline (5 mg BID or 10 mg BID) will remain blinded in this process.

For subjects who do not have any of the risk factors for venous thromboembolism listed above under Amendment 2 and 3, he/she will remain on their assigned tofacitinib dose.

If a subject has any of the risk factors for venous thromboembolism 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 5.11](#)).

Lastly, additional risk factors for venous thromboembolism, such as age, diabetes, obesity (BMI>30), smoking status, hypertension and first degree family history of venous thromboembolism should also be taken into consideration by the investigator and the Sponsor medical monitor when evaluating the benefit:risk for each individual subject whether to modify their dose of tofacitinib.

4. SUBJECT ELIGIBILITY CRITERIA

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

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

4.1. Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Subjects currently enrolled in Study A3921139 who have received tofacitinib 10 mg BID for a minimum of 2 consecutive years in Study A3921139 prior to and including baseline of Study A3921288.
2. Subjects who are in stable remission on tofacitinib 10 mg BID for the 6 month period in Study A3921139 up to and including baseline of Study A3921288, defined as meeting all of the following criteria:
 - a. A partial Mayo score ≤ 2 , with no individual subscore > 1 and a rectal bleeding subscore of 0 at each study visit where data is available during the 6 month period in Study A3921139 prior to and including baseline of Study A3921288;
 - b. **AND** at least one assessment of remission based on Mayo score;
 - If an endoscopy was not completed ≤ 6 months prior to baseline of Study A3921288, then an endoscopy performed in Study A3921139 with an endoscopic subscore of 0 or 1, will be required prior to randomization into Study A3921288.
 - All available assessments based on Mayo score during this period must show remission.
 - c. **AND** subjects must not be receiving any corticosteroid therapy for their UC for at least 4-weeks prior to baseline.

3. Female subjects of childbearing potential must agree to use a highly effective method of contraception throughout the study and for at least 28 days 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 (see [Section 4.4.4](#)).
4. Female subjects of childbearing potential must have a negative urine pregnancy test prior to randomization.
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 has been informed of all pertinent aspects of the study.

4.2. Exclusion Criteria

Subjects with any of the following characteristics/conditions will not be included in the study:

1. Subjects who were initially assigned to tofacitinib 10 mg BID at baseline of Study A3921139 whose tofacitinib dose was reduced to 5 mg BID due to safety or efficacy.
2. Presence of indeterminate colitis, microscopic colitis, ischemic colitis, infectious colitis, or clinical findings suggestive of Crohn's disease.
3. Subjects who 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 3](#)).
5. Subjects who are expected to receive live or attenuated virus vaccination during study period and for 6 weeks after last dose of investigational product.
6. Women who are pregnant or breastfeeding, or planning to become pregnant during the study period.
7. Subjects with evidence of colonic malignancy or any dysplasia (eg, "flat dysplasia"; polyp) identified on endoscopic exam during Study A3921139. 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.

8. Other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior 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.
9. Investigator site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or subjects who are Pfizer employees, including their family members, directly involved in the conduct of the study.
10. Subjects who, in the opinion of the investigator or Pfizer, will be uncooperative or unable to comply with study procedures.
11. Participation in other studies, excluding study A3921139, involving investigational drug(s) during study participation.
12. Subjects with any of the following risk factors for pulmonary embolism at baseline as defined by EMA's PRAC (per Amendment 2 only):
 - 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.

4.3. Randomization Criteria

Eligible subjects will be randomized in a 1:1 allocation ratio to receive either tofacitinib 5 mg BID or 10 mg BID at baseline of Study A3921288. Subjects will be stratified at baseline based on the endoscopic subscore (0 versus 1) of their most recent endoscopy.

4.4. Lifestyle Requirements

4.4.1. Tobacco

Smoking can have an influence on the severity of UC symptoms. For that reason, subjects should discuss with the study investigator if they wish to make changes to their smoking habits during the study. Use of nicotine patch should be recorded as a concomitant medication.

4.4.2. 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 investigational product. 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 3](#)).

4.4.3. Vaccination

Vaccination with live components is prohibited during the study and for 6 weeks after last dose of investigational product. 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.

Some examples of live or attenuated vaccines include but are not limited to: FluMist® (intranasal influenza vaccine), attenuated rotavirus vaccine, varicella vaccine, attenuated typhoid fever vaccine, oral polio vaccine, and Zostavax® (zoster vaccine).

4.4.4. Contraception

Based on preclinical data, tofacitinib has a potential risk of teratogenicity and early fetal loss. Due to this potential risk, female subjects of childbearing potential should not be administered tofacitinib until pregnancy is excluded.

Female subjects of nonchildbearing potential must meet at least 1 of the following criteria:

- a. Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; status may be confirmed with a serum follicle-stimulating hormone (FSH) level confirming the postmenopausal state;
- b. Have undergone a documented hysterectomy and/or bilateral oophorectomy;
- c. Have medically confirmed ovarian failure.

All other female subjects (including female subjects with tubal ligations) are considered to be of childbearing potential.

All female subjects who are of childbearing potential as applicable to the study who are, in the opinion of the investigator, sexually active and at risk for pregnancy with their partner(s) must agree to use a highly effective method of contraception consistently and correctly for the duration of the active treatment period and for at least 28 days after the last dose of investigational product. The investigator or his or her designee, in consultation with the subject, will confirm that the subject has selected an appropriate method of contraception for the individual subject from the permitted list of contraception methods (see below) and will confirm that the subject has been instructed in its consistent and correct use. At time points indicated in the [Schedule of Activities](#), the investigator or designee will inform the subject of the need to use highly effective contraception consistently and correctly and document the conversation and the subject's affirmation in the subject's chart (subjects needs to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the investigator or designee will instruct the subject to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the subject or the partner.

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 the following:

1. Established use of hormonal methods of contraception associated with inhibition of ovulation (eg, oral, inserted, injected, implanted, transdermal) provided the subject or male subject's female partner plans to remain on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness.
2. Correctly placed copper-containing intrauterine device (IUD).
3. Male condom or female condom used WITH a separate spermicide product (ie, foam, gel, film, cream, or suppository). For countries where spermicide is not available or condom plus spermicide is not accepted as highly effective contraception, this option is not appropriate. Note: This option is not appropriate or accepted in the European Union (EU); an alternate form of contraception must be selected.
4. Male sterilization with absence of sperm in the post-vasectomy ejaculate.
5. Bilateral tubal ligation/bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label).

NOTE: Sexual abstinence, defined as completely and persistently refraining from all heterosexual intercourse (including during the entire period of risk associated with the study treatments) may obviate the need for contraception ONLY if this is the preferred and usual lifestyle of the subject.

Subjects in Canada who are females 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 as described below.

Highly effective contraceptive methods may include hormonal contraceptives (eg, combined oral contraceptives, patch, vaginal ring, injectables, and implants), intrauterine device (IUD) or intrauterine system (IUS), vasectomy or tubal ligation.

Effective methods may include barrier methods of contraception (eg, male condom, female condom, cervical cap, diaphragm or contraceptive sponge). The proper use of diaphragm or cervical cap includes use of spermicide and is considered one barrier method. The cervical cap and contraceptive sponge are less effective in parous women. The use of spermicide alone is not considered a suitable barrier method for contraception.

4.4.5. 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.

4.4.6. 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 study portal.

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 product identifiers, subject study numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator 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 investigator 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 investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator 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 investigator site.

5. STUDY TREATMENTS

For the purposes of this study, and per International Council for Harmonisation (ICH) guidelines, investigational product is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference/comparator in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or

packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (ICH E6 1.33).

For this study, the investigational product is tofacitinib.

Subjects will be randomized to one of two dosing groups at baseline of Study A3921288:

- Tofacitinib 5 mg BID.
- Tofacitinib 10 mg BID.

Subjects who meet the protocol definition for flare may have a dose increase to 10 mg BID or remain on 10 mg BID, depending on their initial treatment assignment (see [Section 5.11](#)), provided that the subject does not have any of the risk factors for venous thromboembolism (see [Section 7.3.6](#)).

5.1. Allocation to Treatment

Allocation of subjects to treatment groups will proceed through the use of an interactive response technology (IRT) system (interactive Web-based response [IWR]). The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's identification (ID) and password, the protocol number, and the subject number. The site personnel will then be provided with a treatment assignment, randomization number, and container number(s) when investigational product is being supplied via the IRT system. The IRT system will provide a confirmation report containing the subject number, randomization number, and container number(s) assigned. The confirmation report must be stored in the site's files.

The study-specific IRT reference manual will provide the contact information and further details on the use of the IRT system.

5.2. Breaking the Blind

The study will be subject and investigator blinded to the initial treatment assignment at baseline.

At the initiation of the study, the investigator site will be instructed on the method for breaking the blind. The method will be an electronic process. Blinding codes should be broken only in exceptional circumstances when knowledge of the actual treatment code is absolutely essential for further management of the subject. If an investigator believes that immediate unblinding is necessary and time and circumstances allows, he/she is encouraged to discuss with a member of the study team. However, discussion with a member of the study team in advance of the unblinding is not required. When the blinding code is broken, the reason must be fully documented and entered on the case report form (CRF).

5.3. Subject Compliance

Investigational product compliance will be assessed by the site at each study visit starting at the visit after the baseline visit (Month 1) 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 investigational products 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. Investigational Product Supplies

5.4.1. Dosage Form(s) and Packaging

Blinded tofacitinib and its matched placebo will be provided as tablets for oral administration. The 5-mg tablets and their matching placebos will be supplied in separate bottles and labeled according to local regulatory requirements.

5.4.2. Preparation and Dispensing

The investigational product will be dispensed using an IRT drug management system at each visit according to the [Schedule of Activities](#). A qualified staff member will dispense the investigational product via unique container numbers in the bottles provided, in quantities appropriate for the study visit schedule. The subject/caregiver should be instructed to maintain the product in the bottles provided throughout the course of dosing and return the bottles to the site at the next study visit.

5.5. Administration

Subjects receiving blinded study medication will be dispensed two (2) bottles at each dispensing visit and given clear dosing instructions. Subjects should be instructed to take one (1) tablet from each bottle in the morning and one (1) tablet from each bottle in the evening, approximately 12 hours apart. Subjects receiving blinded study medication will therefore be taking two (2) tablets twice a day, regardless of which blinded treatment arm they are randomized to receive.

If a subject has their tofacitinib dose **adjusted to open-label 5 mg BID** due to having any of the risk factors for venous thromboembolism, they will be dispensed **only one (1)** bottle of 5 mg tablets and should be instructed to take one (1) tablet from the bottle in the morning and one (1) tablet in the evening, approximately 12 hours apart. Therefore, subjects will only be taking one (1) tablet twice a day if the tofacitinib dose is adjusted to open-label 5 mg BID.

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. Subjects will swallow the investigational product whole and will not manipulate or chew the investigational product prior to swallowing.

Table 1. Investigational Product Administration

Treatment Assignment	AM Dosing*	PM Dosing*
5 mg BID (blinded)	Bottle A 5 mg - 1 tablet Bottle B Placebo – 1 tablet	Bottle A 5 mg - 1 tablet Bottle B Placebo – 1 tablet
10 mg BID (blinded or open-label)	Bottle A 5 mg - 1 tablet Bottle B 5 mg - 1 tablet	Bottle A 5 mg - 1 tablet Bottle B 5 mg - 1 tablet
5 mg BID (open-label)	Bottle A 5 mg - 1 tablet	Bottle A 5 mg - 1 tablet

* Bottle A and B designations are used for example purposes only.

5.6. Investigational Product Storage

The investigator or an approved representative, eg, pharmacist, will ensure that all investigational products are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements.

Investigational products should be stored in their original containers and in accordance with the labels.

Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the product label.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated, and/or room-temperature products). This should be captured from the time of investigational product receipt throughout the study. Even for continuous-monitoring systems, a log or site procedure that ensures active evaluation for excursions should be available. The intent is to ensure that the minimum and maximum temperature is checked each business day to confirm that no excursion occurred since the last evaluation and to provide the site with the capability to store or view the minimum/maximum temperature for all non-working days upon return to normal operations. The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure they are maintained in working order.

Any excursions from the product label storage conditions should be reported to Pfizer upon discovery. The site should actively pursue options for returning the product to the storage conditions described in the labeling, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to Pfizer.

Once an excursion is identified, the investigational product must be quarantined and not used until Pfizer provides permission to use the investigational product. It will not be considered a protocol deviation if Pfizer approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to Pfizer approval will be considered a protocol deviation. Specific details regarding information the site should report for each excursion will be provided to the site.

Receipt of materials, door opening and closing, and other routine handling operations where the products are briefly out of the temperature range described in the labeling are not considered excursions.

Site staff will instruct subjects on the proper storage requirements for take home investigational products.

5.7. Investigational Product Accountability

The investigator site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies. All investigational products will be accounted for using a drug accountability form/record. All bottles of study drug must be returned to the investigator by the subject at every visit to assess accountability and at the end of the trial.

5.7.1. Destruction of Investigational Product Supplies

The sponsor or designee will provide guidance on the destruction of unused investigational product (eg, at the site). If destruction is authorized to take place at the investigator 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, and all destruction must be adequately documented.

For all bottles returned to the investigator by the subject, the investigator will maintain the returned supply until destruction is authorized. Pfizer will provide instructions as to the disposition of any unused investigational product.

5.8. Concomitant Medication(s)

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 Study A3921139 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
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 medications*	Indication, start and stop dates	Treatment period Follow-up period

* Includes nonprescription drugs, vitamins, and dietary supplements.

The following therapies for the treatment of UC are allowed:

- Oral 5-aminosalicylic acid (5-ASA) or sulfasalazine.

Subjects receiving either concomitant combined hormonal contraceptives or hormone replacement therapy must have their tofacitinib dose adjusted to open-label 5 mg BID.

5.9. Prohibited Concomitant Medications

The following medications are prohibited throughout the study (see [Appendix 3](#)):

- Azathioprine, 6-mercaptopurine and methotrexate;
- Cyclosporine, mycophenolate mofetil/mycophenolic acid and tacrolimus;
- Interferon;
- Anti-TNF alpha therapy (eg, infliximab, adalimumab, golimumab, or certolizumab);
- Corticosteroids for the treatment of UC: oral, intravenous, or rectally administered;
- 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 3](#) due to potential for drug interactions or confounding of data interpretation.

5.10. Rescue Medication

If a subject requires initiation of a new therapy or re-initiation of a therapy for UC, other than oral 5-ASA or sulfasalazine, the subject should be withdrawn from the study and appropriate agents should be given at the discretion of the investigator.

5.11. Tofacitinib Dose Adjustment Guidelines

Per Amendment 2, all subjects will be reviewed for risk factors for pulmonary embolism as detailed in [Section 3](#) under Amendment 2. Per Amendment 3, all subjects will be reviewed for risk factors for venous thromboembolism as detailed in [Section 3](#) under Amendment 3. Subjects who are identified to have one or more of the risk factors for venous thromboembolism (or risk factors for pulmonary embolism per Amendment 2) will need to have their tofacitinib dose adjusted to open-label 5 mg BID.

If during the course of the study, a subject experiences an increase in clinical symptoms, such as an increase in rectal bleeding or an increase in stool frequency, then an endoscopy should be performed to assess if the subject is experiencing flare. Flare must be confirmed prior to performing any dose adjustments.

In addition, subjects who experience atypical symptoms or features of their usual UC disease course or have significantly worsening disease activity assessments from the previous visit, or have the presence of risk factors such as recent antibiotic use or a recent history of *C. difficile* infection should have *Clostridium difficile* (*C. difficile*) toxin testing performed before assessing for flare and performing any dose adjustments. In addition, subjects should be tested for *C. difficile* toxin prior to being discontinued due to worsening UC, if possible. If confirmed positive, 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 may continue to receive tofacitinib while undergoing treatment for *C. difficile* infection. Subjects with *C. difficile* infection that meets serious infection criteria must be withdrawn from the study. Additional stool testing and treatment for other enteric pathogens is at the discretion of the investigator.

Flare is defined by meeting **one** of the following 4 criteria:

1. An increase in rectal bleeding subscore by at least 1 point and an increase in endoscopic subscore by at least 1 point; OR
2. An increase in rectal bleeding subscore by at least 2 points and an endoscopic subscore >0; OR
3. An increase in stool frequency subscore by at least 2 points and an increase in the endoscopic subscore by at least 1 point; OR
4. An increase in endoscopic subscore by at least 2 points.

Once the subject is confirmed to meet the definition for flare, documented by site read endoscopy, the investigator may adjust the dose through the IRT system provided that the subject does not have any of the risk factors for venous thromboembolism (see [Section 7.3.6](#)). Once confirmed by the investigator, subjects may have a dose increase to 10 mg BID or remain on 10 mg BID, depending on their initial treatment assignment. Dose adjustments for confirmed flare will not be permitted prior to the Month 1 study visit.

Subjects who develop one or more of the risk factors for venous thromboembolism during the study will not be permitted to increase their tofacitinib dose to 10 mg BID should they experience a flare of their UC.

5.12. 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 10 days. If study drug interruption exceeding 10 days is required for a medical reason, the investigator should speak with the Pfizer medical monitor to determine the suitability of the subject to withhold treatment for a longer duration and to discuss the suitability of the subject remaining in the trial.

Per Amendment 3, for subjects with suspected venous thromboembolism, treatment with tofacitinib should be temporarily withheld while the subject is evaluated. If venous thromboembolism is confirmed, discontinue treatment with tofacitinib and withdraw the subject from the study.

6. STUDY PROCEDURES

Refer to [Appendix 9](#) for permitted alternative measures for certain study procedures in response to the ongoing global COVID-19 pandemic.

6.1. Screening

There will be no protocol specified screening period as part of Study A3921288. Screening will occur as part of Study A3921139 and eligibility will be assessed prior to enrolling into Study A3921288.

6.2. Study Period

6.2.1. Baseline (Visit 1)

The baseline visit of Study A3921288 is the same visit as the last visit in Study A3921139. All procedures done at the last visit in A3921139 for subjects enrolled into Study A3921288 will be used as the baseline data for Study A3921288.

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 performed:

- Obtain informed consent.
- Review medical history and concomitant medications. Medical history from Study A3921139 will be used as baseline for Study A3921288. Resolved AEs occurring in Study A3921139 will be captured as part of Baseline Medical History, while ongoing AEs from Study A3921139 will be followed throughout Study A3921288. Ongoing concomitant medications from Study A3921139 will be recorded in Study A3921288.
- Demography, including birth date, sex/gender, ethnicity and race will be collected at the Baseline/Day 1 visit and provided in the case report form as allowed by local regulations.
- Collect stool sample for fecal calprotectin. If a sample cannot be collected at the visit, provide subject with stool collection kit to obtain stool sample at home. Subjects should be instructed to make all efforts to collect the baseline sample as soon as possible, but no later than 7 days of the baseline visit. The stool sample should be returned within 24 hours of collection.
- Provide subject with stool sample collection kit to obtain stool sample at home to be returned for the Month 1 study visit.
- Risk factor check for pulmonary embolism, per Amendment 2.
- Confirmation of all inclusion/exclusion criteria.
- Randomization.
- Investigational product dispensing.
- Subjects will be reminded of instructions for using the phone based bowel movement (BM) diary. Subjects should start completing the BM diary daily approximately 7 days prior to their next scheduled visit. Study site staff should 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.
- Contraception check for females of childbearing potential.
- Adverse event monitoring.

The following study procedures listed as open-label extension (OLE) in the [Schedule of Activities](#) will be performed at the final visit of Study A3921139 and will not be repeated at baseline of Study A3921288:

- Endoscopic procedure.
 - Flexible sigmoidoscopy/colonoscopy (if preferred). Endoscopy will only be performed in subjects who do not have an endoscopy performed within the 6 month period prior to baseline of Study A3921288. Endoscopic assessment will only be done by local site read.
- UC assessments.
 - Mayo score.
- Targeted physical examination.
- Vital signs, including temperature.
- Laboratory:
 - Hematology.
 - Serum Chemistry.
 - hs-CRP.
 - Lipid profile, fasting.
 - Urine beta human chorionic gonadotropin (β -hCG) to be performed only for females of childbearing potential.

6.2.2. Month 1 (± 7 days, Visit 2)

The following procedures will be performed:

- Targeted physical examination.
- Vital signs, including temperature.
- Laboratory:
 - Hematology.
 - Serum chemistry.
 - hs-CRP.

- Urine β -hCG to be performed only for females of childbearing potential.
- Collect stool sample or fecal calprotectin.
- Provide subject with stool sample collection kit to obtain stool sample at home to be returned for the Month 3 study visit.
- UC assessments: review of BM diary and calculate partial Mayo score.
- Investigational product accountability.
- Contraception check for females of childbearing potential.
- Adverse event monitoring.
- Concomitant medication review.
- Risk factor check for pulmonary embolism, per Amendment 2.

6.2.3. Month 3 (± 7 days, Visit 3)

The following procedures will be performed:

- Targeted physical examination.
- Vital signs, including temperature.
- Laboratory:
 - Hematology.
 - Serum chemistry.
 - hs-CRP.
 - Urine β -hCG to be performed only for females of childbearing potential.
 - Collect stool sample for fecal calprotectin.
 - Provide subject with stool sample collection kit to obtain stool sample at home to be returned for the Month 6 study visit. Subjects should be instructed to collect the sample **prior to the subject initiating the bowel preparation for endoscopy.**
- UC assessments: review of BM diary and calculate partial Mayo score.
- Investigational product accountability.

- Contraception check for females of childbearing potential.
- Adverse event monitoring.
- Concomitant medication review.
- Investigational product dispensing.
- Risk factor check for pulmonary embolism, per Amendment 2.

6.2.4. Month 6 (±7 days, Visit 4)

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.

The following procedures will be performed:

- Targeted physical examination.
- Vital signs, including temperature.
- Laboratory:
 - Hematology.
 - Serum chemistry.
 - hs-CRP.
 - Lipid profile, fasting.
 - Urine β -hCG to be performed only for females of childbearing potential.
 - Collect stool sample for fecal calprotectin.
 - Provide subject with stool sample collection kit to obtain stool sample at home to be returned for the Month 9 study visit.
- Endoscopy: flexible sigmoidoscopy/colonoscopy (if preferred). Endoscopic assessment will only be done by local site read.
- UC assessments: review of BM diary and calculate Mayo score.
- Investigational product accountability.
- Contraception check for females of childbearing potential.
- Adverse event monitoring.

- Concomitant medication review.
- Investigational product dispensing.
- Risk factor check for pulmonary embolism, per Amendment 2.

6.2.5. Month 9 (± 7 days, Visit 5)

The following procedures will be performed:

- Targeted physical examination.
- Vital signs, including temperature.
- Laboratory:
 - Hematology.
 - Serum chemistry.
 - hs-CRP.
 - Urine β -hCG to be performed only for females of childbearing potential.
 - Collect stool sample for fecal calprotectin.
 - Provide subject with stool sample collection kit to obtain stool sample at home to be returned for the Month 12 study visit.
- UC assessments: review of BM diary and calculate partial Mayo score.
- Investigational product accountability.
- Contraception check for females of childbearing potential.
- Adverse event monitoring.
- Concomitant medication review.
- Investigational product dispensing.
- Risk factor check for venous thromboembolism.

6.2.6. Month 12 (± 7 days, Visit 6)

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.

The following procedures will be performed:

- Targeted physical examination.
- Vital signs, including temperature.
- Laboratory:
 - Hematology.
 - Serum chemistry.
 - hs-CRP.
 - Lipid profile, fasting.
 - Urine β -hCG to be performed only for females of childbearing potential.
 - Collect stool sample for fecal calprotectin.
 - Provide subject with stool sample collection kit to obtain stool sample at home to be returned for the Month 15 study visit.
 - Tuberculosis (TB) testing using Quantiferon-TB[®] Gold Plus test (QFT) for subjects in specific countries (see [Section 7.3.3.2](#)). All subjects with a positive result must have a chest radiograph performed.
- UC assessments: review of BM diary and calculate partial Mayo score.
- Investigational product accountability.
- Contraception check for females of childbearing potential.
- Adverse event monitoring.
- Concomitant medication review.
- Investigational product dispensing.
- Risk factor check for venous thromboembolism.

6.2.7. Month 15 (± 7 days, Visit 7)

The following procedures will be performed:

- Targeted physical examination.
- Vital signs, including temperature.

- Laboratory:
 - Hematology.
 - Serum chemistry.
 - hs-CRP.
 - Urine β -hCG to be performed only for females of childbearing potential.
 - Collect stool sample for fecal calprotectin.
 - Provide subject with stool sample collection kit to obtain stool sample at home to be returned for the Month 18 study visit. Subjects should be instructed to collect the sample **prior to the subject initiating the bowel preparation for endoscopy.**
- UC assessments: review of BM diary and calculate partial Mayo score.
- Investigational product accountability.
- Contraception check for females of childbearing potential.
- Adverse event monitoring.
- Concomitant medication review.
- Investigational product dispensing.
- Risk factor check for venous thromboembolism.

6.2.8. Month 18 (± 7 days, Visit 8) Visit

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.

The following procedures will be performed:

- Targeted physical examination.
- Vital signs, including temperature.
- Laboratory:
 - Hematology.
 - Serum chemistry.
 - hs-CRP.

- Lipid profile, fasting.
- Urine β -hCG to be performed only for females of childbearing potential.
- Collect stool sample for fecal calprotectin.
- Provide subject with stool sample collection kit to obtain stool sample at home to be returned for the Month 21 study visit.
- Endoscopy: flexible sigmoidoscopy/colonoscopy (if preferred). Endoscopic assessment will only be done by local site read.
- UC assessments: review of BM diary and calculate Mayo score.
- Investigational product accountability.
- Contraception check for females of childbearing potential.
- Adverse event monitoring.
- Concomitant medication review.
- Investigational product dispensing.
- Risk factor check for venous thromboembolism.

6.2.9. Months 21 and 33 (± 7 days, Visits 9 and 13)

The following procedures will be performed:

- Targeted physical examination.
- Vital signs, including temperature.
- Laboratory:
 - Hematology.
 - Serum chemistry.
 - hs-CRP.
 - Urine β -hCG to be performed only for females of childbearing potential.
 - Collect stool sample for fecal calprotectin.
 - Provide subject with stool sample collection kit to obtain stool sample at home to be returned for the Months 24 and 36 study visits.

- UC assessments: review of BM diary and calculate partial Mayo score.
- Investigational product accountability.
- Contraception check for females of childbearing potential.
- Adverse event monitoring.
- Concomitant medication review.
- Investigational product dispensing.
- Risk factor check for venous thromboembolism.

6.2.10. Months 24 and 36 (± 7 days, Visits 10 and 14)

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:

- Targeted physical examination.
- Vital signs, including temperature.
- Laboratory:
 - Hematology.
 - Serum chemistry.
 - hs-CRP.
 - Lipid profile, fasting.
 - Urine β -hCG to be performed only for females of childbearing potential.
 - Collect stool sample for fecal calprotectin.
 - Provide subject with stool sample collection kit to obtain stool sample at home to be returned for the Months 27 and 39 study visits.
 - Tuberculosis (TB) testing using Quantiferon-TB[®] Gold Plus test (QFT) for subjects in specific countries (see [Section 7.3.3.2](#)). All subjects with a positive result must have a chest radiograph performed.
- UC assessments: review of BM diary and calculate partial Mayo score.

- Investigational product accountability.
- Contraception check for females of childbearing potential.
- Adverse event monitoring.
- Concomitant medication review.
- Investigational product dispensing.
- Risk factor check for venous thromboembolism.

6.2.11. Months 27 and 39 (± 7 days, Visits 11 and 15)

The following procedures will be performed:

- Targeted physical examination.
- Vital signs, including temperature.
- Laboratory:
 - Hematology.
 - Serum chemistry.
 - hs-CRP.
 - Urine β -hCG to be performed only for females of childbearing potential.
 - Collect stool sample for fecal calprotectin.
 - Provide subject with stool sample collection kit to obtain stool sample at home to be returned for the Months 30 and 42 study visits. Subjects should be instructed to collect the sample **prior to the subject initiating the bowel preparation for endoscopy**.
- UC assessments: review of BM diary and calculate partial Mayo score.
- Investigational product accountability.
- Contraception check for females of childbearing potential.
- Adverse event monitoring.
- Concomitant medication review.
- Investigational product dispensing.

- Risk factor check for venous thromboembolism.

6.2.12. Months 30 and 42 (± 7 days, Visits 12 and 16) or Early Termination (ET) Visit

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. Subjects who discontinue treatment early from the study will have an early termination (ET) visit performed on the last day the subject takes the investigational product or as soon as possible thereafter.

The following procedures will be performed:

- Targeted physical examination.
- Vital signs, including temperature.
- Laboratory:
 - Hematology.
 - Serum chemistry.
 - hs-CRP.
 - Lipid profile, fasting.
 - Urine β -hCG to be performed only for females of childbearing potential.
 - Collect stool sample for fecal calprotectin.
 - Provide subject with stool sample collection kit to obtain stool sample at home to be returned for the Month 33 study visit (Month 30 only).
- Endoscopy: flexible sigmoidoscopy/colonoscopy (if preferred). Endoscopic assessment will only be done by local site read.
- UC assessments: review of BM diary and calculate Mayo score.
- Investigational product accountability.
- Contraception check for females of childbearing potential.
- Adverse event monitoring.
- Concomitant medication review.
- Investigational product dispensing (Month 30 only).

- Risk factor check for venous thromboembolism.

6.3. Follow-up Visit (4 weeks after last dose \pm 7 days, Visit 17)

This follow-up visit is to occur 4 weeks (\pm 7 days) after the last dose of investigational product administration.

The following procedures will be performed:

- Targeted physical examination.
- Vital signs, including temperature.
- Laboratory:
 - Hematology.
 - Serum chemistry.
 - Lipid profile, fasting.
 - Urine β -hCG to be performed only for females of childbearing potential.
- Contraception check for females of childbearing potential.
- Adverse event monitoring.
- Concomitant medication review.

6.4. Subject Withdrawal

Should a subject withdraw from active treatment, the subject should complete the procedures listed at the Month 42/ET Visit. After completing the procedures for the ET visit, the subject should return for a safety evaluation to occur approximately 4 weeks after discontinuing investigational product as per the follow-up visit (see [Section 6.2.9](#)).

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

- If rescue therapy is initiated or re-initiated for UC with the exception of oral 5-ASA or sulfasalazine.
- If a subject undergoes surgery for UC.

A subject may be withdrawn from the study for any of the safety concerns as listed in [Appendix 4](#).

If venous thromboembolism is confirmed, discontinue treatment with tofacitinib and withdraw the subject from the study ([Appendix 4](#)).

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 7.3.4](#)).

All abnormal laboratory events of clinical significance should be followed until the laboratory values have returned to normal or baseline levels (see [Appendix 4](#)). Subjects who meet the discontinuation criteria described in [Appendix 4](#) will be withdrawn from the study.

Subjects who are withdrawn from this study will not be permitted to return to Study A3921139.

Withdrawal of consent:

Subjects who request to discontinue receipt of study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a subject specifically withdraws consent for any further contact with him or her or persons previously authorized by the subject to provide this information. Subjects should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of investigational product or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

Lost to follow-up:

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to follow-up is defined by the inability to reach the subject after a minimum of 2 documented phone calls, faxes, or e-mails as well as lack of response by the subject to 1 registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use locally permissible methods to obtain the date and cause of death. If the investigator's use of a third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a sponsor-retained third-party representative to assist site staff with obtaining the subject's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If, after all attempts, the subject remains lost to follow-up, then the last-known-alive date as determined by the investigator should be reported and documented in the subject's medical records.

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 (see also the [Withdrawal From the Study Due to Adverse Events](#) section) 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. All attempts to contact the subject and information received during contact attempts must be documented in the subject's medical record. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request that the subject return all unused investigational product, request that the subject return for a final visit, if applicable, and follow up with the subject regarding any unresolved adverse events (AEs).

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 that he or 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 manner.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

7.1. Pregnancy Testing

For female subjects of childbearing potential, a urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed before investigational product administration at the baseline visit, and at all study visits to confirm the subject has not become pregnant during the study. Urine pregnancy testing will also be performed at the early termination visit if applicable and the end of study follow-up visit.

A negative pregnancy test result is required before the subject may receive tofacitinib. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected). Pregnancy tests may also be repeated if requested by institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations.

Urine pregnancy tests must be sensitive to at least 25 mIU/mL and will be conducted with the test kit provided by the central laboratory in accordance with instructions provided in its package insert. Subjects who have missed a menstrual period or who show an indeterminate or positive result on the urine test may not further progress in the study until pregnancy is ruled out using further diagnostic testing (eg, a negative quantitative serum pregnancy test conducted at a certified laboratory).

In the case of a positive confirmed pregnancy, the subject will be withdrawn from administration of tofacitinib and from the study.

7.2. Ulcerative Colitis Assessments

7.2.1. Subject Bowel Movement Diary

Subjects will use a phone-based interactive voice recording system (IVRS) tool to record their BM 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. Daily diary entries are strongly encouraged. Automatic reminders will be sent to the subject before their scheduled visit to remind them to record their BM data. Also, as an additional reminder the site personnel should call the subject 7 days before their next scheduled visit to prompt them to complete their BM 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 will be carried forward based on the data previously collected at the baseline of the induction studies.
- 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).

The data collected in the subject BM diary will be used to determine the stool frequency subscore and the rectal bleeding subscore for the Mayo score, modified Mayo score, partial Mayo score, and modified partial Mayo score.

7.2.2. Partial Mayo Score

A partial Mayo score (PMS) is an instrument designed to measure disease activity of UC 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 will be assessed at each specified study visit (see [Schedule of Activities](#)).

The PMS will be calculated based on the subject's BM diary data (see [Section 7.2.1](#)) recorded over the 3 prior consecutive days.

Endpoints based on partial Mayo score are defined below:

- Remission: partial Mayo score of 2 points or lower, with no individual subscore exceeding 1 point and a rectal bleeding subscore of 0.

Modified partial Mayo score consists of stool frequency and rectal bleeding subscores (ie, PMS without PGA).

Endpoints based on modified partial Mayo score are defined below:

- Remission: stool frequency subscore of 0 or 1, and a rectal bleeding subscore of 0.

7.2.3. Mayo Score

The Mayo score is an instrument designed to measure disease activity of UC. 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 2](#)).

- 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 Baseline, Month 6, Month 18, Month 30 and at Month 42/ET visits per the [Schedule of Activities](#).

The endoscopic findings will be locally read by study site investigator. The Mayo score will be calculated based on the subject's BM diary data (see [Section 7.2.1](#)) recorded over the 3 prior consecutive days.

The mucosal appearance of the sigmoidoscopic portion of endoscopic examination will be assessed for the Mayo endoscopic subscore, based on the definition provided in the protocol (see [Appendix 2](#)).

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 should 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.

Endpoints based on total Mayo score are defined below:

- Remission: total Mayo score of 2 points or lower, with no individual subscore exceeding 1 point and a rectal bleeding subscore of 0.
- Clinical response: decrease from baseline in total Mayo score of the Induction study, of at least 3 points and at least 30%, 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.
- Mucosal healing: an endoscopic subscore of 0 or 1.

Modified Mayo score consists of stool frequency subscore, rectal bleeding subscore and endoscopic subscore (ie, total Mayo score without PGA).

Endpoints based on modified Mayo score are defined below:

- Remission: an endoscopic subscore of 0 or 1, stool frequency subscore of 0 or 1, and rectal bleeding subscore of 0.

7.3. Safety

Safety will be assessed by vital signs, physical examinations, clinical laboratory tests and the spontaneous reporting of AEs, in all subjects who received at least 1 dose of investigational product. 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 4](#).

7.3.1. Vital Signs

Vital signs will be performed at each specified visit according to the [Schedule of Activities](#). 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 oral, axillary or tympanic temperature, but the same method should be used throughout the study, when possible.

7.3.2. Physical Examinations

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 5](#).

7.3.3. Clinical Laboratory Tests

Blood, urine, and stool 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 4](#)). Clinically significant abnormal findings should be recorded as AEs per [Section 8.2](#).

The following laboratory tests will be performed during the study:

Table 3. Laboratory Test Parameters

Hematology	Serum Chemistry	Others
Hemoglobin	Blood urea nitrogen	Follicle stimulating hormone (FSH) ¹
Hematocrit	Creatinine	β-hCG urine pregnancy test ²
Reticulocyte	Glucose (fasting) ⁵	Lipid profile (fasting) ³
Platelet count	Glucose (non-fasting) ⁶	Total cholesterol
White blood cell (WBC) count	Calcium	Low density lipoprotein cholesterol (LDL-C) ⁴
Neutrophils (abs, %)	Sodium	High density lipoprotein cholesterol (HDL-C)
Eosinophils (abs, %)	Potassium	Triglycerides ⁴
Monocytes (abs, %)	Chloride	Hepatitis B virus (HBV) DNA levels (Japan only) ⁷
Basophils (abs, %)	Total carbon dioxide (CO ₂) or bicarbonate	hs-CRP
Lymphocytes (abs, %)	Aspartate aminotransferase (AST)	Fecal calprotectin
Red blood cell (RBC) count	Alanine aminotransferase (ALT)	QFT ⁸
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. Follicle stimulating hormone (FSH) to confirm postmenopausal status at baseline visit or at subsequent study visits only if postmenopausal status has not been previously confirmed.

2. Urine testing performed with a sensitivity of at least 25 mIU/mL using test kits supplied by the central laboratory at baseline and at all study visits for females of childbearing potential.
3. Fasting lipid profile will be obtained according to the [Schedule of Activities](#).
4. If triglycerides >400 mg/dl, LDL-C will be determined by direct measurement.
5. Fasting glucose will be measured at study visits when fasting lipid profile is obtained according to the [Schedule of Activities](#).
6. Non-fasting glucose will be measured at all other study visits according to the [Schedule of Activities](#).
7. Safety monitoring for a subset of subjects in Japan only (see [Appendix 4](#)).
8. TB testing (QFT) will be performed at Months 12, 24 and 36 only for subjects in those countries in which TB prevalence has been reported at a rate of >50 cases per 100,000 persons (see [Section 7.3.3.2](#)).

Abnormal test results determined to be caused from laboratory error should not be reported as adverse events. 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.

7.3.3.1. Stool Samples for Fecal Calprotectin

A stool sample for determination of fecal calprotectin will be obtained at the times specified in the [Schedule of Activities](#) as well as when a subject experiences worsening of disease/flare, when possible.

Study site personnel will provide a sufficient number of stool sample collection kits and instructions to the subject on how best to collect a sufficient stool sample. A sample collected and returned on the day of the visit is preferred, however if this is not possible, a sample may be collected at home and returned within 24 hours of collection. If a sample is collected after the visit, the subject should make all efforts to collect the sample as soon as possible, but no later than 7 days of the Baseline visit, and within 2 weeks for all subsequent study visits.

For stool samples collected for the Months 6, 18, 30 and 42 (ie, study visits when endoscopy will be performed) subjects should be instructed to collect the sample **prior to the subject initiating the bowel preparation for endoscopy**.

Stool samples collected during this study may be aliquoted and stored for future studies. Examples of future studies may include “multi-omic” analyses and/or targeted evaluations for biomarkers of disease activity or predictive classifiers of response to treatment.

Sequencing of the DNA present in the stool may be performed to better understand disease activity and response to therapy. DNA generally comes from microorganisms like bacteria, viruses, fungi and parasites that may be present in the stool. During this process, some human DNA may be inadvertently sequenced, but will not be used for the final analysis.

7.3.3.2. Tuberculosis Testing

Tuberculosis (TB) testing will be conducted at Months 12, 24 and 36 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, 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 Induction Study A3921094 or A3921095 or prior annual visits during A3921139) and/or previously received adequate treatment for TB.

7.3.3.3. Serum Lipids

Total cholesterol, low density lipoprotein cholesterol (LDL-C), direct high density lipoprotein cholesterol (HDL-C) 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 7](#) for recommended clinical management of cholesterol.

7.3.4. Infections

Subjects will be monitored for development of infection. If high-risk behaviour(s) or environmental exposures are identified, subjects may be tested to provide evidence that pre-specified infections (eg, HIV, HCV, HBV) are not present. 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 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 treated 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 5.12](#)). Temporary discontinuation of study drug should be recorded in the CRF.

7.3.5. Safety Events of Interest

The identification of safety events of interest should 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.

The Pfizer Study Team or designee will provide a listing of specific documents needed to support event adjudication by the Adjudication Committees (see [Section 9.7](#) Safety Event Adjudication Committees). Obtaining and submitting the documentation will be the responsibility of the study site. Event documentation will vary with the event requiring adjudication and may include (but not be limited to): hospital discharge summaries, operative reports, clinic notes, electrocardiograms (ECGs), diagnostic tests, pathology reports, autopsy reports and death certificate information, as applicable.

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 5](#) 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 6](#) for the steps to take when gastrointestinal tract biopsies are obtained.

7.3.6. Risk Factor Check for Venous Thromboembolism

All subjects will undergo a risk factor check at each study visit to check for newly-developed risk factors for venous thromboembolism. 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 venous thromboembolism if he/she:

- has heart failure or prior myocardial infarction within the past 3 months;
- 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 or is immobilized.

If a subject is receiving blinded tofacitinib or open-label 10 mg BID and has one or more of the risk factors for venous thromboembolism listed above, the subject's tofacitinib dose should be adjusted to open-label 5 mg BID. If a subject has any newly-developed risk factors for venous thromboembolism identified during the study, they will not be permitted to receive tofacitinib 10 mg BID.

If a subject is receiving tofacitinib open-label 5 mg BID and has one or more of the risk factors for venous thromboembolism listed above, they may remain on tofacitinib open-label 5 mg BID after careful investigator assessment of benefit:risk. However, 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 5.11](#)).

Lastly, if a subject has any of the risk factors listed above, the subject will not be eligible to enroll in Study A3921288, per Amendment 2.

Additional risk factors for venous thromboembolism, such as age, diabetes, obesity (BMI>30), smoking status, hypertension, and first degree family history of venous thromboembolism should also be taken into consideration by the investigator and the Sponsor medical monitor when evaluating the benefit:risk for each individual subject whether to modify their dose of tofacitinib.

8. ADVERSE EVENT REPORTING

8.1. Requirements

The table below summarizes the requirements for recording safety events on the CRF and for reporting safety events on the Clinical Trial (CT) Serious Adverse Event (SAE) Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) non-serious adverse events (AEs); and (3) exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
SAE	All	All
Non-serious AE	All	None
Exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure	All (regardless of whether associated with an AE), except occupational exposure	Exposure during pregnancy, exposure via breastfeeding, occupational exposure (regardless of whether associated with an AE)

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

Events listed in the table above that require reporting to Pfizer Safety on the CT SAE Report Form within 24 hours of awareness of the event by the investigator **are to be reported regardless of whether the event is determined by the investigator to be related to an investigational product under study**. In particular, if the SAE is fatal or life-threatening, notification to Pfizer Safety must be made immediately, irrespective of the extent of available event information. This time frame also applies to additional new (follow-up) information on previously forwarded reports. In the rare situation that the investigator does not become immediately aware of the occurrence of an event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the event.

For each event, the investigator must pursue and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE (see the [Serious Adverse Events](#) section below). In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the CRF. In general, this will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and 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 Safety. Any pertinent additional information must be reported on the CT SAE Report Form; additional source documents (eg, medical records, CRF, laboratory data) are to be sent to Pfizer Safety **ONLY** upon request.

As part of ongoing safety reviews conducted by the sponsor, any non-serious AE 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.

8.1.1. Additional Details On Recording Adverse Events on the CRF

All events detailed in the table above will be recorded on the AE page(s) of the CRF. It should be noted that the CT SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the CT SAE Report Form for reporting of SAE information.

8.1.2. Eliciting Adverse Event Information

The investigator is to record on the CRF all directly observed AEs and all AEs spontaneously reported by the study subject. In addition, each study subject will be questioned about the occurrence of AEs in a non-leading manner.

8.1.3. Withdrawal From the Study Due to Adverse Events (see also the [Subject Withdrawal](#) section)

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

When a subject withdraws from the study because of an SAE, the SAE must be recorded on the CRF and reported, as appropriate, on the CT SAE Report Form, in accordance with the [Requirements](#) section above.

8.1.4. Time Period for Collecting AE/SAE Information

The time period for actively eliciting and collecting AEs and SAEs (“active collection period”) for each subject begins from the time the subject provides informed consent, which is obtained before the subject’s participation in the study (ie, before undergoing any study-related procedure and/or receiving investigational product), through and including a minimum of 28 calendar days; except as indicated below after the last administration of the investigational product.

8.1.4.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a subject during the active collection period are reported to Pfizer Safety on the CT SAE Report Form.

SAEs occurring in a subject after the active collection period has ended are reported to Pfizer Safety 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 must be reported to Pfizer Safety.

Follow up by the investigator continues throughout and after the active collection period and until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

8.1.4.2. Recording Non-serious AEs and SAEs on the CRF

During the active collection period, both non-serious AEs and SAEs are recorded on the CRF.

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.

8.1.5. 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 on the CRF, and report such an assessment in accordance with the SAE 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. 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 that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

8.1.6. Sponsor's Reporting Requirements to Regulatory Authorities

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

8.2. Definitions

8.2.1. Adverse Events

An AE is any untoward medical occurrence in a study 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 signs and symptoms;
- Changes in physical examination findings;
- Hypersensitivity;

- Progression/worsening of underlying disease;
- Drug abuse;
- Drug dependency.

Additionally, AEs may include signs and symptoms resulting from:

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

8.2.2. Abnormal Test Findings

Abnormal objective test findings should be recorded as AEs when any of the following conditions are met:

- 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 any protocol-specified dose adjustments) 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 recording as an AE.

8.2.3. 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.

Or that is considered to be:

- An important medical event.

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.

8.2.4. 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, or 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 is 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 workup of a persistent pretreatment 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;
- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual subject.

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

8.3. Severity Assessment

If required on the AE page of the CRF, 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.

8.4. Special Situations

8.4.1. Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported to Pfizer Safety by the investigator as described in previous sections, and will be handled as SAEs in the safety database.

8.4.2. Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed “tolerators,” while those who show transient liver injury, but adapt are termed “adaptors.” In some subjects, transaminase elevations are a harbinger of a more serious potential outcome. These subjects fail to adapt and therefore are “susceptible” to progressive and serious liver injury, commonly referred to as drug-induced liver injury (DILI). Subjects who experience a transaminase elevation above 3 times the upper limit of normal (\times ULN) should be monitored more frequently to determine if they are an “adaptor” or are “susceptible.”

In the majority of DILI cases, elevations in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) precede total bilirubin (TBili) elevations ($>2 \times$ ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above $3 \times$ ULN (ie, AST/ALT and TBili values will be elevated within the same lab sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy’s law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the subject’s individual baseline values and underlying conditions. Subjects who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy’s law) cases to definitively determine the etiology of the abnormal laboratory values:

- Subjects with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values $>3 \times$ ULN AND a TBili value $>2 \times$ ULN with no evidence of hemolysis and an alkaline phosphatase value $<2 \times$ ULN or not available.
- For subjects with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

- Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND $>3 \times \text{ULN}$; or $>8 \times \text{ULN}$ (whichever is smaller).
- Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least $1 \times \text{ULN}$ or if the value reaches $>3 \times \text{ULN}$ (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The subject should return to the investigator 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 of AST and ALT and TBili, laboratory tests should include albumin, creatine kinase (CK), direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time (PT)/international normalized ratio (INR), total bile acids, alkaline phosphatase and acetaminophen drug and/or protein adduct levels. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the liver function test (LFT) abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

8.4.3. Exposure to the Investigational Product During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the investigational product under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.4.3.1. Exposure During Pregnancy

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

- 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).
- 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 subject or subject's partner becomes or is found to be pregnant during the subject's treatment with the investigational product, the investigator must report this information to Pfizer Safety on the CT 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) to Pfizer Safety 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 Safety 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 fetal 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 to Pfizer Safety 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 the investigational product.

Additional information regarding the EDP may be requested by the sponsor. 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 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.

8.4.3.2. Exposure During Breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated SAE, to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug's administration, the SAE is reported together with the exposure during breastfeeding.

8.4.3.3. 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 Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form, regardless of whether there is an associated SAE. Since the information does not pertain to a subject enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

8.4.4. Medication Errors

Other exposures to the investigational product under study may occur in clinical trial settings, such as medication errors.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

8.4.4.1. Medication Errors

Medication errors may result from the administration or consumption of the investigational product by the wrong subject, or at the wrong time, or at the wrong dosage strength.

Medication errors include:

- 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.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

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

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

Medication errors should be reported to Pfizer Safety within 24 hours on a CT SAE Report Form **only when associated with an SAE**.

9. DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in a statistical analysis plan (SAP), which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Sample Size Determination

Although approximately 130 subjects are estimated to be enrolled into this study (based on availability of eligible subjects from the open label Study A3921139 and based on the conservative assumptions of the attrition rate of 50% - 50% in Study A3921139), the final sample size may exceed 130 subjects. The Sponsor will continue to engage with investigative sites participating in Study A3921139 to assess the ability to enroll additional eligible subjects.

With 130 (65 per group) subjects, the estimated half width of the 95% confidence for treatment difference between tofacitinib 10 mg BID and 5 mg BID in proportion of remission at Month 6 based on the modified Mayo score is about 16%, assuming the remission rates are greater than 70% in both groups.

At the time of Amendment 2, 138 subjects have been enrolled and approximately 122 subjects have crossed their Month 6 study visit, the timepoint of the primary endpoint.

9.2. Efficacy Analysis

9.2.1. Analysis Population

The primary analysis population will be the Full Analysis Set (FAS) defined as all subjects who are randomized into the study and receive at least 1 dose of investigational product.

9.2.2. Primary Analysis

The primary endpoint is remission based on the modified Mayo score at Month 6. The primary analysis will be performed at Month 6 based on the FAS for the estimation of treatment difference between the following two dose groups:

- Tofacitinib 10 mg BID Dose Group: subjects who are initially assigned to tofacitinib 10 mg BID at randomization
- Tofacitinib 5 mg BID Dose Group: subjects who are initially assigned to tofacitinib 5 mg BID at randomization, regardless of whether the dose is escalated back to tofacitinib 10 mg BID or not.

The stratified estimation of the treatment difference between tofacitinib 10 mg BID and 5 mg BID in the proportion of subjects with remission at Month 6 will be presented along with its 95% confidence interval (CI). The Cochran-Mantel-Haenszel (CMH) weight method will be used for the stratified estimation of the treatment difference. The stratified CI will be constructed using the NewCombe method. Subjects with dose escalation prior to Month 6 or with missing values at Month 6 will be treated as non-responders at Month 6.

Sensitivity analyses for handling with missing data will be performed. An analysis using a generalized linear mixed-effects model may be performed for the remission endpoint based on data collected at Month 6, Month 12, Month 18, Month 30, and Month 42 if sufficient data are available at Month 42. Further details will be provided in the statistical analysis plan.

9.2.3. Secondary Analysis

Dose comparison between tofacitinib 5 mg BID and 10 mg BID

For the primary objective, the treatment difference for the binary secondary efficacy endpoints will also be estimated based on the FAS, using the same approach as described above for the primary endpoint. For continuous endpoints, the change from baseline will be analyzed using linear mixed-effects model with baseline value, dose group, the endoscopic

subscore at baseline (0 versus 1), visit, and dose group by visit interaction all as fixed effects, and subject as a random effect. The adjusted estimations and associated 95% CI for the overall difference between the two dose groups will be computed. Kaplan-Meier estimates at the scheduled visits will be computed for time to event endpoint. The log-rank test stratified by endoscopic subscore at baseline (0 versus 1) will also be performed for the comparison between dose groups.

If a subject has a dose escalation back to tofacitinib 10 mg BID, then

- For binary efficacy endpoints, the subject will be considered as a non-responder for any visit after the dose escalation visit.
- For continuous efficacy endpoints, the data collected for any visit after the dose escalation visit will be considered as missing.
- For time to loss of remission, the subject will be considered as having an event at the visit with a dose escalation if the event criteria are met or having a censor time at the visit with a dose escalation if the event criteria are not met.

For continuous endpoints that are measured repeatedly over time, the missing values will be handled in a linear mixed-effects model where the *mechanism of missingness* is assumed to be missing at random.

Regimen comparison between flexible dosing and fixed dosing

For the first secondary objective, analyses will be performed based on the FAS for comparisons of the following two dose regimens:

- Tofacitinib fixed 10 mg BID Dose Regimen: subjects who are initially assigned to tofacitinib 10 mg BID at randomization and stay on tofacitinib 10 mg BID until completion or discontinuation.
- Tofacitinib flexible 5 mg/10 mg BID Dose Regimen: subjects who are initially assigned to tofacitinib 5 mg BID at randomization, staying on tofacitinib 5 mg BID or having dose escalation from tofacitinib 5 mg BID to 10 mg BID.

Analysis methods are the same as the ones described above for comparison between dose groups except that data from subjects with dose escalation back to tofacitinib 10 mg BID will be treated as it is. Only the visits with missing data will be treated as non-responders.

For the second secondary objective, summary descriptive statistics will be reported for the sub-group of subjects who are initially assigned to tofacitinib 5 mg BID and later are retreated with tofacitinib 10 mg BID. Missing data will not be imputed.

9.3. Analysis of Biomarker Endpoints

Fecal calprotectin and hs-CRP data and change from baseline will be summarized descriptively by dose group and by dose regimen. Fecal calprotectin and hs-CRP data will also be log-transformed (natural logarithm) for the analyses. The change from baseline will be analyzed using a linear mixed effects model with baseline value, dose group, the endoscopic subscore at baseline (0 versus 1), visit, and dose group by visit interaction all as fixed effects, and subject as a random effect.

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 investigational product.

Summaries will be performed by dose group and dose regimen as defined in the efficacy sub-section.

9.5. Interim Analysis

No interim analysis is planned for this study. The primary analysis will be performed to assess efficacy and safety when all subjects enrolled complete their Month 6 study visit (or drop out before Month 6 visit) and data are cleaned and locked. However, the final analyses for secondary objectives will be performed after all subjects complete the study. Initial treatment assignment at baseline of the study will remain double-blinded to the site and subject.

9.6. Data Monitoring Committee

This study will use an external data monitoring committee (E-DMC).

The E-DMC will be responsible for ongoing monitoring of the safety of subjects in the study according to the charter. The recommendations made by the E-DMC 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 that 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

Pfizer or its agent will conduct periodic monitoring visits during study conduct 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 are accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification. This verification may also occur after study completion.

During study conduct and/or after study completion, the investigator site may be subject to review by the IRB/EC, 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.

The investigator(s) will notify Pfizer or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with Pfizer or its agents to prepare the investigator site for the inspection and will allow Pfizer or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the subject's medical records. The investigator will promptly provide copies of the inspection findings to Pfizer or its agent. Before response submission to the regulatory authorities, the investigator will provide Pfizer or its agents with an opportunity to review and comment on responses to any such findings.

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 are true. Any corrections to entries made in the CRFs or 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 or the physician subject chart. In these cases, data collected on the CRFs must match the data in those charts.

In some cases, the CRF may also serve as the source document. In these cases, a document should be available at the investigator site and at Pfizer that clearly identifies those data that will be recorded on the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

To enable evaluations and/or inspections/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, and telephone call reports). The records should be retained by the investigator according to the ICH guidelines, according to 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 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/Ethics Committee

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/EC. All correspondence with the IRB/EC should be retained in the investigator file. Copies of IRB/EC approvals should be forwarded to Pfizer.

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

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, legal and regulatory requirements, and the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), ICH Guideline for Good Clinical Practice, and the Declaration of Helsinki.

12.3. Subject Information and Consent

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

When study data are compiled for transfer to Pfizer and other authorized parties, subject names, addresses, and other identifiable data will be replaced by numerical codes based on a numbering system provided by Pfizer in order to de-identify study subjects. The investigator site will maintain a confidential list of subjects who participated in the study, linking each subject's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subjects' personal data consistent with applicable privacy laws.

The informed consent documents and any subject recruitment materials must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent documents used during the informed consent process and any subject recruitment materials must be reviewed and approved by Pfizer, approved by the IRB/EC before use, and available for inspection.

The investigator must ensure that each study subject is fully informed about the nature and objectives of the study and possible risks associated with participation.

The investigator, or a person designated by the investigator, will obtain written informed consent from each subject 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 regulatory authority in any area of the world, or if the investigator is aware of any new information that 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 a sufficient number of 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 Other Participating Countries

End of trial in all other participating countries is defined as Last Subject Last Visit (LSLV) which is the last follow up visit for the last subject.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or investigational product 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, 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 (PCD) for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

PCD 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 European Union (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 PCD for studies in adult populations or within 6 months of the PCD 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 the principal investigator (PI) of the results of the study based on information collected or generated by the PI, 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 it is 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 multicenter study, the investigator agrees that the first publication is to be a joint publication covering all investigator sites, and that any subsequent publications by the PI 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. Abbreviations

This following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
5-ASA	5-aminosalicylic acid
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
ATP	adult treatment panel
AZA	azathioprine
β-hCG	beta human chorionic gonadotropin
BID	twice daily
BM	bowel movement
BMI	body mass index
CCO	Clinical Country Office
CK	creatin kinase
CHD	coronary heart disease
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
COVID-19	Coronavirus disease 2019
CPK	creatin phosphokinase
CRF	case report form
CSA	clinical study agreement
CSR	clinical study report
CTA	clinical trial application
CTCAE	Common Terminology Criteria for Adverse Events
CV EAC	Cardiovascular Endpoint Adjudication Committee
CYP3A	Cytochrome P450, family 3, subfamily A
DILI	drug-induced liver injury
DMC	data monitoring committee
DNA	deoxyribonucleic acid
EC	ethics committee
ECG	electrocardiogram
E-DMC	external data monitoring committee
EDP	exposure during pregnancy
EMA	European Medicines Agency
ET	early termination
EU	European Union
EudraCT	European Clinical Trials Database
FAS	full analysis set
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice

Abbreviation	Term
GGT	Gamma-glutamyl transferase
GIPRC	Gastrointestinal Perforation Review Committee
HBV	hepatitis B virus
HCV	hepatitis C virus
HERC	Hepatic Event Review Committee
HDL-C	high density lipoprotein cholesterol
HIV	human immunodeficiency virus
hs-CRP	high sensitivity C-reactive protein
HZ	herpes zoster
IB	Investigator's Brochure
ICH	International Council for Harmonisation
ID	identification
IFN γ	interferon γ (gamma)
IL	interleukin
ILDRC	Interstitial Lung Disease Review Committee
IND	investigational new drug application
INR	international normalized ratio
IP	investigational product
IRB	institutional review board
IRT	interactive response technology
IUD	intrauterine device
IUS	intrauterine system
IV	intravenous
IVRS	interactive voice recording system
IWR	interactive web response
LDH	lactate dehydrogenase
LFT	liver function test
LTE	long-term extension
JAK	Janus kinase
LDL-C	low density lipoprotein cholesterol
LPD	lymphoproliferative disorder
LSLV	last subject last visit
6-MP	6-mercaptopurine
MAC	Malignancy Adjudication Committee
N/A	not applicable
OIRC	Opportunistic Infection Review Committee
OLE	open-label extension
PCD	primary completion date
PCP	pneumocystis pneumonia
PGA	physician global assessment
PI	principal investigator
PK	pharmacokinetic
PMS	partial Mayo score

Abbreviation	Term
PRAC	Pharmacovigilance Risk Assessment Committee
PROs	patient-reported outcomes
PsA	Psoriatic Arthritis
PT	prothrombin time
QFT	Quantiferon-TB [®] Gold Plus test
RA	Rheumatoid arthritis
SAE	serious adverse event
SAP	statistical analysis plan
SOP	standard operating procedure
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction
t _{1/2}	half-life
TB	tuberculosis
TBili	total bilirubin
TEAE	treatment emergent adverse event
Tmax	time to maximum plasma concentration
TNFi	tumor necrosis factor inhibitor
Tyk2	tyrosine kinase 2
ULN	upper limit of normal
UC	ulcerative colitis
US	United States

Appendix 2. 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.⁴

† 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 3. 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 (Oral, IV or Rectal)
Darunavir	Rifabutin#	5-ASA (Rectal)
	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	Talviraline	Other immunosuppressants
Dronedarone		Other biologics with immunomodulatory properties
Elvitegravir#		
Erythromycin		
Fluconazole		
Fluvoxamine		
Imatinib		
Indinavir#		
Itraconazole#		
Ketoconazole#		
Lopinavir#		
Mibefradil#		
Mifepristone (RU486)		
Nefazodone#		
Nelfinavir#		
Norfloxacin		
Posaconazole#		

Moderate to Potent CYP3A Inhibitors	Moderate to Potent CYP3A Inducers	Other Prohibited Medications
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 4. Guidelines for Monitoring and Discontinuations

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

- Absolute neutrophil count $<1.2 \times 10^9/L$ ($<1200/mm^3$).
- Absolute lymphocyte count $<0.5 \times 10^9/L$ ($<500/mm^3$).
- Any single hemoglobin value <8.0 g/dL.
- Platelet count $<100 \times 10^9/L$ ($<100,000/mm^3$).
- An increase in serum creatinine of $>50\%$ from the A3921139 baseline value; OR an absolute increase in serum creatinine >0.5 mg/dL (>44.2 umol/L) from Study A3921139 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 CK >10 times the upper limit of normal (repeat laboratory testing should also include cardiac troponin).
- For females 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.
- Opportunistic infection judged significant by the investigator (United Kingdom only).
- Two sequential absolute neutrophil counts $<0.75 \times 10^9/L$ ($<750/mm^3$).

- Two sequential absolute lymphocyte counts $<0.5 \times 10^9/L$ ($<500/mm^3$).
- Two sequential hemoglobin <8.0 g/dL.
- Two sequential platelet counts $<75 \times 10^9/L$ ($<75,000/mm^3$).
- Two sequential increases in serum creatinine $>50\%$ over the Study A3921139 baseline value AND an absolute increase in serum creatinine >0.5 mg/dL (>44.2 $\mu\text{mol/L}$).
- 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 CK elevations >10 times the upper limit of normal, unless the causality is known not to be medically serious (eg, exercise induced).
- 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
- Female subjects found to be pregnant during the study.
- Initiation of a new treatment or re-initiation of a prior treatment for UC, except for oral 5-ASA or sulfasalazine.
- Surgery for UC.
- Other serious or severe AEs, after consultation with the Pfizer medical monitor or designee.
- Additional safety monitoring and discontinuation guidelines for JAPAN ONLY (see below).

Per Amendment 3, for subjects with suspected venous thromboembolism, treatment with tofacitinib should be temporarily withheld while the subject is evaluated. If venous thromboembolism is confirmed, discontinue treatment with tofacitinib and withdraw the subject from the study.

- 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.

Additional safety monitoring and discontinuation guidelines for JAPAN ONLY.

Safety monitoring for potential risk of interstitial pneumonia:

Because of the potential higher risk of interstitial pneumonia in Japanese patients than in Western patients, investigators in Japan should carefully evaluate all subjects who exhibit symptoms, especially fever and cough.

If a subject develops fever, cough, or dyspnea, temporary discontinuation of tofacitinib should be considered. The differential diagnosis should include assessment for pneumonia, TB, pneumocystis pneumonia (PCP), and invasive fungal infection.

Additionally, if a subject's absolute lymphocyte count is decreased to $<1.0 \times 10^9/L$ ($<1000/mm^3$), please consider appropriate action based on the subject's condition, such as retest of lymphocyte counts, as warranted.

If the absolute lymphocyte count is decreased to $<0.5 \times 10^9/L$ ($<500/mm^3$) and a sequential retest confirms the result, the subject has to be withdrawn from the study.

Safety monitoring for enrolled subjects who required hepatitis B virus (HBV) DNA testing:

Safety monitoring for subjects in Japan who are enrolled into Study A3921288, who previously required HBV DNA testing per protocol in open-label LTE Study A3921139 and had undetectable HBV DNA levels, will continue to require HBV DNA testing (locally analyzed) and LFT (ie, ALT/AST) monitoring at all scheduled visits and at unscheduled visits at the investigator's discretion. Safety monitoring and discontinuation criteria for AST and ALT will be applied as stated above in [Appendix 4](#). Subjects who have detectable HBV DNA levels during monitoring will be discontinued.

Appendix 5. 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 all biopsies 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 6. 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 7. 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 8. France Appendix

This appendix applies to study sites located in France.

1. GCP Training

Prior to enrollment of any subjects, the investigator and any sub-investigators will complete the Pfizer-provided Good Clinical Practice training course (“Pfizer GCP Training”) or training deemed equivalent by Pfizer. Any investigators who later join the study will complete the Pfizer GCP Training or equivalent before performing study-related duties. For studies of applicable duration, the investigator and sub-investigators will complete Pfizer GCP Training or equivalent every three years during the term of the study, or more often if there are significant changes to the ICH GCP guidelines or course materials.

2. Investigational Product

No subjects or third-party payers will be charged for investigational product.

Appendix 9. Protocol Administrative Changes and Clarification for Study A3921288 During COVID-19 Pandemic

In response to the ongoing global COVID-19 pandemic and the increasing restrictions on travel, the requirement for social distancing, and concerns for public health, the study team has determined that the following changes to the A3921288 protocol study visits are acceptable alternative solutions.

- Subjects who can attend scheduled study visits in the clinic and complete all study procedures as described in the protocol per the [Schedule of the Activities](#) should do so; all other subjects should participate in study visits by telephone. Video contact can be used if permitted by local regulations.
- If a subject is unable to come in person to the study site to receive their study medication, courier delivery of the study medication from study sites will be permitted if allowable by law and local guidance. The study participant must provide verbal consent for providing the contact details for shipping purposes. This verbal consent should be documented in the source document. Tracking records of shipment including the chain of custody of the study medication must be kept in the participant's medical records.
- Risk factor check for pulmonary embolism (per Amendment 2)/venous thromboembolism (per Amendment 3) should be performed prior to the site dispensing additional study medication.
- When conducting a study visit by telephone or video (if permitted), the following procedures should be completed:
 - Review and record any adverse events and serious adverse events since the last study visit (follow protocol reporting procedures in [Section 8](#)).
 - Assess disease activity through review of subject's diary entries leading up to the visit through ICOPhone and calculate the stool frequency and rectal bleeding subscores, as well as perform the physician global assessment. Record the subscores on the 'Partial Mayo Clinic Score CRF'. If sufficient diary entries are not available prior to the visit, advise the subject to enter diary data post visit and inform the study site when available.
 - Review and record changes in concomitant medications.
 - Safety laboratory tests may be performed at a local laboratory and results should be documented on the 'Local Lab Test CRF'.
 - Review and record contraceptive method and result of urine pregnancy tests for female participants who are women of childbearing potential.

- Any deviations to the protocol, except for these approved modifications must be documented as protocol deviations and if related to the pandemic, the reason should clearly state “COVID-19”. These are not required to be reported to health authorities or IRB/ECs unless requested locally; this requirement is meant to allow the study team to quickly assess the impact of the pandemic on our study.

If the sponsor determines that the impact of COVID-19 on protocol visits and procedures and associated timeframe needs to be reported on a case report form (CRF), this will be requested. For participant discontinuation reporting in the CRF: select the most appropriate status for discontinuation; if the discontinuation is associated with the current COVID-19 pandemic, enter “COVID-19” in the “Specify Status” field.