CLINICAL STUDY REPORT SYNOPSIS

Sponsor: Pfizer Inc

Investigational Product: tofacitinib

Clinical Study Report Synopsis: Protocol A3921288

Protocol Title: 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

Investigators: Refer to Appendix 16.1.4.1 for a list of investigators involved in this study.

Study Center(s): A total of 69 sites randomized subjects from the following countries: Belgium (1), Canada (2), Czech Republic (1), France (2), Germany (1), Hungary (3), Italy (1), Japan (14), Republic of Korea (3), Netherlands (1), New Zealand (3), Poland (2), Russian Federation (2), Serbia (5), Slovakia (3), South Africa (4), Spain (1), Ukraine (4), United Kingdom (1), and the United States (15). Refer to Appendix 16.1.4.1 for a list of sites involved in this study.

Publications Based on the Study: None

Study Initiation Date: First Subject First Visit: 16 November 2017

Study Completion Date: Data Cut Off Date: 20 February 2020

Report Date: 22 July 2020

Previous Report Date(s): Not applicable

Phase of Development: Phase 3b/4

Study Objectives and Endpoints:

Table S1. Study Objectives and Endpoints

Type	Objective	Endpoint
Primary Efficacy		
Efficacy	To evaluate the efficacy of tofacitinib in subjects in stable remission on 10 mg twice daily (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.	• Remission based on modified Mayo score at Month 6.
Secondary Efficacy		

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Table S1. Study Objectives and Endpoints

Type	Objective	Endpoint
Efficacy	To evaluate the efficacy 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.	• 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 (PMS), total Mayo score, and PMS. • Change from baseline (of Study A3921288) at all applicable scheduled visits in the following: modified Mayo score, modified PMS, total Mayo score, and PMS. • 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 (FCP) and high sensitivity C-reactive protein (hsCRP) levels.
Safety		
Safety	To evaluate the 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	• Incidence and severity of adverse events (AEs). • Incidence of serious infections.

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Table S1. Study Objectives and Endpoints

Type	Objective	Endpoint
	subjects remaining on 10 mg BID.	• 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).

METHODS

Study Design: This study enrolled subjects from the ongoing open-label long-term extension (LTE) Study A3921139 who were in stable remission (see Diagnosis and Main Criteria for Inclusion below) on tofacitinib 10 mg BID for at least 6 months and not receiving any corticosteroids to treat their ulcerative colitis (UC) for at least 4 weeks prior to enrollment. Subjects must have received tofacitinib 10 mg BID for a minimum of 2 consecutive years in the ongoing open-label LTE Study A3921139 prior to enrollment. Subjects enrolling under Amendment 2 must not have had any risk factors for pulmonary embolism.

Approximately 130 subjects were estimated to be enrolled into this study (based on availability of eligible subjects from the ongoing open-label LTE Study A3921139 and based on the conservative assumptions of the attrition rate of 50% - 60% in the ongoing open-label LTE Study A3921139). Eligible subjects were randomized in a 1:1 allocation ratio to receive either tofacitinib 5 mg BID or 10 mg BID at baseline of this study. Subjects were stratified at baseline based on the endoscopic subscore (ESS) (0 versus 1) of their most recent endoscopy (Figure S1).

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

Any time after Month 1, subjects who experienced flare could have had their dose escalated.

Flare was defined by meeting 1 of the following 4 criteria:

1. An increase in rectal bleeding subscore by at least 1 point and an increase in ESS by at least 1 point; OR

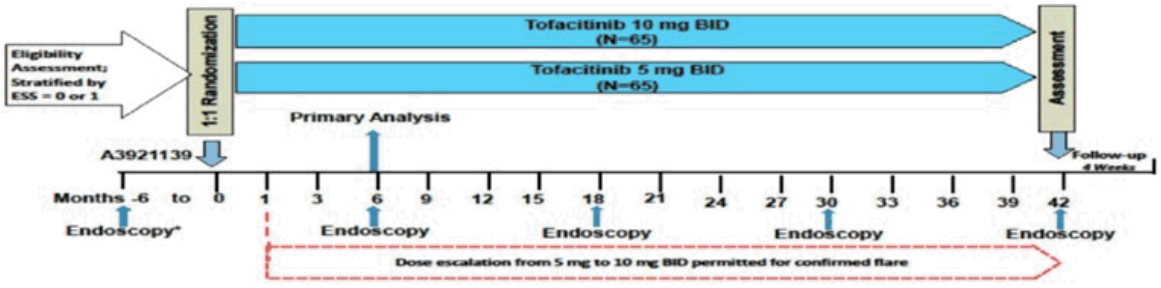
2. An increase in rectal bleeding subscore by at least 2 points and an ESS >0; OR

3. An increase in stool frequency subscore by at least 2 points and an increase in the ESS by at least 1 point; OR

4. An increase in ESS by at least 2 points.

Subjects with confirmed flare were eligible for a dose escalation.

Figure S1. Study Design



*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.

Diagnosis and Main Criteria for Inclusion: Key inclusion criteria were as follows:

1. Subjects enrolled in Study A3921139 who had 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 were 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:

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a. A partial Mayo score ≤2, with no individual subscore >1 and a rectal bleeding subscore of 0 at each study visit where data were available during the 6 month period in Study A3921139 prior to and including baseline of Study A3921288;

b. AND at least 1 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 ESS of 0 or 1, was required prior to randomization into Study A3921288.
- All available assessments based on Mayo score during this period must have shown remission.

c. AND subjects must not have been receiving any corticosteroid therapy for their UC for at least 4-weeks prior to baseline.

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

Subjects who met the protocol definition for flare could have had a dose increase to 10 mg BID or remained on 10 mg BID, depending on their initial treatment assignment, provided that the subject did not have any of the risk factors for pulmonary embolism (beginning with Protocol Amendment 2).

Details of the investigational product used in the is study are shown in Table S2.

Table S2. Investigational Product Description

Investigational Product Description	Vendor Lot Number	Pfizer Lot Number	Strength/Potency	Dosage Form
Placebo for Tofacitinib Citrate 5 mg Film Coated Tablet	R73682	16-005146	0 mg	Tablet
Placebo for Tofacitinib Citrate 5 mg Film Coated Tablet	R73683	16-005147	0 mg	Tablet
Tofacitinib Citrate 5 mg Film Coated Tablet	S26918	17-000460	5 mg	Tablet
Tofacitinib Citrate 5 mg Film Coated Tablet	X20921	18-002302	5 mg	Tablet

Efficacy Evaluations:

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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.

- stool frequency (0-3).
- rectal bleeding (0-3).
- findings of flexible sigmoidoscopy (0-3).
- physician global assessment (PGA) (0-3).

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 ESS of 0 or 1.

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

Endpoints based on modified Mayo score are defined below:

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

Partial Mayo Score

A PMS is an instrument designed to measure disease activity of UC without endoscopy. PMS 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).

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Endpoints based on PMS are defined below:

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

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

Endpoints based on modified PMS are defined below:

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

Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and/or Other Evaluations: No pharmacokinetic, pharmacodynamic or pharmacogenomic evaluations were performed in this study.

Safety Evaluations: Safety was assessed by vital signs (blood pressure, pulse rate, and temperature), physical examinations, clinical laboratory tests (including FCP and hsCRP) and the spontaneous reporting of AEs, in all subjects who received at least 1 dose of investigational product.

Statistical Methods:

Analysis of the Primary Endpoint

The primary efficacy endpoint was remission based on modified Mayo score at Month 6. For dose comparison between tofacitinib 10 mg BID and 5 mg BID, the stratified estimation of the treatment difference between tofacitinib 10 mg BID and 5 mg BID in the proportion of subjects was presented along with its 95% confidence interval (CI) with the ESS at baseline (0 versus 1) as the stratification factor. The Cochran Mantel Haenszel (CMH) weight method was used for the stratified estimation of the treatment difference. The stratified CI was constructed using the NewCombe method by Yan and Su.

In addition, p-values based on CMH Chi-square test stratified by ESS at baseline (0 versus 1) were presented.

Analysis of the Secondary Endpoints

Binary secondary efficacy endpoints were analyzed using the same approach as described for the primary efficacy endpoint.

For continuous efficacy endpoints based on total Mayo score evaluated for primary objective at Month 6, the change from baseline was analyzed using an analysis of covariance (ANCOVA) model with dose group, the ESS at baseline (0 versus 1) as factors and baseline score as a covariate. Otherwise, for continuous efficacy endpoints, the change from baseline was analyzed using linear mixed effects model with baseline value, dose group, the ESS at

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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 2 dose groups was computed for each visit.

Time to loss of remission (flare) based on modified Mayo score was estimated using a log-rank test stratified by ESS at baseline (0 versus 1). In addition, cumulative event rates and associated CIs were estimated from the Kaplan-Meier curves for each dose group. The dose comparison for the proportions of the event were made using Wald test statistics.

FCP and hsCRP, and their change from baseline were summarized descriptively for each visit by dose group.

The FCP and hsCRP data were also log-transformed (natural logarithm) for the analyses. The change from baseline was analyzed using the same approach as the continuous efficacy endpoints.

The safety data were summarized in accordance with Pfizer Data Standards.

RESULTS

Subject Disposition and Demography: Subject disposition is presented in Figure S2**.**

- A total of 140 subjects were randomized into the study, with 70 subjects randomized to each treatment group.
- Discontinuation rates were similar between treatment groups.
- The most common reasons for discontinuation were AEs (5 subjects) and withdrawal by subject (5 subjects) in the tofacitinib 5 mg BID group, and withdrawal by subject (10 subjects) in the tofacitinib 10 mg BID group.

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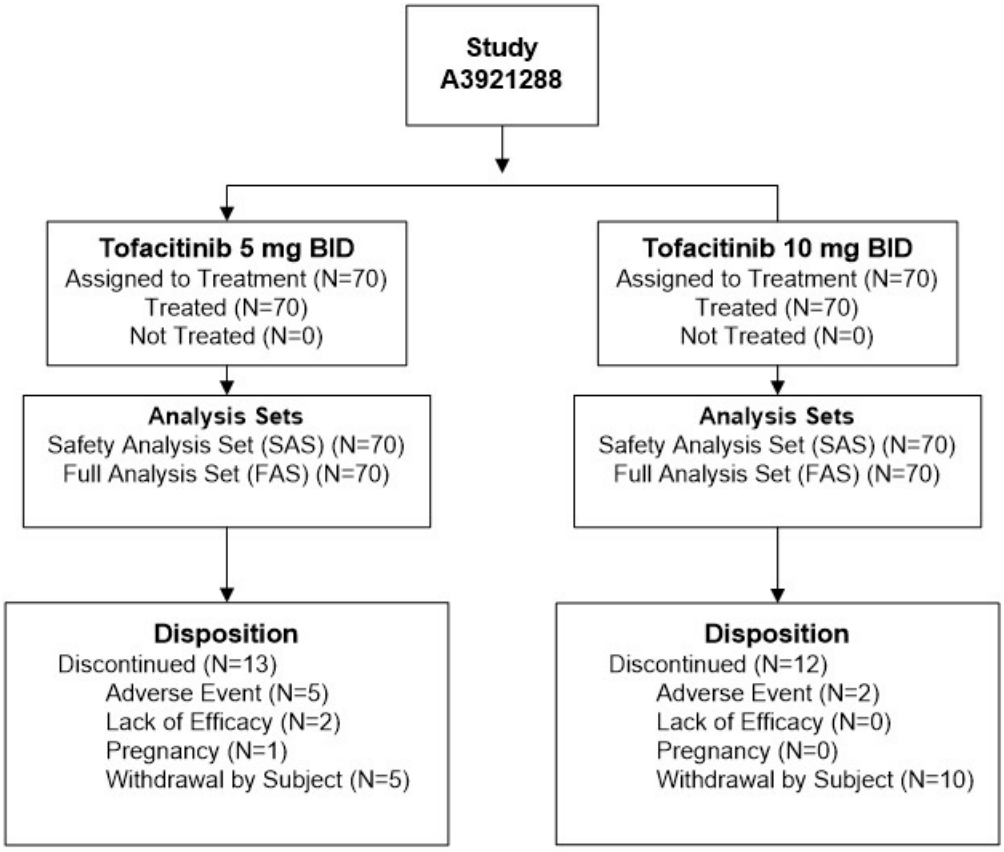
Figure S2. Subject Disposition



Subjects who discontinued due to an AE of 'worsening UC' were summarized under lack of efficacy.

Efficacy Results:

Primary Endpoint Result

Remission Based on Modified Mayo Score at Month 6

The proportion of subjects in remission based on modified Mayo score at Month 6 was higher for the tofacitinib 10 mg BID (90.0%) group compared with the tofacitinib 5 mg BID group (77.1%) with a difference of 12.9% (95% CI: 0.5, 25.0).

Secondary Endpoint Results

Consistent results were observed in the secondary endpoints to support the results of the primary endpoint.

Remission (Based on Total Mayo Score)

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The proportion of subjects in remission based on total Mayo score at Month 6 was higher for the tofacitinib 10 mg BID (87.1%) group compared with the tofacitinib 5 mg BID group (75.7%) with a difference of 11.4% (95% CI: -1.5, 24.1).

Mucosal Healing

The proportion of subjects with mucosal healing at Month 6 was higher for the tofacitinib 10 mg BID (91.4%) group compared with the tofacitinib 5 mg BID group (80.0%) with a difference of 11.4% (95% CI: -0.3, 23.1).

Clinical Response

The proportion of subjects with a clinical response at Month 6 was higher for the tofacitinib 10 mg BID (95.7%) group compared with the tofacitinib 5 mg BID group (84.3%) with a difference of 11.4% (95% CI: 1.3, 22.0).

Remission Based on Modified Partial Mayo Score and Partial Mayo Score

- For all subjects, the proportions of subjects in remission based on modified partial Mayo score (PMS) and PMS were higher for the tofacitinib 10 mg BID group compared with the tofacitinib 5 mg BID group at each time point assessed (Months 1, 3 and 6).
    - At Month 1, 91.4% in the tofacitinib 10 mg BID group and 88.6% in the tofacitinib 5 mg BID group with a difference of 2.9% (95% CI:-7.5, 13.4) for both modified PMS and PMS.
    - At Month 3, 92.9% in the tofacitinib 10 mg BID group and 81.4% in the tofacitinib 5 mg BID group with a difference of 11.4% (95% CI: 0.1, 22.8) for both modified PMS and PMS.
    - At Month 6, 95.7% in the tofacitinib 10 mg BID group and 81.4% in the tofacitinib 5 mg BID group with a difference of 14.3% (95% CI: 2.9, 25.2) for modified PMS and 94.3% in the tofacitinib 10 mg BID group and 80.0% in the tofacitinib 5 mg BID group with a difference of 14.3% (95% CI: 2.4, 25.6) for PMS.

Change From Baseline of Modified Mayo and Total Mayo Score at Month 6

- The least square (LS) mean [standard error (SE)] for the change from baseline of modified Mayo score at Month 6 was lower for the tofacitinib 10 mg BID group (0.3 [0.2]) compared with the tofacitinib 5 mg BID group (0.6 [0.2]) based on ANCOVA.
- The LS mean [SE] for the change from baseline of total Mayo score at Month 6 was lower for the tofacitinib 10 mg BID group (0.4 [0.3]) compared with the tofacitinib 5 mg BID group (0.9 [0.2]) based on ANCOVA.

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Change From Baseline of Modified Partial Mayo Score and Partial Mayo Score

- The LS mean changes (SE) from baseline for the modified PMS and PMS remained low over time (Months 1, 3 and 6) and were either the same or similar for both dose groups.
    - At Month 1, 0.2 (0.1) in the tofacitinib 10 mg BID group and 0.1 (0.1) in the tofacitinib 5 mg BID group for modified PMS and 0.2 (0.1) for both dose groups for PMS.
    - At Month 3, 0.1 (0.1) in the tofacitinib 10 mg BID group and 0.2 (0.1) in the tofacitinib 5 mg BID group for modified PMS and 0.2 (0.1) in the tofacitinib 10 mg BID and 0.3 (0.1) in the tofacitinib 5 mg BID group for PMS.
    - At Month 6, 0.2 (0.1) in the tofacitinib 10 mg BID group and 0.1 (0.1) in the tofacitinib 5 mg BID group for modified PMS and 0.3 (0.1) for both dose groups for PMS.

Subgroup Analyses

Subgroup analyses were conducted for the primary efficacy and secondary efficacy endpoints for ESS at baseline (0, 1), prior tumor necrosis factor inhibitor (TNFi) failure (Y/N) and prior TNFi exposure (Y/N).

<u>Remission Based on Modified Mayo Score at Month 6</u>

- The proportion of subjects in remission based on modified Mayo score at Month 6 was higher in both dose groups for subjects with a baseline ESS=0 compared with subjects with a baseline ESS=1.
- For both subgroups based on baseline ESS=0 and ESS=1, the proportion of subjects in remission based on modified Mayo score at Month 6 was higher in the tofacitinib 10 mg BID group compared with the tofacitinib 5 mg BID group.
- The observed difference between tofacitinib 10 mg BID and 5 mg BID in proportions of subjects in remission at Month 6 was higher in the subgroup with baseline ESS=1 than the subgroup with baseline ESS=0.
    - ESS=0: 92.2% for the tofacitinib 10 mg BID group compared with 82.4% for the tofacitinib 5 mg BID group with a difference of 9.8% (95% CI: -3.0, 22.6).
    - ESS=1: 84.2% for the tofacitinib 10 mg BID group and 63.2% for the tofacitinib 5 mg BID group with a difference of 21.1% (95% CI: -6.1, 48.2).

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- The proportions of subjects in remission based on modified Mayo score at Month 6 in the subgroup with prior TNFi failure and the subgroup without prior TNFi failure were higher in the tofacitinib 10 mg BID group compared with the tofacitinib 5 mg BID group.

- The observed difference between tofacitinib 10 mg BID and 5 mg BID in proportions of subjects in remission at Month 6 was higher in the subgroup with prior TNFi failure than the subgroup without prior TNFi failure.

    - Prior TNFi failure=Yes: 91.4% for the tofacitinib 10 mg BID group compared with 74.1% for the tofacitinib 5 mg BID group with a difference of 17.4% (95% CI: -1.6, 36.3).

    - Prior TNFi failure=No: 88.6% for the tofacitinib 10 mg BID group and 79.1% for the tofacitinib 5 mg BID group with a difference of 9.5% (95% CI: -6.6, 25.6).

- Trends were similar for the subgroup of prior TNFi exposure.

Subgroup results were similar for the secondary endpoints of remission based on total Mayo score at Month 6, remission based on modified partial Mayo score and partial Mayo score, mucosal healing at Month 6, and clinical response.

Time to Loss of Remission (Flare) Based on Modified Mayo Score

Any time after Month 1, subjects who experienced flare may have had their dose escalated.

- In the tofacitinib 10 mg BID group, 4 subjects had a dose escalation action taken although the dose was not actually changed; 3 subjects prior to or at Month 6 (study day ≤190).

- In the tofacitinib 5 mg BID group, 12 subjects had a dose escalation to 10 mg BID; 9 subjects prior to or at Month 6 (study day ≤190).

The estimated rates (%) of having loss of remission were numerically lower in the tofacitinib 10 mg BID group compared with the tofacitinib 5 mg BID group at Months 1, 3 and 6 (Figure S3). Prior to or at Month 6, there were 4 subjects in the tofacitinib 10 mg BID group and 10 subjects in the tofacitinib 5 mg BID group that experienced loss of remission.

- At Month 1: 1.43% in the tofacitinib 10 mg BID group compared with 2.90% in the tofacitinib 5 mg BID group with a difference of -1.47 (95% CI: -6.31, 3.37).

- At Month 3: 1.43% in the tofacitinib 10 mg BID group compared with 5.84% in the tofacitinib 5 mg BID group with a difference of -4.41 (95% CI: -10.62, 1.80).

- At Month 6: 5.74% in the tofacitinib 10 mg BID group compared with 14.77% in the tofacitinib 5 mg BID group with a difference of -9.03 (95% CI: -19.10, 1.03).

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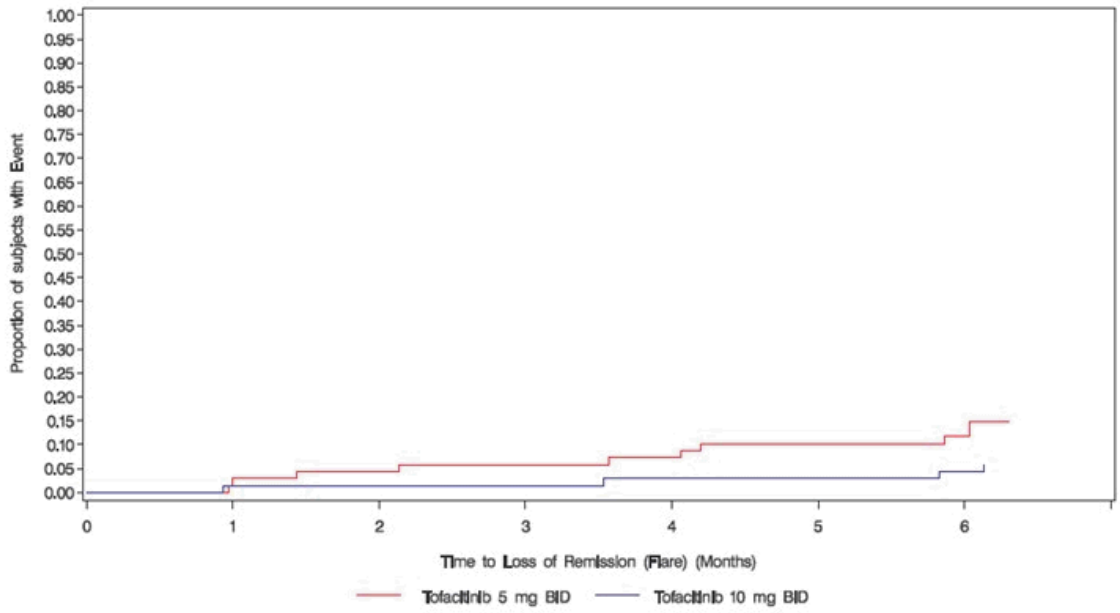
Figure S3. Kaplan-Meier Plot of Time to Loss of Remission (Flare) based on Modified Mayo Score by Dose Group (FAS)



Data cut-off: Feb 20, 2020.
PFIZER CONFIDENTIAL Source Data: Table 14.2.16.a Date of Reporting Dataset Creation : 12MAR2020
Output File: ./ibd_cdisc/A3921288_pcd_lab/km_tt_losrem Date of Generation: 23MAY2020 (19:05)

Change from Baseline in Fecal Calprotectin and hsCRP Levels

FCP Levels

Median baseline FCP values were similar between the treatment groups, 48.0 µg/g and 54.0 µg/g in the tofacitinib 10 mg BID group and tofacitinib 5 mg BID group, respectively.

- There were no meaningful differences in FCP values between the dose groups over time.

hsCRP Levels

Baseline median hsCRP values were similar between the treatment groups, 0.7 mg/L and 0.5 mg/L in the tofacitinib 10 mg BID group and tofacitinib 5 mg BID group, respectively.

- At Months 1 and 3, the LS mean in the tofacitinib 10 mg BID group showed a decrease from baseline (-0.3 and -0.1, respectively) in hsCRP compared with the tofacitinib 5 mg BID group which showed an LS mean increase (0.2 and 0.3, respectively) from baseline using linear mixed-effects model).

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- At Month 6, the tofacitinib 10 mg BID group showed a lower LS mean increase from baseline in hsCRP (0.1) compared with the tofacitinib 5 mg BID group (0.3) using linear mixed-effects model.

Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, Immunogenicity and/or Other Results: No pharmacokinetic, pharmacodynamic or pharmacogenomic evaluations were performed in this study.

Safety Results:

Data collected after dose escalation from tofacitinib 5 mg BID to 10 mg BID was not included in the safety analyses.

- The proportion of subjects who experienced all-causality treatment-emergent adverse events (TEAEs) was similar between the treatment groups (Table S3).
    - The majority of reported all-causality TEAEs were mild to moderate in both treatment groups; with the number of subjects with severe TEAEs lower in the tofacitinib 10 mg BID group (2 [2.9%] subjects) compared with the tofacitinib 5 mg BID group (6 [8.6%] subjects).
- There were 4 (5.7%) subjects with SAEs in each treatment group.
- Two (2.9%) subjects discontinued the study due to AEs in the tofacitinib 10 mg BID group compared with 7 (10.0%) subjects (1 [1.4%] subject discontinued study drug but continued in the study) in the tofacitinib 5 mg BID group.
- Two (2.9%) subjects in the tofacitinib 10 mg BID group and 3 (4.3%) subjects in the tofacitinib 5 mg BID group had temporary discontinuations.
- No deaths were reported in this study.
- No new or unexpected safety findings were observed.
    - Two cardiovascular events were confirmed by adjudication (1 pulmonary embolism in the tofacitinib 10 mg BID group; 1 cerebrovascular accident in the tofacitinib 5 mg BID group).
    - Four herpes zoster events were reported (1 in the tofacitinib 5 mg BID group; 3 in the tofacitinib 10 mg BID group); 1 herpes zoster event was reported in the tofacitinib 10 mg BID group that met criteria for an opportunistic infection (OI). No events classified as serious herpes zoster.
    - No non-herpes zoster OIs were reported.

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- One malignancy excluding nonmelanoma skin cancer (NMSC) was confirmed by adjudication (vulvar cancer in the tofacitinib 5 mg BID group).
- One NMSC event was confirmed by adjudication (basal cell carcinoma in the tofacitinib 5 mg BID group).
- One hepatic event was adjudicated and assessed as unlikely to be drug induced liver injury; no potential or confirmed Hy's Law cases.
- No gastrointestinal perforations were reported.

Table S3. Tofacitinib Protocol A3921288 Treatment-Emergent Adverse Events by Dose Group (All Causalities) - Safety Analysis Set

Number (%) of Subjects	Tofacitinib 5 mg BID n (%)	Tofacitinib 10 mg BID n (%)	Total n (%)
Subjects evaluable for adverse events	70	70	140
Number of adverse events	130	143	273
Subjects with adverse events	46 (65.7)	49 (70.0)	95 (67.9)
Subjects with serious adverse events	4 (5.7)	4 (5.7)	8 (5.7)
Subjects with severe adverse events	6 (8.6)	2 (2.9)	8 (5.7)
Subjects discontinued from study due to adverse events (a)	7 (10.0)	2 (2.9)	9 (6.4)
Subjects discontinued study drug due to AE and continue Study (b)	1 (1.4)	0	1 (0.7)
Subjects with dose reduced or temporary discontinuation due to adverse events	3 (4.3)	2 (2.9)	5 (3.6)

Data cut-off: Feb 20, 2020.
Except for the Number of Adverse Events subjects are counted only once per treatment in each row.
Serious Adverse Events - according to the investigator's assessment.
(a) Subjects who have an AE record that indicates that the AE caused the subject to be discontinued from the study.
(b) Subjects who have an AE record that indicates that Action Taken with Study Treatment was Drug Withdrawn but AE did not Cause the Subject to be
discontinued from Study.
MedDRA v22.1 coding dictionary applied.
PFIZER CONFIDENTIAL SDTM Creation: 12MAR2020 (15:21) Source Data: Table 16.2.7.1.1.a
Output File: ./ibd_cdisc/A3921288_pcd/adae_s020 Date of Generation: 15APR2020 (22:07)
Table 14.3.1.2.1.a is for Pfizer internal use.

Conclusion(s):

Efficacy

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- The proportion of subjects in modified Mayo remission at Month 6 (primary endpoint) were 90.0% and 77.1% for the tofacitinib 10 mg BID and tofacitinib 5 mg BID groups, respectively.

- Consistent findings were observed for the secondary efficacy endpoints – remission, mucosal healing and clinical response.

- Observed differences between tofacitinib 10 mg BID and 5 mg BID across efficacy endpoints at Month 6 were greater in the subgroup with baseline ESS of 1 than the subgroup with baseline ESS of 0, however the confidence intervals overlap.

    - A higher observed proportion of subjects with an ESS of 0 maintained remission or achieved other binary efficacy endpoints at Month 6 than the subjects with a baseline ESS of 1 in the 5 mg BID group (ie, after dose reduction to 5 mg BID).

- Observed differences between tofacitinib 10 mg BID and 5 mg BID across efficacy endpoints at Month 6 were greater in the prior TNFi treatment failure subgroup than in the subgroup without prior TNFi treatment failure, however the confidence intervals overlap.

    - A slightly higher observed proportion of subjects without prior TNFi failure maintained remission or achieved other binary efficacy endpoints at Month 6 than the subjects with prior TNFi failure in the 5 mg BID group (ie, after dose reduction to 5 mg BID).

- The biomarker analyses (hsCRP/FCP) performed were generally consistent between tofacitinib 10 mg BID and tofacitinib 5 mg BID groups.

Safety

- The proportions of subjects with AEs and SAEs were similar between the tofacitinib 10 mg BID and tofacitinib 5 mg BID dose groups.

- No deaths were reported in this study.

- No new or unexpected safety findings were observed.

    - Two cardiovascular events were confirmed by adjudication (1 pulmonary embolism in the tofacitinib 10 mg BID group; 1 cerebrovascular accident in the tofacitinib 5 mg BID group).

    - Four herpes zoster events were reported (1 in the tofacitinib 5 mg BID group; 3 in the tofacitinib 10 mg BID group); 1 herpes zoster event was reported in the tofacitinib 10 mg BID group that met criteria for an opportunistic infection (OI). No events classified as serious herpes zoster.

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- No non-herpes zoster OIs were reported.
- One malignancy excluding nonmelanoma skin cancer (NMSC) was confirmed by adjudication (vulvar cancer in the tofacitinib 5 mg BID group).
- One NMSC event was confirmed by adjudication (basal cell carcinoma in the tofacitinib 5 mg BID group).
- One hepatic event was adjudicated and assessed as unlikely to be drug induced liver injury; no potential or confirmed Hy's Law cases.
- No gastrointestinal perforations were reported.

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SYNOPSIS

Study Title: 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

Study Number: A3921288

Regulatory Agency or Public Disclosure Identifier Number: 2017-002274-39 (EudraCT)

Study Phase: 3b/4

Name of Study Intervention: CP-690,550

Trade Name: Xeljanz

Name of Sponsor/Company: Pfizer Inc.

CSR Version and Report Date:

Document Version	Report Date
Final CSR (PCD 14 February 2020) Version 1.0	22 July 2020
Supplemental CSR (LPLV 18 March 2022) Version 1.0	01 August 2022

Number of Study Center(s) and Investigator(s):

A total of 82 investigators from 82 sites randomized subjects from the following countries: Belgium (9), Canada (3), Czech Republic (3), France (3), Germany (1), Hungary (7), Italy (1), Japan (16), Republic of Korea (12), Netherlands (1), New Zealand (4), Poland (5), Russian Federation (3), Serbia (9), Slovakia (13), South Africa (9), Spain (5), Ukraine (12), United Kingdom (1), and the United States (23).

Publications:

Vermeire S, Su C, Lawendy N, et al. Outcomes of tofacitinib dose reduction in patients with ulcerative colitis in stable remission from the randomised RIVETING trial. J Crohns Colitis. 2021;15(7):1130-41.

Study Period:

16 November 2017 to 18 March 2022

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Rationale:

Prior studies in the ulcerative colitis (UC) Phase 3 program have shown that tofacitinib 10 mg twice daily (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. While the data from a completed open-label long term extension (LTE) study (A3921139) suggested 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 was designed to further evaluate the benefits of dosing flexibility with tofacitinib, and provide additional data for selecting the most appropriate regimen for an individual subject. Therefore this study evaluated the efficacy and safety of tofacitinib in participants in stable remission on 10 mg BID who (1) decreased their dose to 5 mg BID compared to participants remaining on 10 mg BID; (2) who decreased their 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) evaluated the efficacy and safety of tofacitinib in the subset of subjects who have flare on maintenance tofacitinib 5 mg BID and are re-treated with 10 mg BID.

Objectives, Endpoints, and Statistical Methods:

The objectives and endpoints of this study are presented in Table 1.

Table 1. Study Objectives and Endpoints

Type	Objective	Endpoint
Primary Efficacy		
Efficacy	To evaluate the efficacy 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.	• Remission based on modified Mayo score at Month 6.
Secondary Efficacy		
Efficacy	To evaluate the efficacy 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 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.	• 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 (PMS), total Mayo score, and PMS. • Change from baseline (of Study A3921288) at all applicable scheduled visits in the following: modified

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Table 1. Study Objectives and Endpoints

Type	Objective	Endpoint
		Mayo score, modified PMS, total Mayo score, and PMS. • 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 (FCP) and high sensitivity C-reactive protein (hsCRP) levels.
Safety		
Safety	To evaluate the 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. To evaluate the 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 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.	• 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).

This was an estimation study, with no planned hypothesis testing.

Analysis Sets

The primary analysis population was the full analysis set (FAS) defined as all subjects who were randomized into the study and received at least 1 dose of investigational product.

The safety analysis set was defined as all subjects who received at least 1 dose of investigational product.

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Determination of Sample Size

Although approximately 130 subjects were estimated to be enrolled into this study (based on availability of eligible subjects from the open-label LTE Study A3921139 and based on the conservative assumptions of the attrition rate of 50% - 60% in the open-label LTE Study A3921139), the final sample size was 140 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 was about 16%, assuming the remission rates were greater than 70% in both groups.

Analysis of Efficacy Parameters

For the primary endpoint, analyses were performed for comparisons of the following 2 dose groups:

- **Tofacitinib 10 mg BID dose group:** subjects who were initially assigned to tofacitinib 10 mg BID at randomization. For subjects who dose-reduced due to meeting criteria for venous thromboembolism (VTE) risk factors, data collected after the dose reduction were not included in the analyses.

- **Tofacitinib 5 mg BID dose group:** subjects who were initially assigned to tofacitinib 5 mg BID at randomization. For subjects who dose-escalated from 5 mg BID to 10 mg BID, data collected after the dose escalation were not included in the analyses.

For the first secondary objective, analyses were performed for comparisons of the following 2 regimen groups:

- **Tofacitinib 10 mg BID regimen group:** subjects who were initially assigned to tofacitinib 10 mg BID at randomization. For subjects with dose reduction due to VTE risk factors, data collected after the dose reduction were included in the analyses.

- **Tofacitinib 5 mg BID regimen group:** subjects who were initially assigned to tofacitinib 5 mg BID at randomization, regardless of whether the dose was escalated to tofacitinib 10 mg BID or not. Data collected after the dose escalation were included in the analyses.

For the second secondary objective (see Table 1), summary descriptive statistics were reported for the subgroup of subjects who were initially assigned to tofacitinib 5 mg BID and later were re-treated with tofacitinib 10 mg BID based on the observed case data using the original windowing rules. In addition, the efficacy data after the dose escalation were summarized using the new windowing rule by resetting the baseline (Day 0) at the dose escalation time.

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Analysis of Primary Endpoint

The primary efficacy endpoint was remission based on modified Mayo score at Month 6. For dose comparison between tofacitinib 10 mg BID and 5 mg BID, the stratified estimation of the treatment difference between tofacitinib 10 mg BID and 5 mg BID in the proportion of subjects was presented along with its 95% confidence interval (CI) with the endoscopic subscore (ESS) at baseline (0 versus 1) as the stratification factor. The Cochran-Mantel-Haenszel (CMH) weight method was used for the stratified estimation of the treatment difference. The stratified CI was constructed using the Newcombe method.

In addition, p-values based on CMH Chi-square test stratified by ESS at baseline (0 versus 1) were presented.

The same analysis method was used for comparisons between regimen groups.

As sensitivity analyses for handling of missing data, remission based on modified Mayo score and remission based on total Mayo score were analyzed using a generalized linear mixed-effects model with a logit link and with dose group, visit, dose group by visit interaction, ESS at baseline (0 versus 1) all as fixed effects, and subject as a random effect based on data collected at Month 6, Month 18, Month 30 and Month 42 if sufficient data are available at Month 42. The estimated mean, mean difference, with p-values and 95% confidence interval based on the model are presented at each time point for dose group and regimen group.

Analysis of Secondary Efficacy Endpoints

Binary secondary efficacy endpoints were analyzed using the same approach as described for the primary efficacy endpoint.

For continuous efficacy endpoints based on total Mayo score evaluated for primary objective at Month 6, the change from baseline was analyzed using an analysis of covariance (ANCOVA) model with dose group, the ESS at baseline (0 versus 1) as factors and baseline score as a covariate. Otherwise, for continuous efficacy endpoints, the change from baseline was analyzed using linear mixed effects model with baseline value, dose group or regimen group, the ESS at baseline (0 versus 1), visit, and dose group or regimen 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 2 dose groups or 2 regimen groups was computed for each visit.

Time to loss of remission (flare) based on modified Mayo score was tested using a log-rank test stratified by ESS at baseline (0 versus 1). In addition, cumulative event rates and associated CIs were estimated from the Kaplan-Meier curves for each dose group and each regimen group. The dose comparison for the proportions of the event were made using Wald test statistics.

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Fecal calprotectin and hsCRP, and their change from baseline were summarized descriptively for each visit by dose group and by regimen group.

The fecal calprotectin and hsCRP data were also log-transformed (natural logarithm) for the analyses. The change from baseline was analyzed using the same approach as the continuous efficacy endpoints.

Safety Analysis

Safety data were summarized based on observed-case data by dose group, regimen group and the subgroup of subjects who are initially assigned to tofacitinib 5 mg BID and later are retreated with tofacitinib 10 mg BID (retreatment group). Missing data were not imputed.

For the dose group, data collected after the dose escalation from tofacitinib 5 mg BID to 10 mg BID were not included in the analyses. Data collected after the dose reduction from tofacitinib 10 mg BID to 5 mg BID were not included in the dose group analyses as well.

For the regimen group, data from subjects with dose escalation from tofacitinib 5 mg BID to 10 mg BID were treated as is. For subjects with dose reduction from tofacitinib 10 mg BID to 5 mg BID due to meeting criteria for the presence of VTE risk factors, data collected after the dose reduction were included in the analyses.

The safety data were summarized in accordance with Pfizer Data Standards.

Serious adverse event presentations were derived from a combination of data in the clinical study database and the corporate safety database. The corporate safety database is a separate, centralized, adverse event monitoring database that is continuously updated based on rapidly communicated reports from the investigators to the sponsor. The clinical study database was based on information provided from the case report forms (CRFs)/ data collection tools (DCTs). Consequently, occasional differences in data may exist between the centralized safety database and the clinical study database.

Adverse Events

An AE was considered treatment emergent relative to a given treatment if the event starts after the first dose. The first dose was defined as the first dose in Study A3921288. A 3-tier approach was used to summarize AEs. Under this approach, AEs were classified into 1 of 3 tiers and different analyses were performed for different tiers. Herpes zoster events were pre-specified as Tier 1 events; Tier 2 events were events that were reported at least 4 times in any treatment group; and Tier 3 events were all other events that were not Tier 1 or Tier 2 events.

Clinical Laboratory Parameters

Clinical laboratory data were summarized descriptively by dose group, regimen group and retreatment group.

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Other Safety Parameters

Vitals Signs and Physical Examination

Vital sign and physical examination data were summarized descriptively by dose group.

Methodology:

This study enrolled subjects from the completed open-label LTE Study A3921139 who were in stable remission on tofacitinib 10 mg BID for at least 6 months and not receiving any corticosteroids to treat their UC for at least 4 weeks prior to enrollment. Subjects must have received tofacitinib 10 mg BID for a minimum of 2 consecutive years in the open-label LTE Study A3921139 prior to enrollment. Subjects enrolled under Amendment 2 must not have had any risk factors for pulmonary embolism (PE).

One-hundred and forty (140) subjects were enrolled into this study. Eligible subjects were randomized in a 1:1 allocation ratio to receive either tofacitinib 5 mg BID or 10 mg BID at baseline of this study. Subjects were stratified at baseline based on the ESS (0 versus 1) of their most recent endoscopy.

This study had a total of 42 months of treatment duration. The primary analysis was conducted after the last subject enrolled reached their Month 6 study visit. The initial treatment assignment at baseline remained double-blinded to the site and the subject. Study visits occurred 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 withdrew early or who completed this study, had a 4-week safety follow up evaluation after the last dose of investigational product.

Any time after Month 1, subjects who experienced flare could have had their dose escalated.

Flare was defined by meeting 1 of the following 4 criteria:

1. An increase in rectal bleeding subscore by at least 1 point and an increase in ESS by at least 1 point; OR

2. An increase in rectal bleeding subscore by at least 2 points and an ESS >0; OR

3. An increase in stool frequency subscore by at least 2 points and an increase in the ESS by at least 1 point; OR

4. An increase in ESS by at least 2 points.

Subjects with confirmed flare were eligible for a dose escalation provided that the subject did not have any of the risk factors for PE/VTE.

Subjects who were identified to have one or more of the risk factors for PE/VTE had their tofacitinib dose adjusted to open label 5 mg BID.

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Number of Participants (planned and analyzed):

This study was conducted at 82 sites. A total of 140 participants were enrolled at 93 centers in 20 countries.

A total of 140 participants were randomized into the study, with 70 participants randomized to each treatment group.

Diagnosis and Main Criteria for Inclusion and Exclusion:

Key inclusion criteria were as follows:

1. Subjects enrolled in Study A3921139 who had 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 were 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 were available during the 6 month period in Study A3921139 prior to and including baseline of Study A3921288;

   b. AND at least 1 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 ESS of 0 or 1, was required prior to randomization into Study A3921288.

      - All available assessments based on Mayo score during this period must have shown remission.

   c. AND subjects must not have been receiving any corticosteroid therapy for their UC for at least 4 weeks prior to baseline.

Key exclusion criteria were as follows:

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 reasons.

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

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

4. 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 enrollment.

Beginning with Protocol Amendment 2, subjects with any of the following risk factors for PE at baseline as defined by European Medicines Agency's Pharmacovigilance Risk Assessment Committee (this only impacted the last subject enrolled):

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

Study Interventions, Dose, Mode of Administration, and Batch Number(s):

Table 2. Study Intervention(s) Administered

Investigational Product Description	Vendor Lot Number	Pfizer Lot Number	Strength/ Potency	Dosage Form
Placebo for Tofacitinib Citrate 5 mg Film Coated Tablet	R73682	16-005146	0 mg	Tablet
Placebo for Tofacitinib Citrate 5 mg Film Coated Tablet	R73683	16-005147	0 mg	Tablet
Placebo for Tofacitinib Citrate 5 mg Film Coated Tablet	T95848	18-000343	0 mg	Tablet
Placebo for Tofacitinib Citrate 5 mg Film Coated Tablet	X88704	18-003619	0 mg	Tablet
Tofacitinib Citrate 5 mg Film Coated Tablet	AJ6947	19-000910	5 mg	Tablet
Tofacitinib Citrate 5 mg Film Coated Tablet	DR8453	20-002711	5 mg	Tablet
Tofacitinib Citrate 5 mg Film Coated Tablet	S26918	17-000460	5 mg	Tablet

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Table 2. Study Intervention(s) Administered

Investigational Product Description	Vendor Lot Number	Pfizer Lot Number	Strength/ Potency	Dosage Form
Tofacitinib Citrate 5 mg Film Coated Tablet	X20921	18-002302	5 mg	Tablet

Duration of Study Intervention:

Subjects were randomized into 1 of 2 dosing groups at baseline of Study A3921288:

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

Subjects who met the protocol definition for flare may have had a dose increase to 10 mg BID or remained on 10 mg BID, depending on their initial treatment assignment provided that the subject did not have any of the risk factors for PE/VTE. Subjects who were identified to have one or more of the risk factors for PE/VTE had their tofacitinib dose adjusted to open label 5 mg BID.

The manufacturing lot numbers for the study intervention(s) dispensed in this study are provided in Table 2. Prior studies in the UC Phase 3 program have shown that 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.

Summary of Results:

Demographic and Other Baseline Characteristics:

Selected demographic characteristics were as follows:

- The mean age of subjects between both treatment groups was 47.8 years.
- The majority of subjects were White (71.4 %); 20.7% of all subjects were of Asian descent and 4.3% of subjects in the tofacitinib 5 mg BID group (0.0% in the tofacitinib 10 mg BID group) were Black or African American.

Selected baseline and clinical characteristics were as follows:

- There were 70 (100.0%) and 68 (97.1%) subjects in remission at baseline in the tofacitinib 10 mg BID and tofacitinib 5 mg BID groups, respectively (Table 3).
- At baseline, 51 (72.9%) subjects in each dose group had ESS of 0 (Table 3).

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- Mean and median baseline partial Mayo and baseline total Mayo scores were similar between the treatment groups (Table 3).

Table 3. Tofacitinib Protocol A3921288 Baseline and Clinical Characteristics, per data from baseline of A3921288 study - FAS

	Tofacitinib 5 mg BID (N=70) n (%)	Tofacitinib 10 mg BID (N=70) n (%)	Total (N=140) n (%)
Endoscopic Subscore at baseline			
N1	70	70	140
0	51 (72.9)	51 (72.9)	102 (72.9)
1	19 (27.1)	19 (27.1)	38 (27.1)
Remission at baseline			
N1	70	70	140
No	2 (2.9)	0	2 (1.4)
Yes	68 (97.1)	70 (100.0)	138 (98.6)
Modified Mayo Remission at baseline			
N1	70	70	140
No	1 (1.4)	0	1 (0.7)
Yes	69 (98.6)	70 (100.0)	139 (99.3)
Mucosal Healing at baseline			
N1	70	70	140
No	0	0	0
Yes	70 (100.0)	70 (100.0)	140 (100.0)
Clinical Response at baseline			
N1	70	70	140
No	0	0	0
Yes	70 (100.0)	70 (100.0)	140 (100.0)
Modified Mayo score			
N1	70	70	140
Mean(SD)	0.6 (0.7)	0.6 (0.7)	0.6 (0.7)
Median	0.0	0.0	0.0
Min-Max	(0.0- 2.0)	(0.0- 2.0)	(0.0- 2.0)
Total Mayo score			
N1	70	70	140
Mean(SD)	0.6 (0.7)	0.7 (0.8)	0.6 (0.8)

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Table 3. Tofacitinib Protocol A3921288 Baseline and Clinical Characteristics, per data from baseline of A3921288 study - FAS

	Tofacitinib 5 mg BID (N=70) n (%)	Tofacitinib 10 mg BID (N=70) n (%)	Total (N=140) n (%)
Median	0.0	0.0	0.0
Min-Max	(0.0- 3.0)	(0.0- 2.0)	(0.0- 3.0)
Partial Mayo score			
N1	70	70	140
Mean(SD)	0.4 (0.5)	0.4 (0.5)	0.4 (0.5)
Median	0.0	0.0	0.0
Min-Max	(0.0- 2.0)	(0.0- 2.0)	(0.0- 2.0)
BMI (kg/m**2)			
N1	70	70	140
< 25	29 (41.4)	23 (32.9)	52 (37.1)
25 - < 30	24 (34.3)	32 (45.7)	56 (40.0)
>= 30	17 (24.3)	15 (21.4)	32 (22.9)
Primary Diagnosis - Duration Since Onset (Years)*			
N1	70	70	140
Mean(SD)	12.5 (7.9)	13.6 (7.7)	13.0 (7.8)
Median	10.3	11.2	10.6
Min-Max	(4.4- 45.9)	(4.6- 44.8)	(4.4- 45.9)

Data cut-off: Final Data.
N = number of randomized subjects in the total population.
N1 = number of subjects in the specified category with non-missing values.
n = number of subjects with the specified response within the given category. % = n/N1.
* Duration of diagnosis is computed per A3921288 randomization date.
PFIZER CONFIDENTIAL SDTM Creation: 13APR2022 (12:03) Source Data: adsl
Output File: ./ibd_cdisc/A3921288_finalcsr/baseclin_1288 Date of Generation: 02JUN2022 (03:20)
Table 14.1.2.1.1 is for Pfizer internal use.

Exposure:

The duration of treatment for the majority of all participants was between 991 and 1260 days. The median (range) duration of treatment was 1225.5 (29, 1288) days in the tofacitinib 5 mg BID group and 1179.5 (267, 1269) days in the tofacitinib 10 mg BID group.

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Efficacy Results

Efficacy

- The proportion of subjects in modified Mayo remission at Month 6 (primary endpoint) by dose group was 90.0% and 77.1% for the tofacitinib 10 mg BID and tofacitinib 5 mg BID group, respectively, with a difference (95% CI) of 12.9% (0.5%, 25.0%). When analyzed by regimen group, the proportion of subjects in modified Mayo remission at Month 6 was 90.0% and 85.7% for the tofacitinib 10 mg BID and tofacitinib 5 mg BID group, respectively, with a difference (95% CI) of 4.3% (-6.9%, 15.5%).

- While the proportion of subjects in remission based on modified Mayo score gradually declined numerically over time, efficacy was maintained with the majority of subjects in remission through Month 30 when evaluated by either dose group or regimen group.

- Evaluating by either dose group or regimen group, the proportion of subjects in remission based on modified Mayo score was higher for the tofacitinib 10 mg BID group compared with the tofacitinib 5 mg BID group, at both Month 18 and Month 30. Data at Month 42 were impacted by early study termination.

- Consistent findings were observed for the additional secondary efficacy endpoints – remission based on total Mayo score, mucosal healing and clinical response when analyzed by either dose group or regimen group.

- Observed differences between tofacitinib 10 mg BID and 5 mg BID across efficacy endpoints were generally greater in the subgroup with baseline ESS of 1 than the subgroup with baseline ESS of 0; however, the confidence intervals overlap.

- Generally, a higher observed proportion of subjects with a baseline ESS of 0 maintained remission or achieved other binary efficacy endpoints up to Month 30 than the subjects with a baseline ESS of 1 in the 5 mg BID group (ie, after dose reduction to 5 mg BID).

- Except for clinical response, observed differences between tofacitinib 10 mg BID and 5 mg BID across the timepoints for the additional efficacy endpoints were generally greater in the prior tumor necrosis factor inhibitor (TNFi) treatment failure subgroup than in the subgroup without prior TNFi treatment failure; however, the confidence intervals overlap.

- Generally, a slightly higher observed proportion of subjects without prior TNFi failure maintained remission or achieved other binary efficacy endpoints up to Month 30 than the subjects with prior TNFi failure in the 5 mg BID group (ie, after dose reduction to 5 mg BID).

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- The biomarker analyses (FCP/hsCRP) performed were generally consistent between tofacitinib 10 mg BID and tofacitinib 5 mg BID groups when evaluated by either dose group or regimen group.

Safety Results:

By dose group or regimen group, the number of participants with all causality treatment-emergent adverse events (TEAEs) was 55 (78.6%) and 58 (82.9%) in the tofacitinib 5 mg BID and tofacitinib 10 mg BID treatment groups, respectively. When evaluated by either dose group or regimen group, the majority of the TEAEs in each treatment group were mild to moderate.

For the TEAEs by dose group, the following observations were noted:

- The proportion of participants with severe TEAEs was 11.4% (8 participants) and 14.3% (10 participants) in the tofacitinib 5 mg BID group and tofacitinib 10 mg BID group, respectively (Table 4).

- The number of participants with serious adverse events (SAEs) was lower in the tofacitinib 5 mg BID group (7 [10.0%]) compared with the tofacitinib 10 mg BID group (16 [22.9%]) (Table 4).

- Eleven (11) participants (15.7%) discontinued the study due to AEs in the tofacitinib 5 mg BID group compared with 13 participants (18.6%) in the tofacitinib 10 mg BID group (Table 4).

- Six (6) participants (8.6%) in the tofacitinib 5 mg BID group and 8 participants (11.4%) in the tofacitinib 10 mg BID group had dose reduced or temporary discontinuation due to AEs (Table 4).

For the TEAEs by regimen group, the following observations compared to the analysis by dose group were noted in the tofacitinib 5 mg BID group:

- One (1) additional participant reported a severe TEAE.

- Three (3) additional participants reported SAEs.

- Two (2) additional participants discontinued the study due to AEs.

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Table 4. Tofacitinib Protocol A3921288 Treatment-Emergent Adverse Events by Dose Group (All Causalities) - Safety Analysis Set

Number (%) of Subjects	Tofacitinib 5 mg BID n (%)	Tofacitinib 10 mg BID n (%)	Total n (%)
Participants evaluable for adverse events	70	70	140
Number of adverse events	206	241	447
Participants with adverse events	55 (78.6)	58 (82.9)	113 (80.7)
Participants with serious adverse events	7 (10.0)	16 (22.9)	23 (16.4)
Participants with severe adverse events	8 (11.4)	10 (14.3)	18 (12.9)
Participants discontinued from study due to adverse events (a)	11 (15.7)	13 (18.6)	24 (17.1)
Participants with dose reduced or temporary discontinuation due to adverse events	6 (8.6)	8 (11.4)	14 (10.0)

Data cut-off: Final Data.
Except for the Number of Adverse Events subjects are counted only once per treatment in each row.
Serious Adverse Events - according to the investigator's assessment.
(a) Subjects who have an AE record that indicates that the AE caused the subject to be discontinued from the study.
MedDRA v24.1 coding dictionary applied.
PFIZER CONFIDENTIAL SDTM Creation: 13APR2022 (14:45) Source Data: adae
Output File: ./ibd_cdisc/A3921288_finalcsr/adae_s020 Date of Generation: 02JUN2022 (03:19)
Table 14.3.1.2.1.a is for Pfizer internal use.

Safety

- When evaluated by either dose group or regimen group, the proportions of participants with TEAEs were similar between the tofacitinib 10 mg BID and tofacitinib 5 mg BID groups. The proportion of participants with SAEs in the tofacitinib 10 mg BID group was numerically higher than that of the tofacitinib 5 mg BID group.

- There were 24 participants who discontinued from the study due to adverse events by dose group. Two (2) additional participants discontinued from the study due to adverse events when evaluated by regimen group.

- One (1) death was reported in the tofacitinib 10 mg BID group in this study. The cause of death was respiratory failure and cardiac arrest due to complications of coronavirus disease 2019 (COVID-19) pneumonia.

- No new or unexpected safety findings were observed.

  - Serious infections were reported in 9 participants when evaluated by dose group (3 in the tofacitinib 5 mg BID group; 6 in the tofacitinib 10 mg BID group). One (1)

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additional serious infection (appendicitis) was reported in the tofacitinib 5 mg BID group when evaluated by regimen group (ie, while receiving tofacitinib 10 mg BID).

- When evaluated by dose group, herpes zoster infections were reported in 8 participants (2 in the tofacitinib 5 mg BID group; 6 in the tofacitinib 10 mg BID group). In the tofacitinib 10 mg BID group, 1 herpes zoster event met criteria for an opportunistic infection (OI), 1 herpes zoster event met criteria for a special interest infection, and 1 herpes zoster event (herpes zoster oticus) classified as serious herpes zoster. An additional herpes zoster event (mild severity) was reported in the tofacitinib 10 mg BID group when evaluated by regimen group (ie, while receiving tofacitinib 5 mg BID).

- No non-herpes zoster OIs were reported.

- Four (4) CV/neurovascular events were confirmed by adjudication in the dose group (1 PE in the tofacitinib 10 mg BID group; 1 fatal COVID-19 pneumonia in the tofacitinib 10 mg BID group; 1 deep vein thrombosis [DVT] in the tofacitinib 5 mg BID group; 1 cerebrovascular accident in the tofacitinib 5 mg BID group). No additional events were reported when evaluated by regimen group.

- Four (4) malignancies excluding non-melanoma skin cancer (NMSC) were confirmed by adjudication in the dose group (vulvar cancer in the tofacitinib 5 mg BID group; colorectal cancer in the tofacitinib 5 mg BID group; non-Hodgkin lymphoma in the tofacitinib 10 mg BID group; prostate cancer in the tofacitinib 10 mg BID group). No additional events were reported when evaluated by regimen group.

- Three (3) subjects reported NMSC events confirmed by adjudication in the dose group (cutaneous squamous cell carcinoma in the tofacitinib 5 mg BID group (4 events in 1 participant); basal cell carcinoma in the tofacitinib 5 mg BID group; basal cell carcinoma in the tofacitinib 10 mg BID group). No additional events were reported when evaluated by regimen group.

- One (1) hepatic event in the tofacitinib 10 mg BID group was adjudicated and assessed as unlikely to be drug-induced liver injury; no potential or confirmed Hy's Law cases.

- No gastrointestinal perforations were confirmed by adjudication.

- Clinical laboratory values remained stable throughout the treatment period. Two (2) participants met criteria for discontinuation of study drug for laboratory values when evaluated by dose group (1 in each of the tofacitinib 5 mg BID and tofacitinib 10 mg BID groups). An additional participant met criteria in the tofacitinib 5 mg BID group when evaluated by regimen group (ie, while receiving tofacitinib 10 mg BID).

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- No clinically meaningful findings in the vital signs measurements, or physical examination assessments were observed in this study.

Conclusions:

- The primary efficacy endpoint results (proportion of subjects in remission based on modified Mayo score at Month 6) were 90.0% and 77.1% for the tofacitinib 10 mg BID and tofacitinib 5 mg BID groups, respectively, when evaluated by dose group. When evaluated by regimen group, the proportion of subjects in remission based on modified Mayo score was 90.0% and 85.7% for the tofacitinib 10 mg BID and 5 mg BID groups, respectively.

- The majority of subjects in the tofacitinib 5 mg BID and tofacitinib 10 mg BID groups maintained modified Mayo remission up to Month 30 when evaluated by either dose group or regimen group.

- No new safety signals specific to the UC population treated with tofacitinib were identified.