CLINICAL STUDY REPORT SYNOPSIS

Sponsor: Pfizer, Inc

Investigational Product: CP-690,550 (Tofacitinib)

Clinical Study Report Synopsis: Protocol A3921139

Protocol Title: A Multi-Center, Open-Label Study of CP-690,550 in Participants With Moderate to Severe Ulcerative Colitis

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

Study Center(s): A total of 298 sites randomized participants from the following countries: Australia (8), Austria (3), Belgium (4), Brazil (2), Canada (7), Colombia (3), Croatia (5), Czech Republic (5), Denmark (5), Estonia (5), France (9), Germany (9), Hungary (16), Israel (5), Italy (4), Japan (27), Republic of Korea (9), Latvia (3), Netherlands (5), New Zealand (7), Poland (13), Romania (8), Russian Federation (11), Serbia (8), Slovakia (8), South Africa (7), Spain (6), Taiwan (1), Ukraine (14), United Kingdom (5), and the United States (76). Refer to Appendix 16.1.4.1 for a list of sites involved in this study.

Publications Based on the Study:

Sandborn WJ, Panés J, D'Haens GR, et al. Safety of tofacitinib for treatment of ulcerative colitis, based on 4.4 years of data from global clinical trials. Clin Gastroenterol Hepatol 2019; 17(8):1541-50.

Sands BE, Armuzzi A, Marshall JK, et al. Efficacy and safety of tofacitinib dose de-escalation and dose escalation for patients with ulcerative colitis: results from OCTAVE open. Aliment Pharmacol Ther 2020; 51(2):271-80.

Study Initiation Date: 01 October 2012

Study Completion Date: 06 August 2020

Report Date: 16 March 2021

Previous Report Date(s): 20 December 2016

Phase of Development: Phase 3

CLINICAL STUDY REPORT SYNOPSIS

Primary and Secondary Study Objectives and Endpoints:

Table S1. Study Objectives and Endpoints

Type	Objective(s)	Endpoints
Primary		
Safety	To assess the safety and tolerability of long-term tofacitinib therapy in participants with ulcerative colitis (UC).	• Incidence and severity of adverse events (AEs). • Incidence of serious infections. • Incidence and severity of clinical laboratory abnormalities and change from baseline in clinical laboratory values. • Incidence of vital sign abnormalities and change from baseline in vital signs. • Incidence of clinically significant changes in physical examinations from baseline. • Incidence of electrocardiogram (ECG) abnormalities during study intervention. • Summary of adjudicated safety events (eg, cardiovascular, malignancy, opportunistic infections). • Proportion of participants with addition of lipid lowering agents.
Secondary		
Efficacy	To evaluate the efficacy of long-term tofacitinib therapy in participants with UC. To evaluate the effect of long-term tofacitinib therapy on quality of life in participants with UC.	• The proportion of participants in remission at Month 2, Month 12, Month 24, and Month 36. Remission in this study is defined as a Mayo score ≤2 with no individual subscore >1, and rectal bleeding subscore of 0. • The proportion of participants in clinical remission at Month 2,

CLINICAL STUDY REPORT SYNOPSIS

Table S1. Study Objectives and Endpoints

Type	Objective(s)	Endpoints
		Month 12, Month 24 and Month 36. Clinical remission in this study is defined as a Mayo score ≤2 with no individual subscore >1. • The proportion of participants in PMS (partial Mayo score) remission over time. PMS remission in this study is defined as a partial Mayo score ≤2 with no individual subscore >1. • The proportion of participants who achieve mucosal healing at Month 2, Month 12, Month 24 and Month 36. Mucosal healing is defined as a Mayo endoscopic subscore of 0 or 1. • The proportion of participants with total score in the Inflammatory Bowel Disease Questionnaire (IBDQ) ≥170 over time.
Exploratory		
		• PMS and change from baseline (of Study A3921139) over time. • Total Mayo score and change from Baseline (of Study A3921139) at Month 2, Month 12, Month 24 and Month 36. • The absolute scores and change from baseline (of Study A3921139) in total IBDQ score and domains (Bowel Symptoms, Systemic Symptoms, Emotional Function and Social Function) over time.

CLINICAL STUDY REPORT SYNOPSIS

Table S1. Study Objectives and Endpoints

Type	Objective(s)	Endpoints
		• The absolute scores and change from baseline (of Study A3921139) in Short Form 36 (SF-36), version 2, acute (physical and mental component summary scores, and 8 domain scores) over time through Month 33. • The scores and change from baseline (of Study A3921139) in EQ-5D/VAS over time. • The scores and change from baseline (of Study A3921139) in the Work Productivity and Activity Impairment (WPAI) questionnaire domains (Absenteeism, Presenteeism, Work Productivity Loss, Activity Impairment) over time through Month 33. • The proportion of subjects who utilize the healthcare services and the frequency of utilization of such services specified in the Ulcerative Colitis Healthcare Resource Utilization Questionnaire-All (UC-HCRU-All) over time. • The number and length of UC-related hospitalizations. • The proportion of subjects requiring colectomy for UC or UC-related complications. • Summary of absolute counts and change from baseline in the following lymphocyte subsets: CD4+ T cells, CD8+ T cells, B cells, and natural killer (NK)

CLINICAL STUDY REPORT SYNOPSIS

Table S1. Study Objectives and Endpoints		
Type	**Objective(s)**	**Endpoints**
		cells (United Kingdom (UK) only).

METHODS

Study Design: This was a Phase 3, multi-center, open-label study in participants who completed or demonstrated treatment failure in the maintenance study A3921096, or who were non-responders after completing induction studies A3921094 or A3921095. Individual participant duration of participation varied depending on when the participant was enrolled into the study and the first market approval.

Eligible participants were assigned to either tofacitinib 5 mg twice daily (BID) or 10 mg BID depending on whether the participant was in remission at baseline of Study A3921139. Eligible participants who were in remission at Week 52 of Study A3921096 were assigned to receive tofacitinib 5 mg BID and comprised the maintenance remission subpopulation. Participants who completed Study A3921096 but did not meet the remission definition or who were early withdrawals due to treatment failure in Study A3921096 were eligible to receive tofacitinib 10 mg BID and comprised the maintenance treatment failures and other maintenance completers subpopulations. Participants who completed induction studies A3921094 or A3921095 and were classified as non-responders were also eligible to receive tofacitinib 10 mg BID and comprised the induction non-responders subpopulation.

The maintenance remission subpopulation was defined as participants who completed the maintenance Study A3921096 in remission. Remission was defined by a total Mayo score ≤ 2 with no individual subscore >1, and rectal bleeding subscore of 0.

The maintenance treatment failures subpopulation was defined as those participants who were treatment failures or dropped out due to lack of efficacy from maintenance Study A3921096 and received tofacitinib 10 mg BID or placebo from induction Study A3921094 or A3921095.

The other maintenance completers subpopulation was defined as all other completed participants from maintenance Study A3921096; that is, those participants who were neither in remission nor fulfilled the definition of treatment failure.

The induction non-responder subpopulation was defined as participants who were enrolled from induction Study A3921094 or A3921095 directly, but did not achieve clinical response and received tofacitinib 10 mg BID or placebo in the induction studies.

Participants from the induction studies A3921094 or A3921095 (ie, non-responders) who failed to demonstrate clinical response at Month 2 of this study were withdrawn from the

CLINICAL STUDY REPORT SYNOPSIS

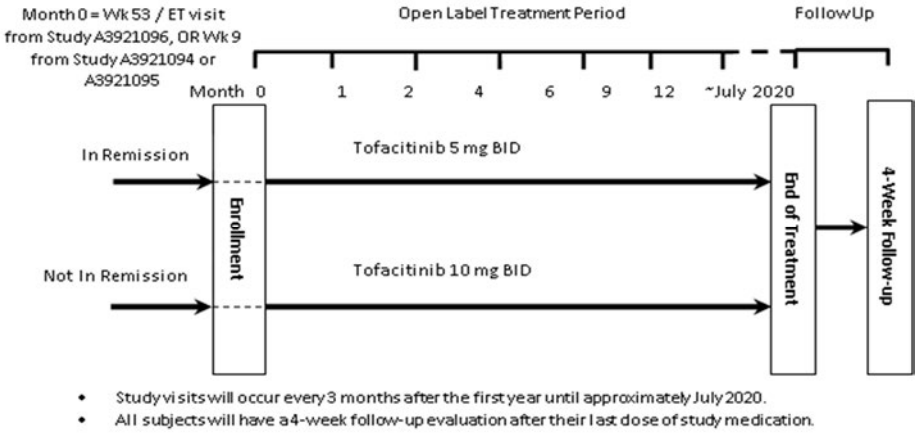
study. Clinical response was defined by a decrease from the induction study baseline (A3921094 or A3921095) Mayo score of at least 3 points and at least 30%, with an accompanying decrease in the rectal bleeding subscore of at least 1 point or an absolute rectal bleeding subscore of 0 or 1. The endoscopic subscore based on central reading was used to assess clinical response.

The maximum tofacitinib dose allowed in this study was 10 mg BID. Dose adjustments only occurred after a participant had received at least 8 weeks of treatment in Study A3921139. Tofacitinib dose was adjusted from 5 mg BID to 10 mg BID for efficacy and from 10 mg BID to 5 mg BID after meeting specific laboratory abnormalities or other protocol defined criteria regarding efficacy. If a participant who received tofacitinib 5 mg BID experienced loss of response, then the participant should have been scheduled for endoscopy to determine if the participant experienced a flare.

In addition, participants were evaluated for pulmonary embolism (PE) risk factors. If a participant had a risk factor and was receiving 10 mg BID, the participant was required to have their dose reduced to 5 mg BID. Participants who were receiving tofacitinib 5 mg BID and who developed one or more of the risk factors for PE during the study were not permitted to increase their dose to tofacitinib 10 mg BID.

A schematic of the study design is shown in Figure S1.

Figure S1. Study Design



CLINICAL STUDY REPORT SYNOPSIS

Diagnosis and Main Criteria for Inclusion:

Key Inclusion Criteria were as follows:

1. Participants who previously participated in Study A3921096 who either:

    - completed 52-week maintenance treatment in Study A3921096, or

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

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

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

    - had an endoscopic subscore at Week 8 that was either the same or higher (worse) than the endoscopic subscore at Week 0 of Study A3921094 or A3921095. NOTE: endoscopic subscores based on central reading were used to determine eligibility.

Study Treatment: Tofacitinib was self-administered at 5 or 10 mg BID. Details of the study intervention used are shown in Table S2.

CLINICAL STUDY REPORT SYNOPSIS

Table S2. Study Intervention Description

Study Intervention Description	Vendor Lot Number	Pfizer Lot Number	Strength/Potency	Dosage Form
CP-690,550-10 5 mg Immediate Release Filmcoated Tablet	9634233017	11-009938	5 mg	Tablet
CP-690,550-10 5 mg, Film-Coated Tablet, Commercial Image	H90273	14-000544	5 mg	Tablet
CP-690,550-10 5 mg, Film-Coated Tablet, Commercial Image	L73080	15-005244	5 mg	Tablet
CP-690,550-10 5 mg, Film-Coated Tablet, Commercial Image	H15758	13-110032	5 mg	Tablet
CP-690,550-10 5 mg, Film-Coated Tablet, Commercial Image	H000005938/ H14621	13-108395	5 mg	Tablet
CP-690,550-10 5 mg Immediate Release Filmcoated Tablet	9634233025	12-005920	5 mg	Tablet
CP-690,550-10 5 mg, Film-Coated Tablet, Commercial Image	R36837	16-003831	5 mg	Tablet
CP-690,550-10 5 mg, Film-Coated Tablet, Commercial Image	W20887	17-00321	5 mg	Tablet
CP-690,550-10 5 mg, Film-Coated Tablet, Commercial Image	H90274	14-000545	5 mg	Tablet

Primary Efficacy Evaluations: As this was an open-label extension study, there were no primary efficacy endpoints. The primary analysis was safety.

CLINICAL STUDY REPORT SYNOPSIS

Secondary Efficacy Evaluations:

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

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

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

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

- The proportion of participants with total score in IBDQ ≥170 through Month 84.

Exploratory Efficacy Evaluations:

- PMS and change from baseline (of Study A3921139) over time.

- Total Mayo score and change from baseline (of Study A3921139) at Month 2, Month 12, Month 24, and Month 36.

- The absolute scores and change from baseline (of Study A3921139) in total IBDQ score and domains (Bowel Symptoms, Systemic Symptoms, Emotional Function, and Social Function) over time.

- The absolute scores and change from baseline (of Study A3921139) in SF-36, version 2, acute (physical and mental component summary scores, and 8 domain scores) over time through Month 33.

- The scores and change from baseline (of Study A3921139) in EQ-5D/VAS over time.

- The scores and change from baseline (of Study A3921139) in the WPAI questionnaire domains (Absenteeism, Presenteeism, Work Productivity Loss, and Activity Impairment) over time through Month 33.

- The proportion of participants who utilize the healthcare services and the frequency of utilization of such services specified in the UC-HCRQ-All over time.

- The number and length of UC-related hospitalizations.

CLINICAL STUDY REPORT SYNOPSIS

- The proportion of participants requiring colectomy for UC or UC-related complications.
- Summary of absolute counts and change from baseline in the following lymphocyte subsets: CD4+ T cells, CD8+ T cells, B cells, and natural killer (NK) cells (United Kingdom [UK] only).

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, ECGs, clinical laboratory tests, incidence of serious infections, summary of adjudicated safety events (eg, cardiovascular, malignancy, opportunistic infections), and the spontaneous reporting of AEs, in all participants who received at least 1 dose of study drug.

Statistical Methods:

Efficacy Endpoints

Efficacy endpoints were based upon the Mayo score and partial Mayo score. All efficacy endpoints were considered as secondary or exploratory. Descriptive summary statistics were reported at scheduled visits in the full analysis set (FAS), and in subpopulations of the FAS: maintenance remission, maintenance treatment failures, other maintenance completers, and induction non-responders subpopulations. However, the endpoints of proportion of participants with dose increase from tofacitinib 5 mg BID to 10 mg BID were summarized for the maintenance remission subpopulation only.

For FAS or each subpopulation, the data were summarized as in Table S3.

Table S3. Statistical Summaries for Efficacy Endpoints

Efficacy Analysis Population/Subpopulation	Treatment group (the default is the assigned dose for initial assignment in A3921139)	By group
FAS	Overall Tofacitinib 5 mg BID Tofacitinib 10 mg BID	Overall
Maintenance Remission subpopulation	Tofacitinib 5 mg BID	Overall By maintenance treatment (4 groups: 10 mg, 5 mg, placebo, 5mg+10mg)
Maintenance Treatment Failure subpopulation	Tofacitinib 10 mg BID	Overall By dose combination received in induction and maintenance (6 groups) and a 7th group of

CLINICAL STUDY REPORT SYNOPSIS

Table S3. Statistical Summaries for Efficacy Endpoints

Efficacy Analysis Population/Subpopulation	Treatment group (the default is the assigned dose for initial assignment in A3921139)	By group
		Tofacitinib 10 mg in induction and Tofacitinib 5 mg + placebo in maintenance
Other Maintenance Completers subpopulation	Tofacitinib 10 mg BID	Overall By maintenance treatment (4 groups: tofacitinib 10 mg, Tofacitinib 5 mg, placebo, Tofacitinib 10 mg and 5 mg combined)
Induction Non-responder subpopulation	Tofacitinib 10 mg BID	Overall By Induction treatment (Tofacitinib 10 mg, Placebo)

In addition, subgroup summaries of prior tumor necrosis factor (TNF) failure and prior TNF exposure were provided for the 4 subpopulations of the FAS.

PRO Endpoints

Descriptive summary statistics were reported at scheduled visits for the FAS, and for the four subpopulations of the FAS (maintenance remission, maintenance failure, other maintenance completers, and induction non-responders) using the same methods as for the efficacy endpoints for IBDQ, EQ-5D/VAS, and SF-36.

Descriptive summary statistics were reported in the FAS for the WPAI-UC; the UC-HCRU was based on observed-case data only.

Frequencies and percentages of missing data for the patient reported outcome (PRO) endpoints, and the reasons for the missing data, were summarized by treatment group based on the FAS.

Safety Endpoints

The safety data were summarized in accordance with Pfizer data standards. Missing data were not imputed.

RESULTS

Participant Disposition and Demography: participant disposition is presented in Figure S2.

A total of 944 participants were enrolled into the study and included in the FAS; 175 were assigned to the tofacitinib 5 mg BID group and 769 to the tofacitinib 10 mg BID group. Participants were allocated into treatment groups according to randomization via the interactive voice recording system (IVRS) and baseline stratification factors. The safety analysis set (SAS) consists of all randomized participants who received at least one dose of

CLINICAL STUDY REPORT SYNOPSIS

study intervention. The laboratory data consists of all participants that had data collected at both baseline and at least one of the post-baseline visits.

Participants eligible for this study were those who completed or demonstrated treatment failure in the maintenance Study A3921096, or who were non-responders after completing Induction Studies A3921094 or A3921095.

Of the 944 participants in the FAS, 84 (48.0%) discontinued from the tofacitinib 5 mg BID group and 665 (86.5%) discontinued from the tofacitinib 10 mg BID group.

- The most frequent reasons for discontinuation in the FAS were insufficient clinical response (20 [11.4%] in the tofacitinib 5 mg BID group and 326 [42.4%] in the tofacitinib 10 mg group) and no longer willing to participate in the study (24 [13.7%] and 79 [10.3%], respectively). Insufficient clinical response included those participants who discontinued due to an AE of worsening UC.

For the induction non-responder subpopulation of the FAS (n=429), the most frequent reason for discontinuation was insufficient clinical response (214, 49.9%). Participants that were induction non-responders were mandated to discontinue from the study if they continued to show no clinical response at the Month 2 study visit.

Discontinuations from the study due to other reasons were as follows:

- Enrolled to Study A3921288: 2 participants (1.1%) in the tofacitinib 5 mg BID group and 138 participants (17.9%) in the tofacitinib 10 mg BID group.

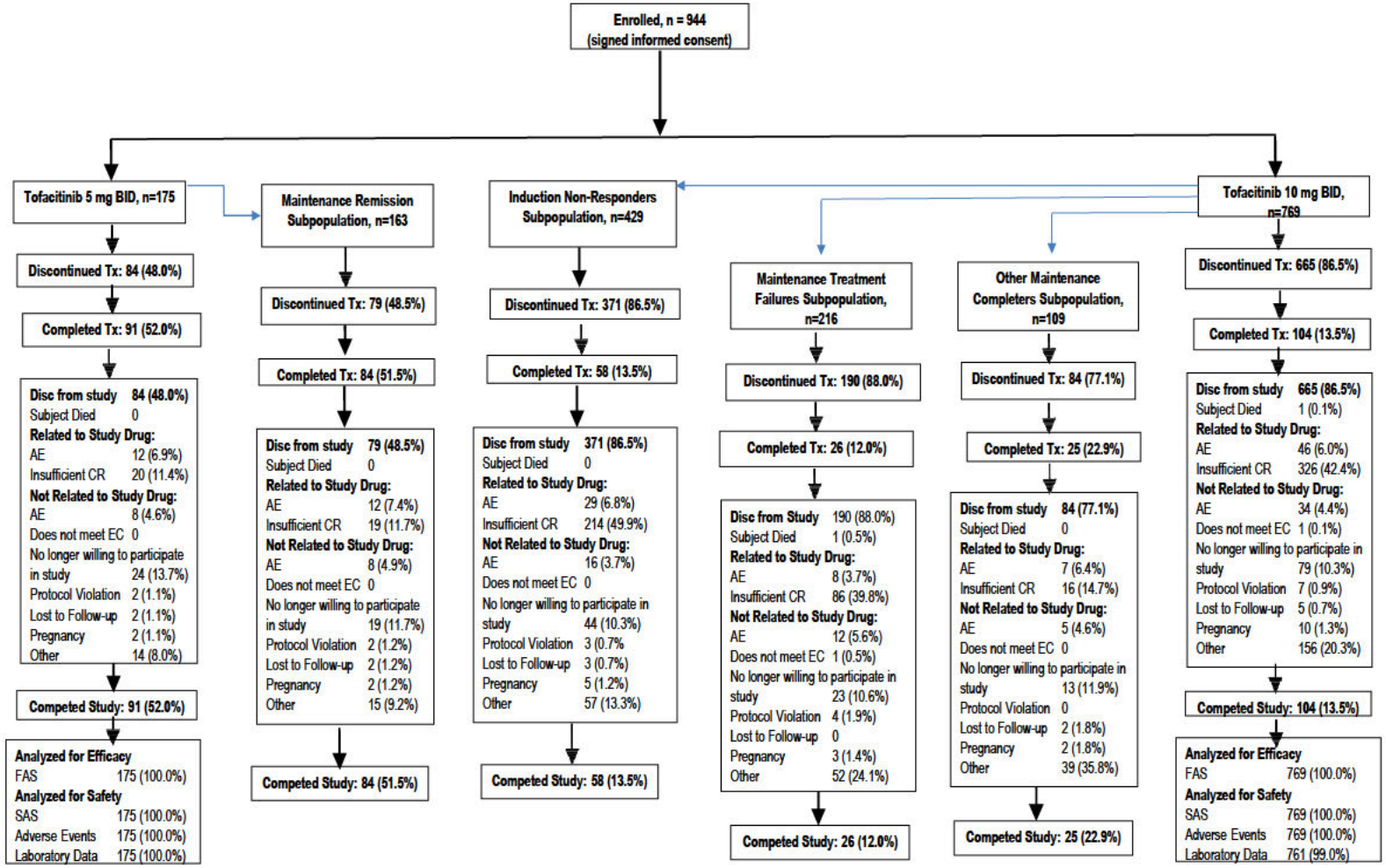
- Enrolled to post-marketing surveillance (participants in Japan only): 8 participants (4.6%) and 4 participants (0.5%) respectively.

- Regulatory approval (participants in Japan only): 1 participant (0.6%) and 2 participants (0.3%), respectively.

- All other reasons for withdrawal: 3 participants (1.7%) and 12 participants (1.6%), respectively.

CLINICAL STUDY REPORT SYNOPSIS

Figure S2. Participant Disposition



CLINICAL STUDY REPORT SYNOPSIS

Efficacy Results:

Primary Endpoint Result

There were no primary efficacy endpoints in this study.

Secondary Endpoint Results

- In the maintenance remission subpopulation, continued treatment with open-label tofacitinib 5 mg BID in participants in remission after completing the 52-week maintenance Study A3921096 with either tofacitinib 10 mg BID or 5 mg BID generally showed persistency of tofacitinib efficacy through Month 36.

- In the maintenance treatment failures subpopulation, treatment with open-label tofacitinib 10 mg BID recaptures efficacy in participants who previously received tofacitinib 10 mg BID from induction Studies A3921094 or A3921095 and subsequently had treatment failure on tofacitinib 5 mg BID or placebo in the A3921096 maintenance Study. In participants who previously received tofacitinib 10 mg BID in the induction Studies and either tofacitinib 5 mg BID or placebo in the maintenance Study (Induction 10 mg/Main 5 mg and Induction 10 mg/Main Placebo), treatment with tofacitinib 10 mg BID resulted in a notable increase in the proportion of participants achieving a clinical response at Month 2.

- In the other maintenance completers subpopulation, persistence of tofacitinib efficacy s measured by clinical response (and improvement of efficacy as measured by remission, clinical remission, and mucosal healing) was observed with continued open-label tofacitinib 10 mg BID treatment in completed participants from the A3921096 maintenance Study who were neither in remission nor fulfilling the definition of treatment failure.

- In the induction non-responders subpopulation, continued treatment with open-label tofacitinib 10 mg BID for an additional 2 months resulted in increases from baseline for all binary efficacy endpoints at Month 2 in participants who failed to achieve a clinical response after the initial 8 weeks of tofacitinib 10 mg BID in the induction Studies A3921094 and A3921095; the increase from baseline was most notable for the proportion of participants who had a clinical response.

- The binary efficacy endpoint of PMS remission over time was maintained through Month 36 for the maintenance remission subpopulation. This endpoint increased through Month 6, then slightly increased or maintained through the remainder of the study for the other maintenance completers subpopulation; and increased through Month 9, then slightly increased or generally maintained for the maintenance treatment failures and induction non-responder subpopulations.

CLINICAL STUDY REPORT SYNOPSIS

- The exploratory efficacy endpoints of change in PMS over time and change in Mayo score over time both maintained over the course of the study for the maintenance remission and other maintenance completers subpopulations, and decreased slightly over the course of the study for the maintenance treatment failures and induction non-responder subpopulations.

Consistent findings were observed for the patient reported outcome efficacy endpoints for the subpopulations of the FAS as follows:

- In the maintenance remission subpopulation, continued treatment with open-label tofacitinib 5 mg BID in participants in remission after completing the 52-week maintenance Study A3921096 with either tofacitinib 10 mg BID or 5 mg BID showed participants maintained HRQoL through Month 48, as demonstrated by the following PRO endpoints: IBDQ scores over time and change from baseline, and EQ-5D/VAS scores. Participants also maintained HRQoL through Month 33, as demonstrated by SF-36 scores.

- In the other maintenance completers subpopulation, treatment with open-label tofacitinib 10 mg BID in completed participants from the A3921096 maintenance Study who were neither in remission nor fulfilling the definition of treatment failure showed participants maintained HRQoL through Month 48, as demonstrated by the following endpoints: IBDQ scores over time and change from baseline, and EQ-5D/VAS scores. Participants also maintained HRQoL through Month 33, as demonstrated by SF-36 scores.

- In the maintenance treatment failures subpopulation, treatment with open-label tofacitinib 10 mg BID in participants with treatment failure on tofacitinib 5 mg BID or placebo in the A3921096 maintenance Study who received tofacitinib 10 mg BID from induction Studies A3921094 or A3921095 showed participants experienced an improvement HRQoL through Month 48, as demonstrated by increases in the following endpoints: IBDQ scores over time and change from baseline, and EQ-5D/VAS scores. Participants also maintained HRQoL through Month 33, as demonstrated by SF-36 scores.

- In the induction non-responders subpopulation, continued treatment with open-label tofacitinib 10 mg BID for an additional 2 months in participants failing to achieve a clinical response after the initial 8 weeks of tofacitinib 10 mg BID in the induction Studies A3921094 and A3921095 showed participants experienced an improvement in HRQoL through Month 48, as demonstrated by increases in the following endpoints: IBDQ scores over time and change from baseline, and EQ-5D/VAS scores. Participants also demonstrated improvement in HRQoL as demonstrated by SF-36 scores through Month 33.

The observations for the IBDQ and SF-36 domains over time also support the efficacy per the PRO results described above for all four subpopulations.

CLINICAL STUDY REPORT SYNOPSIS

WPAI-UC scores were not analyzed for the subpopulations of the FAS, but results of this endpoint in the tofacitinib 5 mg BID and tofacitinib 10 mg BID treatment groups support the overall conclusions regarding HRQoL, which was maintained (<7% change from baseline for all 4 domains) in the 5 mg BID group and improved (>11% decrease from baseline in the Absenteeism, Work Productivity Loss, and Non-Work Productivity Impairment domains) in the 10 mg BID group.

The number of UC-related hospitalizations were both higher in the tofacitinib 10 mg BID group. No participants in the tofacitinib 5 mg BID group, and only a small percentage of participants in the tofacitinib 10 mg BID group, required UC-related surgery or colectomy.

Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, Immunogenicity and/or Other Results: Not applicable.

Safety Results:

- The proportion of participants who experienced all-causality treatment-emergent adverse events (TEAEs) was similar between the treatment groups (Table S4).
- The majority of reported all-causality TEAEs mild to moderate in both treatment groups, and the proportion of participants with severe TEAEs was similar between treatment groups.
- The proportion of participants with serious adverse events (SAEs) in each treatment group were similar.
- The proportion of participants who discontinued the study due to AEs in the tofacitinib was similar between treatment groups.
- The proportion of participants with temporary discontinuations was similar between treatment groups.
- The proportions of participants with dosage of lipid-lowering agents increased during the study were similar between the two treatment groups.
- There were no meaningful changes in vital signs, ECG, or physical examination results.

CLINICAL STUDY REPORT SYNOPSIS

Table S4. Summary of Treatment-Emergent Adverse Events, All Causalities

	Tofacitinib 5 mg BID		Tofacitinib 10 mg BID		Total	
Number (%) of Subjects:	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Subjects evaluable for adverse events	175		769		944	
Number of adverse events	951		3461		4412	
Subjects with adverse events	154	(88.0)	626	(81.4)	780	(82.6)
Subjects with serious adverse events	39	(22.3)	147	(19.1)	186	(19.7)
Subjects with severe adverse events	25	(14.3)	104	(13.5)	129	(13.7)
Subjects discontinued due to adverse events	30	(17.1)	166	(21.6)	196	(20.8)
Subjects with dose reduced or temporary discontinuation due to adverse events	16	(9.1)	65	(8.5)	81	(8.6)

Includes events from study database, even those that occur after last dose of study drug.
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.
Severity counts are based on the maximum severity of events.
Per Adverse Event Case Report Form (CRF), the subjects that permanently discontinued the study drug due to Adverse Event are summarized.
Medical Dictionary for Regulatory Activities (MedDRA, v23.0) coding dictionary applied.
PFIZER CONFIDENTIAL Source Data: Table 16.2.7 Date of Reporting Dataset Creation: 26AUG2020 Date of Table Generation: 17NOV2020 (17:43)
Path: /Volumes/app/cdars/prod/prjA392/ibd_uc/A3921139_finalcsr_intext/ae411s rtf

- The mean duration of treatment was approximately 1305 days for the tofacitinib 5 mg BID group and approximately 823 days for the tofacitinib 10 mg BID group. The median (range) of duration of treatment was 1529 (36-2422) and 668 (1-2561) days, respectively.
- Most AEs were mild to moderate in severity.
- The most frequent AE leading to discontinuation was colitis ulcerative (worsening of UC).
- Six (6) participant deaths occurred during the study, all in the tofacitinib 10 mg BID group. All deaths occurred in the setting of an underlying malignancy.
- The most frequent SAEs were Colitis ulcerative and Condition aggravated (worsening of UC).
- Proportions of infection TEAEs were similar in both treatment groups. The most frequent infection AE in both treatment groups was Nasopharyngitis.

CLINICAL STUDY REPORT SYNOPSIS

- Proportions of serious infection AEs and treatment-emergent herpes zoster AEs were similar in both treatment groups.

- Proportions of adjudicated OIs, cardiovascular/neurovascular events, and GI perforations (all cases) were similar between the two treatment groups. Proportions of MACE and malignancy events were slightly higher in the tofacitinib 5 mg BID group, while the proportion of TE events was slightly higher in the tofacitinib 10 mg BID group. Regarding adjudicated hepatic injury events, proportions of mild events were similar between the two treatment groups, while proportions of moderate events were slightly higher in the tofacitinib 5 mg BID group and proportions of severe events were slightly higher in the tofacitinib 10 mg BID group. There were no confirmed Hy's Law cases.

- Decreases from baseline in ALC were observed over time in both treatment groups.

- There were minimal changes from baseline between treatment groups in laboratory parameters for ANC, CK, serum creatinine, creatinine clearance, hemoglobin, HDL-C, LDL-C, LFTs, total cholesterol, and triglycerides.

- The proportions of participants with dosage of lipid-lowering agents increased during the study were similar between the two treatment groups.

- There were no meaningful changes in vital signs, ECG, or physical examination results.

Conclusion(s):

Efficacy

Consistent findings were observed for the secondary efficacy endpoints – remission, clinical remission, mucosal healing, and clinical response. Persistence of tofacitinib efficacy was observed for these endpoints in the maintenance remission and other maintenance completers subpopulations. Recapture of tofacitinib efficacy was observed in the maintenance treatment failures and induction non-responders subpopulations.

Consistent findings were observed for the patient reported outcome efficacy endpoints. Participants in the maintenance remission and other maintenance completers subpopulations maintained HRQoL, while those participants in the maintenance treatment failures and induction non-responders subpopulations experienced an improvement in HRQoL.

CLINICAL STUDY REPORT SYNOPSIS

Safety

This study demonstrated that tofacitinib administered as 5 mg BID or 10 mg BID had an acceptable safety profile and was well tolerated during long-term therapy for UC. No new or unexpected safety findings were observed.

- Most AEs were mild to moderate in severity. The proportions of participants with AEs, SAEs, and serious infection AEs were similar between the tofacitinib 5 mg BID and tofacitinib 10 mg BID dose groups.

- Proportions of adjudicated OIs, cardiovascular/neurovascular events, and GI perforations (all cases) were similar between the two treatment groups. There were slight differences between the two treatment groups regarding MACE, as well as TE, malignancy, and hepatic injury events.

- Six deaths were reported in this study, all in the tofacitinib 10 mg BID group. All deaths occurred in the setting of an underlying malignancy.