All subjects reporting an unexplained skin rash should be referred to a local dermatologist according to local guidelines for formal comprehensive dermatologic evaluation. A 4 mm punch biopsy should be taken and sent to the local laboratory for histological investigation of the rash in order to gain insight into potential etiology of the rash. If the rash is present on the face or other cosmetically exposed area, biopsy can be at the discretion of the dermatologist.

All de-identified dermatologic consultation reports, biopsy results, culture results, photographs, and any additional relevant test results will be forwarded to Pfizer/designee for review within 30 days of receipt by the PI.

An independent dermatologist contracted by Pfizer will review all relevant data and summarize the data at the end of the study.

7.2.12. Audiogram

All subjects will have an audiogram at times specified in the Schedule of Activities. Audiograms may be performed within a ±2 week window relative to the study visit. When possible, the subject should have the audiogram performed at the same evaluation center during the study.

Audiogram testing at screening must be completed and results available by the baseline visit (Week 0). Audiogram testing at each time specified in the Schedule of Activities must be completed and results available by the next scheduled visit. For subjects that terminate early from the study, if possible, efforts must be made to complete the audiology testing and obtain the results.

If there is a clinically meaningful, treatment related decline in hearing from baseline, the subject will be followed off treatment with appropriate testing at regular intervals, until hearing returns to baseline or is determined to be clinically stable.

The information from the audiogram will be entered into the data collection tool.

Any de-identified audiogram results/reports and any additional relevant test results (if applicable) may be requested to be forwarded to Pfizer (and/or designee) at any time during the study.

Audiogram results may be reviewed by an external audiologist.

7.2.13. Electrocardiogram

Twelve (12)-lead ECGs should be collected at times specified in the Schedule of Activities.

ECGs should be performed before laboratory blood collection and endoscopic procedure.

Study Procedure	**Screening**	**Baseline**	**Induction Period**			**Chronic Dosing Period**					**Follow-up**
Visit Identifier[a]	**Week -1 to -6**	**Week 0**	**Week 2**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 32/ Early Termination**[b]	**Week 36**
Study Day/Visit Window	**Day -42 -0**	**1**	**15±2**	**29±2**	**57±2**	**85±4**	**113±4**	**141±4**	**169±4**	**225±4**	**253±7**
Serum β-HCG[o]	X										
Urine β-HCG[o]		X	X	X	X	X	X	X	X	X	X
Tuberculosis screening[p]	X										
hsCRP		X		X	X		X		X	X	
[redacted]											
Fecal calprotectin[q]	X			X	X		X		X	X	
[redacted]											
Contraception check	X	→	→	→	→	→	→	→	→	→	X
Eligibility assessment	X	X									
Randomization		X			X						
Study treatment											
Investigational product dispensing		X	X	X	X	X	X	X	X		
Investigational product accountability			X	X	X	X	X	X	X	X	
Investigational product dosing (at site)		X	X	X	X	X	X	X	X	X	
Assessments											
Endoscopy (flexible sigmoidoscopy or colonoscopy) and intestinal tissue biopsies[s]	X[t]				X[u]					X[u]	
Bowel movement diary, [redacted] instruction/review data[v]	X	X	X	X	X	X	X	X	X	X	
Mayo score		X[w]			X					X	
Partial Mayo score		X	X	X	X	X	X	X	X	X	
[redacted]											
IBDQ		X		X	X					X	
SF-36 v.2, acute		X		X	X					X	

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CCI [redacted]

1.4.1.1.2. Study B7981003

B7981003 was a Phase 1, open-label, single-dose, 3-way crossover study to evaluate the bioavailability (BA) of a solid dose formulation of PF-06651600 relative to an oral solution formulation under fasting conditions and the effect of a high fat meal on the BA of the solid dosage formulation of PF-06651600 in healthy subjects. A total of 14 subjects were randomized to study treatment and treated with 50 mg PF-06651600 solution/tablets under fasted and fed conditions completed the study.

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1.4.1.1.3. Study B7981008

Study B7981008 is a completed Phase 1, randomized, double-blind, third-party open, placebo-controlled study to evaluate the safety, tolerability, PK and pharmacodynamics after multiple oral doses of PF-06651600 in healthy Japanese adult subjects. Four subjects received oral PF-06651600 200 mg QD for 10 days, and 2 subjects received the matched placebo

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1.4.1.1.4. Study B7981006

B7981006 was a Phase 2a, randomized, double-blind, parallel group, placebo-controlled, multi-center study to assess the efficacy and safety profile of PF-06651600 in seropositive subjects with moderate to severe active Rheumatoid Arthritis (RA) with an inadequate response to Methotrexate (MTX). A total of 70 subjects were randomized to study treatment, 28 subjects received placebo and 42 subjects received PF-06651600.

1.4.1.1.4.1. Analysis of Adverse Events

The majority of all causality TEAEs (28 out of 36) were mild in severity. Overall, the most frequently reported TEAEs were:

- Influenza (3 [4.3%] subjects in total: 3 [7.1%] subjects in the PF-06651600 group and 0 subjects in the placebo group);
- Pruritus (3 [4.3%] subjects in total: 2 [4.8%] subjects in the PF-06651600 group and 1 [3.6%] subject in the placebo group);

- Lymphopenia (3 [4.3%] subjects in total: 3 [7.1%] subjects in the PF-06651600 group and 0 subjects in the placebo group);

- Headache (3 [4.3%] subjects in total: 0 subjects in the PF-06651600 group and 3 [10.7%] subjects in the placebo group).

The majority of all treatment-related TEAEs (9 out of 11) were mild in severity. Overall, the most frequently reported treatment-related TEAE was Lymphopenia (2 [2.9%] subjects in total: 2 [4.8%] subjects in the PF-06651600 group and 0 subjects in the placebo group).

1.4.1.1.4.2. Permanent Discontinuations due to Adverse Events

A total of 3 subjects (7.1%) in the PF-06651600 group and 0 subjects in the placebo group permanently discontinued due to TEAEs. One (1) subject discontinued due to suicidal ideation, 1 subject discontinued due to lymphopenia, and the third subject discontinued due to hepatotoxicity.

1.4.1.1.4.3. Deaths

There were no deaths among subjects who participated in Study B7981006.

1.4.1.1.4.4. Serious Adverse Events

There were no SAE in subjects who participated in study B7981006.

1.4.1.1.4.5. Analysis and Discussion of Deaths, Other Serious Adverse Events and Other Significant Adverse Events

No deaths occurred in this study. No SAEs were reported in this study. A total of 3 subjects experienced TEAEs that led to permanent discontinuation due to TEAEs during the study. No clinically meaningful differences between the PF-06651600 treatment group and placebo were observed with regard to AEs of special interest.

1.4.1.1.4.6. Clinical Laboratory Evaluation

Without regard to baseline abnormality, 70 (100%) of the 70 treated subjects experienced laboratory abnormalities. Overall, the most frequently occurring laboratory abnormality was erythrocyte sedimentation rate, reported by 68 (97.1%) subjects.

Three (3) subjects (7.1%) in the PF-06651600 treatment group met the discontinuation criterion of hemoglobin <8 g/dL. One (1) subject (2.4%) in the PF-06651600 treatment group met the discontinuation criterion of lymphocytes (absolute) $<0.5 \times 10^3/mm^3$.

By the Week 8 time point (as early as 2 weeks), in the PF-06651600 group, there were decreases in the median platelet counts (25% change from baseline), lymphocyte counts (21% change from baseline), neutrophil counts (24% change from baseline), and hemoglobin (3% change from baseline). None of these were deemed to be clinically relevant by the investigator and values returned to near baseline by the 12-week follow-up visit.

1.4.1.1.5. Study B7981007

B7981007 is a Phase 2a, randomized, double-blind, placebo-controlled, parallel group, multicenter study to examine the efficacy of PF-06651600 and PF-06700841 in subjects with moderate to severe active Crohn's disease (CD). The entire study consists of: 1) a screening period of up to 6-weeks, 2) a 12-week induction period, 3) a 52-week open label extension (OLE) period, and 4) a 4-week follow up period. Approximately 250 subjects in total will be randomized into the study.

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placebo-controlled period that includes a 4-week loading phase and a 20-week maintenance phase. The study will enroll a total of approximately 330 subjects. The study will be conducted globally at approximately 85 sites.

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1.4.1.1.8. Study B7981032

Study B7981032 is an ongoing 2-year Phase 3 open-label, multicenter study to evaluate the safety and efficacy of PF-06651600 in adult and adolescent subjects ≥12 years of age with alopecia areata. The study will have a maximum duration of approximately 26 months. This includes up to a 5-week screening period, a 24-month open-label treatment period, and a 4-week follow up period. Study B7981032 includes eligible subjects who are given the opportunity to enroll from the index studies B7931005 and B7981015, as well as de novo subjects (ie, those who have not previously received study intervention in Study B7931005 or B7981015).

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discontinuations were due to AEs. There were no discontinuations due to AEs in the SAD or BA cohorts.

1.4.2.1.1.2. Common Adverse Events in Study B7931001

In the SAD cohort, the most commonly reported AEs by System Organ Classes (SOCs) were Investigations, reported by 2 participants, and Nervous System Disorders, reported by 3 participants. The most frequently reported AEs were blood creatinine increased and headache, each of which was experienced by 2 participants. All TEAEs were mild in severity.

In the MAD cohort, the most commonly reported AEs by SOCs were Investigations, reported by 13 participants, and Nervous System Disorders, reported by 3 participants. The most frequently reported AEs were blood creatinine increased, experienced by 11 participants, and neutrophil count decreased, experienced by 3 participants. All TEAEs were mild or moderate in severity.

In the psoriasis cohort, the most commonly reported AEs by SOCs were gastrointestinal disorders, reported by 7 participants, investigations, reported by 15 participants, and nervous system disorders, reported by 4 participants. The most frequently reported AEs were constipation, experienced by 6 participants and blood creatinine increased, experienced by 14 participants. All TEAEs were mild in severity.

In the BA cohort, the most commonly reported AEs by SOCs were gastrointestinal disorders, injury, poisoning, and procedural complications, and nervous system disorders, each reported by 1 participant. The most frequently reported AEs were nausea, contusion, and headache, each of which was experienced by 1 participant. All TEAEs were mild in severity.

1.4.2.1.1.4. Clinical Laboratory Evaluations

In the SAD and MAD cohorts, 40 participants (7 in the placebo; 4 each in the 1 and 3 mg; 6 each in the 10, 30 and 100 mg; and 7 in the 200 mg treatment groups) in the SAD group and 32 participants (6 in the placebo; 5 each in the 10 and 50 mg; 4 in the 30 mg; and 6 each in the 100 and 175 mg treatment groups) in the MAD group had laboratory abnormalities.

The most frequently reported laboratory abnormalities were elevations of low-density lipoprotein (LDL) >1.2 × upper limits of normal (ULN), 26 participants during SAD and 22 participants during MAD.

Serum creatinine ≥1.5 × ULN occurred in 1 participant in the PF-06700841 100 mg group during SAD, 4 participants (1, 2, and 1 participants in the PF-06700841 10 mg QD, 100 mg QD, and 50 mg BID groups, respectively) in the MAD period. Participants in the MAD and psoriasis cohorts that had increased SCr ≥0.3 mg/dL did demonstrate a change in S Cystatin-C based estimated glomerular filtration rate (eGFR).

Abnormally low neutrophil counts were observed in 3 participants (1 participant each in the 1 mg, 200 mg, and placebo groups) in the SAD cohort and 14 participants in the MAD cohort (1, 3, 3, 5, and 2 participants in the 10 mg QD, 100 mg QD, 50 mg BID, 175 mg QD, and placebo QD groups, respectively). There were no clinically meaningful changes from baseline in other hematology parameters during SAD and MAD.

In the SAD group, there was a slight increase in alanine amino transferase (ALT) in the 30 mg group on Day 8. Overall there were no clinically significant abnormalities in aspartate amino transferase (AST), ALT and total bilirubin during SAD and MAD.

In the psoriasis cohort, 27 participants (7 in the Placebo, 13 in the 30 mg and 7 in the 100 mg PF-06700841 treatment groups) had laboratory abnormalities.

The most frequently reported laboratory abnormalities during the psoriasis period were LDL >1.2 × ULN (16 participants: 5 in Placebo, 7 in the 30 mg and 4 in the 100 mg PF-06700841 treatment groups) and uric acid >1.2 × ULN (10 participants: 4 in Placebo, 4 in the 30 mg and 2 in the 100 mg PF-06700841 treatment groups).

In the psoriasis group, 6 participants (1 and 5 participants in the 30 mg QD and 100 mg QD groups, respectively) had neutrophil counts meeting the criteria for abnormally low levels. Overall there were no clinical meaningful changes from baseline in other hematology parameters during psoriasis period.

In the BA cohort, there were 9 participants that had laboratory abnormalities. The most frequently reported laboratory abnormalities during the BA period were total neutrophils <0.8 × LLN (4 participants) and lymphocytes <0.8 × LLN (3 participants). There were no other clinically significant abnormalities during BA period.

There were no participants with clinically significant laboratory abnormalities during the study.

1.4.2.1.1.5. Vital Signs, Physical Findings, Electrocardiogram (ECG) and Other Observations Related to Safety

There were no clinically meaningful findings in vital signs, and ECG in any of the 4 groups.

1.4.2.1.2. Study B7931009

This study was a Phase 1 randomized, double-blind, third-party open, placebo-controlled, multiple dose study in healthy Japanese adult participants.

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1.4.2.1.8. Study B7931004

This was a Phase 2a, randomized, double-blind, placebo-controlled, parallel group, multicenter study in adult participants with moderate to severe plaque psoriasis. Following a screening period (up to 6 weeks), the study consisted of a 4-week induction treatment period with double-blind daily treatment (PF-06700841 30 mg QD, 60 mg QD or matched placebo). At the end of Week 4, all participants switched to their predefined double-blind maintenance treatment regimen (PF-06700841 10 mg QD, 30 mg QD, 100 mg once weekly (QW) or matched placebo) for Week 5 through Week 12. Subsequent to the induction and maintenance periods, the study had an 8-week safety follow up period.

1.4.2.1.8.1. Disposition and Demographic Characteristics of Phase 2 Study B7931004

A total of 212 participants were randomized and received at least 1 dose of study treatment. All treated participants were analyzed for efficacy and safety. Participants randomized to treatment received either PF-06700841 60 mg QD or PF-06700841 30 mg QD for the first 4 weeks of treatment (induction) after which those on 60 mg QD were switched to either 30 mg QD, 10 mg QD, 100 mg QW or placebo in the maintenance period. Those who received 30 mg QD during the first 4 weeks of induction were switched to either 30 mg, 10 mg QD, or 100 mg QW in the maintenance period.

Overall, 164 of 212 (77.4%) participants completed the study. The majority of the treated participants were male (69.8%) and white (89.2%). The mean age was 46.0 years (median: 48.0, range: 18 to 75). The mean weight was 94.7 kg (median: 91.6, range: 45.1 to 204.3), and mean body mass index (BMI) was 31.9 kg/m^2 (median: 30.9, range: 18.9 to 64.7). The mean duration of psoriasis since first diagnosis was 17.9 years, with a mean baseline PASI score of 20.8, which was comparable for participants in all treatment groups.

1.4.2.1.8.2. Treatment-Emergent Adverse Events (All-causality and Treatment Related) in Phase 2 Study B7931004

The proportion of participants with all-causality TEAEs was comparable across all treatment groups but numerically higher in the active treatment groups (64.0% to 76.7%) than the placebo group (56.5%). The majority of participants in all the treatment groups experienced mild or moderate all-causality TEAEs, and only 11 (5.2%) out of 212 participants experienced severe all-causality TEAEs. Overall, there were no dose dependent increases in

the all-causality TEAEs. The most reported non-serious TEAEs were in the SOC of Infections and Infestations with 25.9% of participants. There were more participants experiencing mild to moderate infections and infestations, such as nasopharyngitis, upper respiratory tract infection, bronchitis, sinusitis, or urinary tract infection in the active treatment groups relative to the placebo group. Other non-serious TEAEs in SOCs occurring >5% of participants were Gastrointestinal Disorders, Musculoskeletal and Connective Tissue Disorders, Skin and Subcutaneous Tissue Disorders, and Nervous System Disorders. Incidence occurring in other SOCs except Infections and Infestations was comparable between all treatment groups.

A total of 13 participants discontinued from the study due to TEAEs.

One participant in the 30 to 10 mg group was found to have a positive urine human chorionic gonadotropin test at the Week 6 (Day 42) visit after which confirmation with serum pregnancy test led to permanent discontinuation from study on Day 53. On Day 165, an obstetrical ultrasound demonstrated a right-sided cleft lip with a gap of 10 millimeters in the fetus, with no definite cleft palate. The Day 176 obstetrical ultrasound confirmed presence of cleft lip in the fetus, with all other findings appearing within normal limits. This event of fetal cleft lip was unexpected in the single reference safety document for the study drug and was assessed as related per sponsor.

1.4.2.1.8.3. Serious Adverse Events in Phase 2 Study B7931004

Five (5) participants experienced a total of 6 SAEs during the study; 3 of the SAEs were considered to be related to study drug by the investigator, of which 2 SAEs (pneumonia and sepsis) reported by 1 participant in the 60 mg QD to 100 mg QW group were considered not related to study drug by the sponsor. This participant had 1 dose of PF-06700841 60 mg on Day 1 and had 2 SAEs of pneumonia and sepsis on Day 2 before dosing and was permanently discontinued from study due to the SAE of pneumonia.

One post-therapy death occurred due to gunshot wound after the participant was discontinued from the study due to noncompliance with study drug, which was considered unrelated to the study treatment by the investigator.

1.4.2.1.8.4. Laboratory Evaluation, Vital Signs, and ECG in Phase 2 Study B7931004

There were no clinically meaningful dose dependent neutropenia, lymphopenia, thrombocytopenia, and anemia among the active treatment groups, except for 1 SAE of anemia reported by 1 participant in the 60 to 10 mg QD group.

No participants met the laboratory test discontinuation criteria (laboratory test abnormalities confirmed through re-testing within 48 hours) during study treatment. There was no potential Hy's Law case reported during the study.

1.4.2.1.8.4.1. Hematology

During the induction period, there was a dose-dependent decrease of in reticulocyte count in the active treatment groups compared to the placebo group. During the 8-week maintenance period, the reticulocytes levels appeared to rebound for all the active treatment groups, except for the 30 to 10 mg QD group. There were no clinically meaningful changes from baseline observed in hemoglobin across treatment groups during the study, except for 1 SAE of anemia reported by 1 participant in the 60 to 10 mg QD group.

During the induction period, dose-dependent decreases from baseline in neutrophils were observed for the 60 mg QD induction dose group, compared to the 30 mg QD induction dose group and the placebo group at Week 4. During the maintenance period at Week 12, the neutrophils levels for all the treatment groups were similar to placebo.

During the induction period and maintenance periods, lymphocyte levels in all active treatment groups were similar to placebo at Week 4 and Week 12. A total of 6 participants (3 participants in the 60 mg QD to 100 mg QW group and 1 participant each in the 60 to 10 mg QD group, the 60 mg QD to placebo group, and the placebo group, respectively) had lymphocyte values meeting the criteria for low levels. There were no clinically meaningful changes from baseline observed in lymphocytes across treatment groups during the study.

During the induction period and maintenance periods, platelet levels in all active treatment groups were similar to placebo at Week 4 and Week 12.

1.4.2.1.8.4.2. Liver Function Tests

There were no clinically meaningful changes from baseline observed in AST and ALT across treatment groups during the study. Two (2) participants (1 participant each in the 30 mg QD group and the 30 mg QD to 100 mg QW group) had AST meeting the criteria of AST >3.0 × ULN. One participant in the 30 to 10 mg QD group had ALT meeting the criteria for high levels. The participant was permanently discontinued from the study due to a moderate AE of liver function test (LFT) abnormal.

1.4.2.1.8.4.3. Creatine Kinase

There were no clinically meaningful changes from baseline observed in creatine kinase (CK) during the study. A total of 24 participants (5 participants each in the 60 mg QD to 100 mg QW and 30 to 10 mg QD groups; 4 participants each in the 60 to 30 QD and 30 QD groups; and 3 participants each in the 60 to 10 mg QD and 60 mg QD to placebo groups) had CK meeting the criteria of CK >2 ×ULN. CK levels >10 × ULN were observed in 2 participants without AE. One moderate AE of CK-MB increased reported by 1 participant in the 30 to 10 mg QD group during the induction period, which was considered to be related to the study drug by the investigator. No participant was discontinued from the study due to CK elevation.

In the Initial 24 weeks Treatment Period; There were no deaths during the Initial 24-Week Treatment Period. A total of 4 participants discontinued from the study due to TEAEs and 5 participants discontinued study drug due to TEAEs and continued in the study. Two (2) participants in brepocitinib treatment group experienced an SAE of Rhabdomyolysis which resulted in permanent discontinuation from the study. The most frequently laboratory abnormality which met retest criterion was total neutrophils (absolute) $<2 \times 10^3/mm^3$ in 20 (14.2%) participants: 9 (19.6%) participants in placebo group and 8 (17.0%) participants in brepocitinib treatment group. Two (2) participants in brepocitinib treatment group experienced Grade 3 decreased neutrophil count. There were 2 participants in placebo group and 13 participants in brepocitinib treatment group experienced a decline of ≥30% from baseline in SCr-based eGFR during the Initial 24-Week Treatment Period but none of these declines were accompanied by a concomitant decline of ≥30% in serum cystatin C-based eGFR. Elevated CK levels of at least 3 × ULN were reported in 9 participants in brepocitinib treatment group. There were no clinically significant findings in ECG and vital signs except increased diastolic BP in 3 participants (one in each group). There were no clinically significant auditory changes in the active treatment groups. A mild TEAE of Deafness neurosensory was reported in 1 participant in placebo group.

In the SBE Period; There were no deaths during the SBE Period. Two (2) participants discontinued from the study due to TEAEs (Abnormal liver function test in 1 active non-responder on PF-06651600 and Lower limb fracture in 1 retreated brepocitinib responder). One (1) active non-responder on brepocitinib discontinued from brepocitinib due to AE of Proteinuria but completed the study. Five (5) participants (2 placebo non-responders on brepocitinib, 1 non-retreated PF-06651600 responder, 1 non-retreated brepocitinib responder, and 1 retreated brepocitinib responder) had temporary discontinuation due to TEAEs (Increased blood creatine phosphokinase in 2 participants, Increased blood creatinine and Decreased glomerular filtration rate in 1 participant, Palpitations in 1 participant, and Rhabdomyolysis in 1 participant). One (1) retreated brepocitinib responder experienced a treatment-emergent SAE of Lower limb fracture which was considered not related to study drug. The most frequently met retest criterion was total neutrophils (absolute) $<2 \times 10^3/mm^3$ which was reported in 11 participants receiving brepocitinib and 3 participants receiving placebo. There were no clinically relevant changes in lipid profile. Elevated CK levels of at least 3 × ULN were reported in 2 participants

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1.4.2.1.11. Study B7931030

This is a Phase 2B, randomized, double blind, placebo-controlled, dose range, parallel group study of brepocitinib to evaluate the efficacy of brepocitinib at 16 weeks and to evaluate the safety and efficacy up to 1 year in participants with active psoriatic arthritis.

As of 20 August 2020, 8 cases reporting a total of 9 treatment emergent SAEs have been reported in the ongoing blinded Study B7931030. Six (6) of these SAEs are assessed by the Investigator as not related to treatment. The SAEs are Appendicitis, Duodenal ulcer, Cholecystitis chronic, Psoriasis, Synovitis, and Varicella.

There were 2 cases reporting 3 SAEs assessed by the Investigator as treatmentrelated; [redacted]

1.4.2.1.12. Study B7931023

Study B7931023 is a Phase 2b, randomized, double blind, vehicle-controlled, parallel-group, dose ranging study to assess efficacy, safety, tolerability and pharmacokinetics of brepocitinib topical cream applied once or twice daily for 12 weeks in participants with mild to moderate chronic plaque psoriasis.

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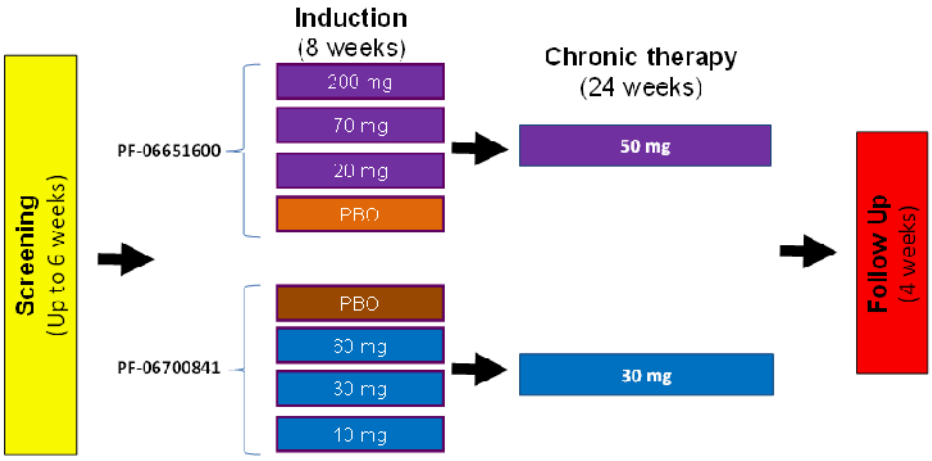
• To evaluate the efficacy of PF-06651600 and PF-06700841 in induction of remission at Week 8 in subjects with moderate to severe UC.	• Proportion of subjects achieving remission* based on total Mayo score of ≤2 with no individual subscore >1 and a rectal bleeding subscore of 0 at Week 8.
• To evaluate the efficacy of PF-06651600 and PF-06700841 in improvement of endoscopic appearance at Week 8 in subjects with moderate to severe UC.	• Proportion of subjects achieving improvement in endoscopic appearance (defined as a Mayo endoscopic subscore of ≤1) at Week 8.
• To evaluate the effect of PF-06651600 and PF-06700841 in induction of other clinical outcomes in subjects with moderate to severe UC.	• Proportion of subjects achieving clinical response at Week 8. • Proportion of subjects in endoscopic remission at Week 8. • Proportion of subjects in symptomatic remission at Week 8. • Proportion of subjects achieving deep remission at Week 8. • Partial Mayo scores and change from baseline over time at Weeks 2, 4 and 8. • Change from baseline at Week 8 in total Mayo score.
• To evaluate the effect of PF-06651600 and PF-06700841 in induction on patient reported outcomes (PRO) in subjects with moderate to severe UC.	• The scores and change from baseline in Inflammatory Bowel Disease Questionnaire (IBDQ) Total score and domains (Bowel Symptoms, Systemic Symptoms, Emotional Function and Social Function) at Weeks 4 and 8. • The proportion of subjects with IBDQ total score ≥170 at Weeks 4 and 8. • The proportion of subjects with ≥16 point increase in IBDQ total score from baseline at Weeks 4 and 8. • Proportion of subjects with improvement in IBDQ bowel symptom domain at Weeks 4 and 8. The improvement is defined as an increase of at least 1.2 points from baseline in average score among IBDQ bowel symptom domain (items 1, 5, 9, 13, 17, 20, 22, 24, 26, 29). • The scores and change from baseline in Short Form 36 version 2, acute (SF-36v2) (physical and mental component summary scores: PCS & MCS, and 8 domain scores) at Weeks 4 and 8. • The scores and change from baseline in EuroQoL 5 Dimensions (EQ-5D-3L & EQ-5D VAS) at Weeks 4 and 8.
Tertiary/Exploratory Objective(s):	**Tertiary/Exploratory Endpoint(s):**
C C I [redacted]	[redacted]
• To assess the effect of PF-06651600 and PF-06700841 compared to placebo on disease and mechanistic biomarkers over time during induction.	• Change from baseline in serum hsCRP levels over time. • Change from baseline in fecal calprotectin. C [redacted]

Tertiary/Exploratory Objective(s):	Tertiary/Exploratory Endpoint(s):
CCI [redacted]	[redacted]
• To explore the effect of PF-06651600 and PF-06700841 in subjects with moderate to severe UC in the chronic dosing period.	• Proportion of subjects achieving clinical response at Week 32. • Proportion of subjects in endoscopic remission at Week 32. CCI [redacted] • Change from baseline at Week 32 in total Mayo score.
CCI [redacted]	[redacted]
• To assess the effect of PF-06651600 and PF-06700841 compared to placebo on disease and mechanistic biomarkers over time during chronic period.	• Change from baseline in serum high-sensitivity C-reactive protein (hsCRP) levels over time. • Change from baseline in fecal calprotectin. CCI [redacted] • Change from baseline in hematological values including reticulocytes, hemoglobin, neutrophils, platelets, and T-cell, B-cell, CCI [redacted]



Approximately 318 subjects in total will be randomized into the study. Following the screening period, subjects who meet the eligibility criteria at the baseline visit will be randomly assigned to receive one of 8 treatments. In the induction period, three oral dose levels (20, 70, and 200 mg daily) of PF-06651600 plus matching placebo in a 4:4:4:1 ratio and three oral doses (10, 30, and 60 mg daily) of PF-06700841 plus matching placebo in a 4:4:4:1 ratio will be investigated. For analysis of the induction period, placebo groups will be combined to yield final drug: placebo ratios of 2:2:2:1 for each drug at week 8.

Following the induction period of the study, all subjects will enter the chronic dosing period in which there will be no placebo arms (Protocol Amendments 5, 6, 7). All subjects (including placebo subjects) from the double-blind PF-06651600 treatment/placebo induction period will receive 50 mg of PF-06651600 for 24 weeks. All subjects (including placebo subjects) from the double-blind PF-06700841/placebo induction period will receive 30 mg of PF-06700841 for 24 weeks. Prior to Amendment 5, subjects were assigned to placebo and active during the chronic period within their respective treatment using a 2:1 ratio.

Any subject who discontinues early from the induction period prior to the Week 8 visit should undergo the procedures for an Early Termination visit on the last day the subject takes the investigational product or as soon as possible thereafter, and will not be permitted to enter the chronic dosing period. For subjects who discontinue early from the chronic dosing period (after the Week 8 visit, but prior to the Week 32 visit), the procedures scheduled for an Early Termination visit will be performed on the last day the subject takes the investigational product or as soon as possible thereafter. After completion of the Early Termination visit subjects will enter the follow-up period.

3.2. Duration of Subject Participation

The duration of participation for eligible subjects will be approximately 42 weeks. This includes a screening period of up to 6 weeks, an 8 week double-blind induction period followed by a 24 week open label chronic dosing period and a 4 week follow up visit after the last dose of investigational product.

7.2. Safety

7.2.1. Laboratory

The following safety laboratory tests will be performed at times defined in the Schedule of Activities.

Laboratory Tests

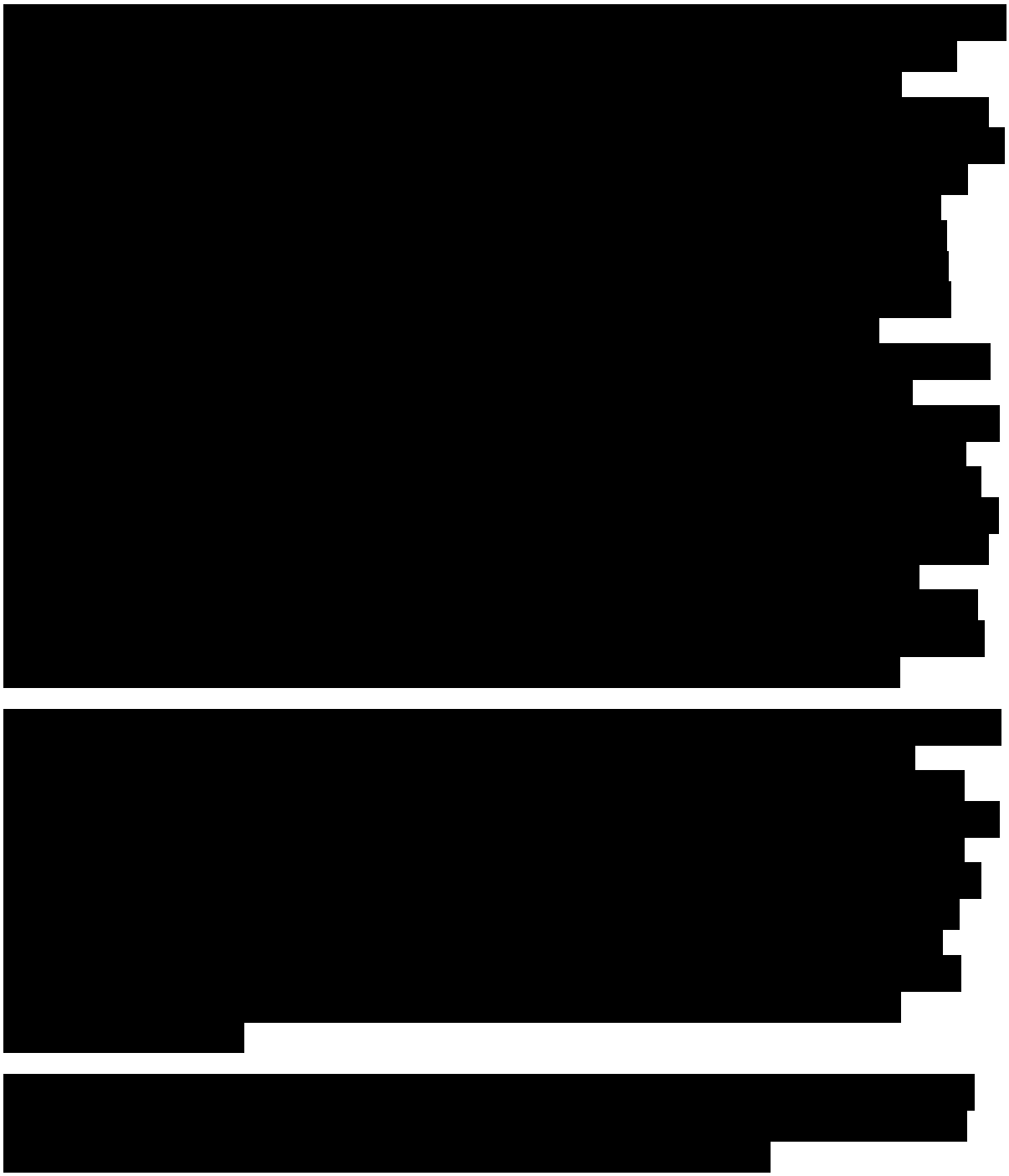
Hematology	Chemistry	Urinalysis	Other
Hemoglobin Hematocrit RBC count Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs) PT/INR/PTT Reticulocytes (% and Abs)	BUN/Urea and Creatinine Cystatin C Glucose Calcium Sodium Potassium Chloride AST, ALT Total Bilirubin Direct bilirubin[a] Alkaline phosphatase Uric acid Albumin Total protein Creatine kinase (CK) CK fractionation[b] Total Cholesterol[c] Triglycerides[c] HDL[c] LDL[c]	pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Microscopy[d] Spot urine albumin/creatinine ratio[e]	FSH[f,g] β-hCG[h] HbA_{1C} Hepatitis B, C and HIV[g] QFT-G or other IGRA[g] hsCRP IP-10 CCI Stool sample[g] to detect enteric infections and C. difficile toxins A and B CCI Stool sample for fecal calprotectin CCI Skin biopsies/swabs[i]

a. Only if total bilirubin is elevated.
b. Only if CK is elevated.
c. Fasting.
d. Microscopy analysis is indicated if urinalysis is positive for blood, nitrite, leukocyte esterase and/or protein. Urine culture is performed if urinalysis is positive for nitrite and/or leukocyte esterase or if clinically indicated.
e. At screening only.
f. In females who are amenorrheic for at least 12 consecutive months.
g. Complete at screening.
h. Serum/Urine for women of childbearing potential. Serum pregnancy test must be performed at screening. If serum pregnancy test is borderline positive, the central lab will run a FSH test to confirm menopause.
i. When required in cases of skin rash adverse events.

endoscopy report and any photographs and/or video recordings taken during the procedure should be filed in the subject's chart. Colonoscopy should be performed at the Early Termination (ET) visit unless the previous colonoscopy was less than 8 weeks prior to this.

Endoscopy subscores will be reported per Mayo score based on Central Reader, and for Mayo endoscopy subscore of 1, presence or absence of friability will be noted.

CCI



- European Quality of Life Questionnaire – 5 Dimensions-3 Levels (EQ-5D-3L) & Visual Analog Scale (EQ-5D VAS).
- [redacted]

7.3.6.1. Inflammatory Bowel Disease Questionnaire (IBDQ)

IBDQ is a psychometrically validated PRO instrument for measuring the disease-specific quality of life in subjects with IBD, including UC. The IBDQ is comprised of 32-items, which are grouped into 4 dimensions: bowel function, emotional status, systemic symptoms and social function.[11] The 4 domains are scored as follows:

- Bowel symptoms: 10 to 70.
- Systemic symptoms: 5 to 35.
- Emotional function: 12 to 84.
- Social function: 5 to 35.

The total IBDQ score ranges from 32 to 224. For the total score and each domain, a higher score indicates better quality of life. A score of at least 170 corresponds to clinical remission and an increase of at least 16 points is considered to indicate a clinically meaningful improvement.[11,12] See Appendix 5.

7.3.6.2. Short Form – 36, Version 2, Acute (SF-36)

The SF-36 v2 Acute is a psychometrically valid and reliable health status questionnaire that assesses 8 domains of functional health and well-being: Physical Functioning, Role Limitations due to Physical Health Problems, Bodily Pain, Social Functioning, Mental Health, Role Limitations due to Emotional Problems, Vitality, and General Health Perceptions. A physical health component summary score (PCS) and mental health component summary score (MCS) are calculated from the 8 domain scores. The acute form uses a recall period of one week. Higher scores indicate a better health-related quality of life. See Appendix 6.

7.3.6.3. Euro Quality of Life Questionnaire 5 Dimensions 3 Levels and Visual Analog Scale (EQ-5D-3L & VAS)

The EQ-5D 3L and EQ-5D VAS is a patient completed questionnaire designed to assess impact on health related quality of life in five domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Additionally, scores from the five domains may be used to calculate a single index value, also known as a utility score. The validity and reliability of the EQ-5D-3L has been established in a number of disease states, including UC.[13] The EQ-5D/VAS records the respondent's self-rated health on a scale from 0 (worst imaginable health state) to 100 (best imaginable health state). See Appendix 7.

CCI [redacted]

7.4. Pharmacodynamics

The pharmacodynamics (PD) samples must be processed and shipped as indicated in the laboratory manual to maintain sample integrity. Any deviations from the PD processing steps, including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised. Depending on sampling and transport constraints, it is possible that not all biomarker samples will be collected in all study regions.

All efforts will be made to obtain the PD samples at the exact nominal time relative to dosing. Please consult the laboratory manual(s) for final instructions on sample collection, storage, and shipping requirements. These manual(s) supersede the instructions listed in the applicable protocol sections. Samples that are handled according to the respective manual guidance are considered "per protocol".

Samples will be analyzed using fit for purpose or validated analytical methods in compliance with Pfizer standard operating procedures.

CCI [redacted]

7.4.1. High-Sensitivity C-Reactive Protein (hsCRP)

Blood samples for determination of hsCRP will be obtained at the times specified in the Schedule of Activities.

CCI [redacted]

This information is more detailed than that recorded on the CRF. In general, this will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety. Any pertinent additional information must be reported on the CT SAE Report Form; additional source documents (eg, medical records, CRF, laboratory data) are to be sent to Pfizer Safety **ONLY** upon request.

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

8.1.1. Additional Details on Recording Adverse Events on the CRF

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

8.1.2. Eliciting Adverse Event Information

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

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

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

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

8.1.4. Time Period for Collecting AE/SAE Information

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

For subjects who are screen failures, the active collection period ends when screen failure status is determined.

8.1.4.1. Reporting SAEs to Pfizer Safety

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

SAEs occurring in a subject after the active collection period has ended are reported to Pfizer Safety if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product must be reported to Pfizer Safety.

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

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

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

Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

8.1.5. Causality Assessment

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

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

8.1.6. Sponsor's Reporting Requirements to Regulatory Authorities

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

- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or
- Test result is considered to be an AE by the investigator or sponsor.

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

8.2.3. Serious Adverse Events

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

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

Or that is considered to be:

- An important medical event.

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

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

8.2.4. Hospitalization

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

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Same-day surgeries (as outpatient/same-day/ambulatory procedures).

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

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

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

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

- Subjects with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available;

- For subjects with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

    - Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN **or** if the value reaches >3 × ULN (whichever is smaller).

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

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

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

9.2.2. Analysis of Secondary Endpoints During Induction Period

Analysis of the secondary endpoints, including the endpoints collected during the 24 week chronic dosing period, will be outlined in the SAP. For the binary endpoints such as remission, improvement in endoscopic appearance, and so on, missing data will be treated as non-responders and the risk differences between treatment and placebo will be computed along with exact confidence intervals. Continuous and discrete modelling techniques will be applied whenever applicable. The statistical summaries will be presented by dose groups. The correlations between the endpoints will be analyzed.

9.2.3. Analysis of Secondary Endpoints During Chronic Period

Total Mayo score at Week 32 is one of the secondary endpoint during the chronic period. The analysis model will be similar to the primary analysis using cLDA.

The model will include treatment (active doses and placebo), visit (baseline, Week 8 and Week 32) and treatment by visit interaction as fixed effects. An unstructured variance-covariance matrix will be allowed. This model will not include the data from the chronic period for the subjects assigned to placebo during this period. For the remaining secondary endpoints of Remission and, improvement in endoscopic appearance, missing data will be treated as non-responders and and the risk differences between treatment and placebo will be computed along with exact CI. Additional details will be described in the SAP.

9.3. Analysis of Other Endpoints During Induction and Chronic Period

Analysis of other endpoints will be conducted as deemed appropriate. Continuous and discrete modelling techniques will be applied whenever applicable. Distribution summaries will be presented by means of summary tables and data visualization methods.

9.3.1. Pharmacokinetic Analysis During Induction and Chronic Period

The PK concentration population is defined as all enrolled subjects who received at least one dose of PF-06651600 or PF-06700841 and in whom at least one concentration value is reported.

PK concentrations will be summarized and presented with summary statistics and, if appropriate, non-compartmental PK parameter estimates will be provided. A population PK model may be developed for the purpose of estimating PK parameters. Any population PK model developed to characterize the PK data will be reported separately.

Data permitting, the relationship between exposure and clinical responses (efficacy, safety and pharmacodynamic) from the 8 week induction period of treatment in subjects with moderate to severe active UC may be explored using either observed or modeled exposures. Similar analyses may be conducted with data collected from the chronic dosing period. Any population analyses conducted will not be part of the clinical study report (CSR) and may be reported separately.

9.3.2. PK/PD Unblinding Plan

A PK/PD unblinding plan approved by the clinical lead, clinical pharmacology lead and statistical lead will be in place to describe the procedures to be employed in safeguarding the study blind for members of the study team. These procedures will be in accordance with applicable Pfizer SOPs for releasing randomization codes and breaking the study blind. Under this plan a group of statisticians, PK/PD data provider, PK/PD analyst and PK/PD support would be unblinded in order to initiate the building of statistical models of the PK, dose/response as well as exposure/response analysis models and conduct associated simulations. The aim of this work would be to facilitate a fuller interpretation of the study upon completion (at appropriate interim milestone). This group will not serve on the study team during the period of early unblinding. The unblinding may occur after the last subject has been randomized. The details of the procedures will be described in the PK/PD Unblinding Plan for Modelling and Simulation for study B7981005 which will be finalized prior to the start of the PK/PD unblinding.

9.3.3. Biomarkers Unblinding Plan

In order to expedite the analyses of the biomarkers, an unblinded team may review the biomarker data (including exploratory biomarkers) [excluding any biomarker data that is or contributes to a primary endpoint] and exposure data on an ongoing basis. This group will minimally be comprised of a bioanalyst and statistician, but may also include clinicians/precision medicine personnel, clinical pharmacologist and PK/PD analyst/support staff. This group will be unblinded when needed in order to conduct the analyses of the biomarkers in accordance with a biomarker data analysis plan, and will be independent of the study team. This unblinding process will be in accordance with Pfizer SOPs related to Releasing Randomization Codes and Breaking the Blind and will not have any impact on the conduct of the study. The biomarker plan, approved by the clinical lead, clinical pharmacology lead and statistical lead, will be in place to describe the procedures to be employed in safeguarding the study blind for members of the study team. The biomarker plan will outline the range of possible analyses and provide details of the decision-making process regarding unblinding.

9.4. Safety Analysis During the Induction and Chronic Period

All clinical AEs, SAEs, TEAEs, withdrawal due to AEs, ECGs, vital signs and safety laboratory data will be reviewed and summarized on an ongoing basis during the study to evaluate the safety of subjects.

The safety analysis set will include all subjects who have received at least one dose of IP. Safety data will be presented in tabular and/or graphical format for both the induction and chronic period and summarized descriptively, where appropriate. All safety endpoints will be listed and summarized in accordance with Pfizer Data Standards. Categorical outcomes (eg, AEs) will be summarized by subject counts and percentage. Continuous outcome (eg, BP, heart rate, etc) will be summarized using N, mean, median, standard deviation, etc. Change from baseline in laboratory data, ECGs and vital signs will also be summarized. Subject listings will be produced for these safety endpoints accordingly.

Appendix 4. Mayo Scoring System for Assessment of Ulcerative Colitis Activity

The Mayo score ranges from 0 to 12, with higher scores indicating more severe disease. Data are from Schroeder et al.

Stool frequency†:

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

Rectal bleeding‡:

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

Findings on endoscopy:

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

Physician's global assessment§:

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

† Each subject serves as his or her own control to establish the degree of abnormality of the stool frequency.

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

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

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

    A. ALL OF THE TIME

    B. MOST OF THE TIME

    C. A GOOD BIT OF THE TIME

    D. SOME OF THE TIME

    E. A LITTLE OF THE TIME

    F. HARDLY ANY OF THE TIME

    G. NONE OF THE TIME

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

    A. ALL OF THE TIME

    B. MOST OF THE TIME

    C. A GOOD BIT OF THE TIME

    D. SOME OF THE TIME

    E. A LITTLE OF THE TIME

    F. HARDLY ANY OF THE TIME

    G. NONE OF THE TIME

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

    A. ALL OF THE TIME

    B. MOST OF THE TIME

    C. A GOOD BIT OF THE TIME

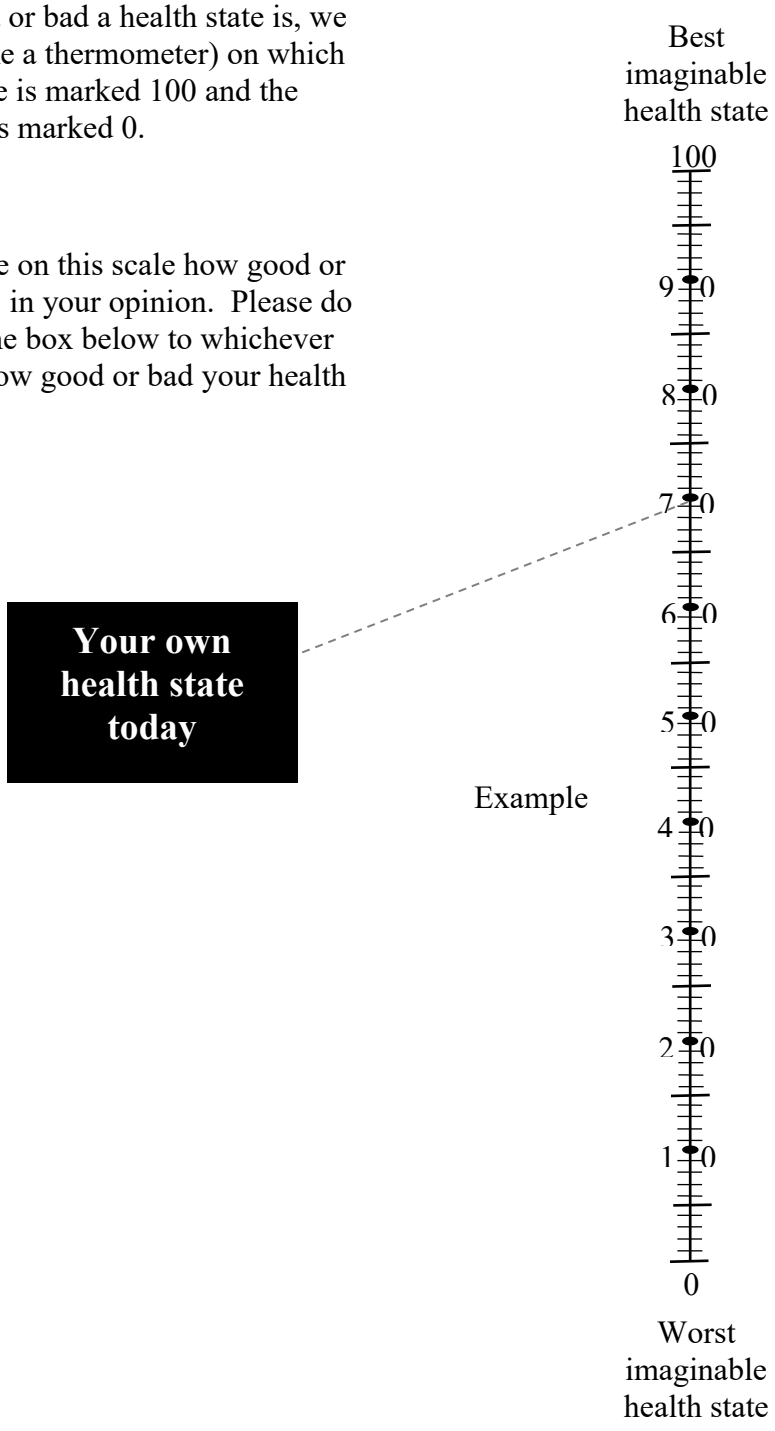
    D. SOME OF THE TIME

    E. A LITTLE OF THE TIME

    F. HARDLY ANY OF THE TIME

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.



Study participants must be reminded to promptly notify site staff about any change in their health status.

Appendix 10.3. Alternative Facilities for Safety Assessments

Appendix 10.3.1. Laboratory Testing

If a study participant is unable to visit the site for protocol-specified safety laboratory evaluations, testing may be conducted at a local laboratory if permitted by local regulations. The local laboratory may be a standalone institution or within a hospital. The following safety laboratory evaluations may be performed at a local laboratory: See SoA.

If a local laboratory is used, qualified study site personnel must order, receive, and review results. Site staff must collect the local laboratory reference ranges and certifications/accreditations for filing at the site. Laboratory test results are to be provided to the site staff as soon as possible. The local laboratory reports should be filed in the participant's source documents/medical records. Relevant data from the local laboratory report should be recorded on the CRF.

If a participant requiring pregnancy testing cannot visit a local laboratory for pregnancy testing, a home urine pregnancy testing kit with a sensitivity of at least 25 IU/mL may be used by the participant to perform the test at home, if compliant with local regulatory requirements. The pregnancy test outcome should be documented in the participant's source documents/medical records and relevant data recorded on the CRF. Confirm that the participant is adhering to the contraception method(s) required in the protocol.

Appendix 10.4. Investigational Product

If the safety of a trial participant is at risk because they cannot complete required evaluations or adhere to critical mitigation steps, then discontinuing that participant from study intervention (investigational product) must be considered.

Investigational product may be shipped by courier to study participants if permitted by local regulations and in accordance with storage and transportation requirements for the investigational product. Pfizer does not permit the shipment of investigational product by mail. The tracking record of shipments and the chain of custody of investigational product must be kept in the participant's source documents/medical records.

Appendix 10.5. Home Health Visits

A home health care service may be utilized to facilitate scheduled visits per the Schedule of Activities. Home health visits include a healthcare provider conducting an in-person study visit at the participant's location, rather than an in-person study visit at the site. The following may be performed during a home health visit: See SoA.

Appendix 10.6. Adverse Events and Serious Adverse Events

If a participant has COVID-19 during the study, this should be reported as an adverse event (AE) or serious adverse events (SAE) and appropriate medical intervention provided. Temporary discontinuation of the study intervention (investigational product) may be medically appropriate until the participant has recovered from COVID-19. See Section 6.5 guidelines for monitoring and discontinuations.

It is recommended that the investigator discuss temporary or permanent discontinuation of study intervention (investigational product) with the study medical monitor.

For participant discontinuation reporting in the CRF, select the most appropriate status for discontinuation; if the discontinuation is associated with the current COVID-19 pandemic, enter "COVID-19" in the "Specify Status" field.

Appendix 10.7. Patient Reported Outcomes (PROs)

Patient-Centered Outcome Assessments (PCOAs) that were to be administered (via a provisioned site-based device) at the site per protocol may be administered by qualified site personnel via telehealth, if permitted by local regulations, laws, and guidance from regulatory authorities.

- To avoid influencing the study participants' responses, it is recommended that the PCOA questionnaires be administered via telehealth prior to any site staff interactions for other reasons.

- Site staff performing the PCOA administration via telehealth should:

    - Conduct this telehealth interaction in a quiet, private area and ask the study participant also to go to a similar setting in which the study participant's safety, privacy and ability to complete the assessment and provide accurate data without interruption or 3rd party input or influence is adequate;

    - Read the full text including all instructions, questions, and response choices verbatim and mark the response choice selected by the participant; site staff can read the PCOA from the paper source or provisioned site-based device, but the site staff must read exactly as that specific PCOA appears on the paper source or site provisioned device;

    - Speak clearly and at a comfortable pace;

    - Let the study participant know that the instructions, question, or response options can be re-read at any time if needed.

- Not interpret any part of the questionnaire for the study participant. If the study participant does not understand, the site staff should repeat the question and response choices verbatim and ask the participant to select the response that they feel best represents his/her experience.

- Encourage the study participant to answer based on his/her first instincts and remind the study participant that there are no right or wrong answers. If needed, use a prompt such as "Which answer most closely matches what you are thinking or feeling?"

- Confirm the study participant's response selection before you record the answer (eg, you would like me to select "moderate pain," is that right?

- Indicate that the PCOA was administered via telehealth.

- For the telehealth administration of a paper PCOA, indicate this on the participant worksheet (ie, the participant facing source document). Include the name of the site staff administering the PCOA and confirm that the study participant was the one to answer the questions.

- For PCOAs that are collected via telehealth, the PCOA CRF must be completed. Document the administration and completion date in the CRF.

Abbreviation	Term
CNS	Central nervous system
CRF	case report form
CSA	clinical study agreement
CSF	cerebrospinal fluid
CSR	clinical study report
C-SSRS	Columbia Suicide Severity Rating Scale
CTA	clinical trial application
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
CYP450	cytochrome P450
DDI	Drug drug interaction
DILI	drug-induced liver injury
DMC	data monitoring committee
CCI	[redacted]
DU	dispensable unit
EC	ethics committee
ECG	Electrocardiogram
E-DMC	external data monitoring committee
EDP	exposure during pregnancy
EFD	Embryo fetal development
eGFR	Estimated glomerular filtration rate
E_{max}	Maximal effect model
EU	European Union
EudraCT	European Clinical Trials Database
FIH	First in human
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GGT	Gamma-glutamyl transferase
GI	Gastrointestinal
GST	glutathione-S-transferase
HbA_{1C}	Glycosylated hemoglobin
HBsAg	Hepatitis B Surface Antigen
HBcAb	Hepatitis B Core Antibody
HBsAb	Hepatitis B Surface Antibody
HCVAb	Hepatitis C antibody
HCV RNA	HCV ribonucleic acid
HDL	High density lipoprotein
HEENT	head, eyes, ears, nose and throat
HIV	human immunodeficiency virus
HRQL	health-related quality of life
IB	Investigators brochure

All scheduled ECGs should be performed after the subject has rested quietly for at least 10 minutes in a supine position. When the timing of these measurements coincides with a blood collection, the ECG should be obtained prior to the nominal time of the blood collection, BP, and pulse rate.

To ensure safety of the subjects, a qualified individual (eg, sub-investigator) at the investigator site will make comparisons to baseline studies taken at screening. A copy of the ECG should be available as source documents for review. ECGs will be read locally during the dosing period.

In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality. It is important that leads are placed in the same positions each time in order to achieve precise ECG recordings. If a machine-read QTc value is prolonged, repeat measurements may not be necessary if a qualified physician's interpretation determines that the QTc values are in the acceptable range. QTc prolongations are defined as a QTc ≥480 msec or an absolute change in QTc >60 msec.

7.2.14. Chest Radiograph

Chest x-ray (posterior-anterior and lateral views are recommended however local guidelines should be followed) with no current evidence of untreated latent or active TB infection or evidence of currently active TB, general infections, heart failure or malignancy taken at screening or within the 12 weeks prior to screening and read by a qualified radiologist. If a subject had a CT scan of the chest (with or without IV contrast) within 12 weeks prior to screening, the CT scan results can substitute for chest radiograph results. Documentation of the official reading must be located and available in the source documentation.

7.3. Diagnostic and Efficacy Assessments

7.3.1. Endoscopy

Endoscopy (colonoscopy or flexible sigmoidoscopy) should be performed (during the screening period and preferably after all other eligibility criteria have been verified) within 10 days of baseline, preferably 5 to 7 days prior to the baseline to allow total Mayo score calculation.

The endoscopic subscore by the Central Reader must be available at the baseline visit. The assessment by the Central Reader will be used to derive the total Mayo score for study eligibility. The stool frequency, rectal bleeding and centrally-read endoscopic subscores for the endoscopy performed during the screening period and the PGA obtained at baseline will be used to determine eligibility. The endoscopic report and pathology report must be available in the source documents.

Endoscopy is also performed during the Week 8 and Week 32/early withdrawal visit where possible, but may be performed up to – 7 days prior to the site visit if necessary. If it is necessary, a bowel prep should be conducted as per local routine. The position of the endoscope will be based on the length of the instrument at various levels of insertion as well as the morphological features of the intestine as seen during screening endoscopy. The

Study Procedure	Screening	Baseline	Induction Period			Chronic Dosing Period					Follow-up
Visit Identifier[a]	**Week -1 to -6**	**Week 0**	**Week 2**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 32/ Early Termination[b]**	**Week 36**
Study Day/Visit Window	**Day -42 -0**	**1**	**15±2**	**29±2**	**57±2**	**85±4**	**113±4**	**141±4**	**169±4**	**225±4**	**253±7**
EQ-5D-3L & EQ-5D-VAS		X		X	X					X	
CCI [redacted]											
Prior/Concomitant Treatment(s)	X	X	→	→	→	→	→	→	→	→	X
Serious and non-serious adverse event monitoring	X	→	→	→	→	→	→	→	→	→	X

Abbreviations: →= ongoing/continuous event; β-HCG = beta human chorionic gonadotropin; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; EQ-5D-3L-VAS = Euro quality of life questionnaire 5 dimensions 3 levels and visual analog scale; CCI [redacted] FSH = follicle stimulating hormone; HbA_{1C} = Glycosylated hemoglobin; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HCV Ab = hepatitis C antibody; HCV RNA = hepatitis C virus ribonucleic acid; HDL= high-density lipoprotein; HIV = human immunodeficiency virus; hsCRP = high sensitivity C-reactive protein; IBDQ = inflammatory bowel disease questionnaire; CCI [redacted] LDL=low-density lipoprotein; CCI [redacted] SF-36 = short form 36; CCI [redacted]

a. Day relative to start of study treatment (Day 1).

b. For subjects who discontinue early from either the induction (double-blind period prior to Week 8 visit), or from the chronic dosing period (after Week 8 and prior to the Week 32 visit), the procedures scheduled for Week 32/ET will be performed on the last day the subject takes the investigational product or as soon as possible thereafter before entering the follow-up period.

c. Medical history includes detailed histories of conditions specified in Study Procedures Section 6.1.

d. Complete physical examination consists of general appearance, skin, head, eyes, ears, nose and throat (HEENT), heart, lungs, breast (optional), abdomen, external genitalia (optional), extremities, neurologic function, back, and lymph nodes. Targeted physical examination consists of skin, heart, lungs, abdomen, and examination of body systems where there are symptom complaints by the subject. Full and targeted physical examinations must include a full body skin examination. Skin examinations should include visual inspection of the breasts and external genitalia to assess for rashes, even if a subject does not wish to have the examination of breast and/or external genitalia (these are optional) done as a part of the physical examination.

e. Audiograms may be performed within a ±2 week window relative to study visit.

f. Vital signs (including temperature) and ECG should be performed before laboratory blood collection and endoscopic procedure.

g. Height and weight will be measured without shoes.

CCI

[redacted]

1.4.1.1.6. Study B7981015

B7981015 is a Phase 2b/3, randomized, double-blind, placebo-controlled, dose-ranging study to investigate PF-06651600 in AA. The study has a maximum duration of approximately 57-weeks. This includes an up to 5-week Screening period, a 48-week treatment period, and a 4-week follow-up period (for subjects who do not roll over into the open-label, long-term study B7981032). The treatment period is comprised of a placebo-controlled period that includes a 4-week loading phase and a 20-week maintenance phase, followed by a 24-week extension phase. The study will enroll a total of approximately 660 subjects. The study will be conducted at approximately 120 sites.

CCI

[redacted]

CCI [redacted]

1.4.2.1.3. Study B7931014

This study is a Phase 1, open-label, non-randomized, 2-period, fixed sequence, single-dose study of PF-06700841 in healthy male participants to characterize the absorption, distribution, metabolism, and excretion (ADME) of 14C PF-06700841; and to evaluate the absolute oral bioavailability (F) and fraction absorbed (Fa) of PF-06700841 following oral administration of unlabeled PF-06700841 and IV and oral administration of 14C-PF-06700841 to healthy male participants. A 2-period design will be used to minimize variability and enable within-subject comparison of the urinary excretion of radioactivity with both routes for the estimation of Fa. Fa will be estimated by comparing total 14C urine recovery following IV and oral administration of 14C-PF-06700841. There was a 10- to 17-day washout between the 2 treatment periods.

CCI [redacted]

1.4.2.1.8.4.4. Serum Creatinine, Serum Cystatin-C, and eGFR (serum Cystatin C Based)

During the induction period, increases from baseline in SCr were observed in all the active treatment groups (range from 10.9% to 25.0%), compared to the placebo group (1.8%) at Week 4. During the maintenance period, the SCr levels returned close to baseline for all the active treatment groups, except for the 60 to 30 mg QD, 60 to 10 mg QD, and 30 mg QD groups. A total of 4 participants (1 participant each in the 60 to 30 mg QD, 60 to 10 mg QD, 30 mg QD and 30 to 10 mg QD groups) had SCr meeting the criteria of SCr 1.3 × ULN.

There were no clinically meaningful changes from baseline observed in serum cystatin C across treatment groups during the study. Two (2) participants (1 participant each in the 60 to 30 mg QD and 60 to 10 mg QD groups) had elevated serum cystatin C meeting the criteria of serum cystatin C >1.3 × ULN.

There were no clinically meaningful changes from baseline observed in serum cystatin-C based eGFR across treatment groups during the study.

1.4.2.1.8.4.5. Lipids

During the induction period, dose-dependent increases from baseline in LDL were observed in the active treatment groups (13.5% for the 60 mg QD induction dose group, 5.1% for the 30 mg QD induction dose group), compared to placebo (-6.0%) at Week 4.

During the induction period, dose-dependent increases from baseline in HDL were observed in the active treatment groups (22.5% for the 60 mg QD induction dose group, 15.6% for the 30 mg QD induction dose group), compared to placebo (-1.44%) at Week 4.

There were no clinically meaningful changes from baseline observed in LDL/High density lipoprotein (HDL) ratio across treatment groups during the study.

1.4.2.1.8.5. Vital Signs, ECG, and Suicidal Behavior or Ideation

There were no clinically meaningful findings in vital signs, ECG, and suicidal behavior or ideation during the study.

1.4.2.1.9. Study B7931005

This was a Phase 2a, randomized, double blind, placebo-controlled, parallel group, multicenter study to investigate the efficacy and safety of both PF-06651600 and PF-06700841 in treatment of alopecia areata. The study was to have a maximum duration of approximately 113 weeks, consisting of 3 periods: a 24-week double-blind treatment period, an up to 48-week SBE period, and a 24-week cross over extension (COE) period. The study included 2 drug holiday periods of 4 weeks each, and 2 follow-up periods of 4 weeks each.

1.4.2.1.9.1. Summary of Adverse Events

There were no deaths reported.

receiving brepocitinib and 3 participants receiving placebo. TEAEs of increased blood creatine phosphokinase were reported in placebo non-responder on brepocitinib, and 1 retreated brepocitinib responder; none of these TEAEs were considered as treatment-related by the investigator. There were no clinically significant findings in ECG and vital signs except increased diastolic BP in participants. There were no clinically significant changes from baseline in auditory tests. There were no increased risks with re-exposure to brepocitinib.

In the CO period: There were no deaths during the COE Period. No participants discontinued from the study or discontinued study drug due to TEAEs. Two (2) participants (1 participant in each treatment group) had temporary discontinuation due to TEAEs (moderate bronchitis in the brepocitinib CO treatment group; moderate influenza like illness and moderate torticollis in the PF-06651600 CO treatment group). One (1) participant in the brepocitinib CO treatment group experienced a treatment-emergent SAE of gastroenteritis salmonella which was considered not related to study drug. The most frequently met retest criterion was total neutrophils (absolute) $<2 \times 10^3/mm^3$ which was reported by 6 (26.1%) participants: 5 (27.8%) participants in the brepocitinib CO treatment group. One (1) participant in the brepocitinib CO treatment group experienced Grade 3 decreased neutrophil count. There were no clinically relevant changes in lipid profile. Elevated CK levels of at least 3 × ULN were reported in 1 participant in brepocitinib CO treatment group. There were no clinically significant findings in ECG and vital signs except increased diastolic BP in 1 participant. There were no clinically significant changes from baseline in auditory tests. There were no increased risks observed after cross-over to treatment with brepocitinib.

1.4.2.1.10. Study B7931028

This is a Phase 2b, double blind, randomized, placebo controlled, parallel design, multicenter, dose ranging study to assess the efficacy and safety of brepocitinib in participants with active, moderate to severe generalized systemic lupus erythematosus (SLE). This is the first study of brepocitinib in participants with moderate to severe active, generalized SLE that have inadequate response to standard of care. After an up to 5 week screening period, eligible participants will be randomized in a 1:2:2:2 ratio such that participants will receive either 1 of 3 brepocitinib QD dose levels (15 mg, 30 mg and 45 mg) or placebo every day for 52 weeks. All participants will receive blinded dosing throughout the study treatment period in order to maintain the study blind.

CCI

[redacted]

CCI [redacted]

1.4.2.2. Pharmacokinetics of PF-06700841

PK data from single doses of 1, 3, 10, 30, 100 and 200 mg and multiple doses of 10, 30, 100 and 175 mg QD and 50 mg BID mg administered for 10 days are summarized in Table 3 and Table 4, respectively. Following single oral doses of 1 mg to 200 mg under fasted conditions, PF-06700841 was absorbed rapidly with median T_{max} of 1 hour or less. Following the attainment of C_{max}, concentrations appeared to decline in monophasic fashion. Mean terminal t½ ranged from 3.8 to 7.5 hours. In general, both AUC_{inf} and C_{max} appeared to increase proportionally with dose from 1 mg to 100 mg, and there appeared to be a trend toward more than proportional increases from 100 mg to 200 mg for AUC_{inf} and C_{max}.

Table 3. Summary of Plasma PF-06700841 Pharmacokinetic Parameters Following Single Oral Doses, Study B7931001

	PF-06700841 Parameter Summary Statistics[a] by Treatment					
Parameter, units	1 mg	3 mg	10 mg	30 mg	100 mg	200 mg
N, n	7, 2	6, 5	6, 6	6, 6	8, 7	8, 8
AUC_{inf}, ng.hr/mL	NR	145.8 (61)	353.8 (31)	1439 (65)	4797 (62)	18410 (46)
AUC_{last}, ng.hr/mL	17.71 (114)	79.18 (239)	340.4 (30)	1431 (65)	5041 (59)	18400 (46)
C_{max}, ng/mL	5.138 (52)	18.21 (92)	79.30 (35)	271.3 (21)	748.4 (35)	2460 (37)
T_{max}, hr	1.00 (0.500-2.00)	1.00 (0.500-1.00)	0.500 (0.500-1.00)	1.00 (0.500-1.02)	1.00 (0.500-2.00)	1.00 (0.500-2.00)
t½, hr	NR	4.55 ± 1.81	3.85 ± 1.16	4.36 ± 2.41	7.52 ± 2.82	6.81 ± 1.99

[a] Geometric mean (geometric %CV) for all except: median (range) for T_{max}; arithmetic mean ± SD for t½.
N = Number of subjects in the treatment group and contributing to the mean; n= number of subjects where t½, AUC_{inf} were determined.
NR = Not reported. Summary statistics are not presented if fewer than 3 subjects have reportable parameter values.

On Day 10 of multiple-dose administration, PF-06700841 was absorbed rapidly with median T_{max} of 1.5 hours or less across the entire range of doses, from a total daily dose of 30 mg up to 175 mg. Following attainment of C_{max}, the disposition of PF-06700841 was similar with that observed following single-dose administration. Mean terminal t½ ranged from 4.9 to 10.7 hours. In general, both AUC_{tau} and C_{max} appeared to increase proportionally with dose from 10 mg to 175 mg. The mean apparent clearance (CL/F) was 10.8 L/hr to 23.7 L/hr, and the mean apparent volume of distribution (Vz/F) was 106.2 L to 249.4 L.

	CCI • Change from baseline in hematological values including reticulocytes, hemoglobin, neutrophils, platelets,CCI .
• To explore outcomes based on investigational criteria in induction.	• Proportion of subjects in remission* based on modified Mayo score (Total Mayo score minus PGA). • Proportion of subjects with partial Mayo score ≤2 with no individual subscore >1 in response to treatment over time. • Proportion of subjects with reduction of ≥2 points from baseline in partial Mayo score over time. • Proportion of subjects in endoscopic response at Week 8. Endoscopic response is defined by a decrease from baseline in the endoscopic subscore of 1 point or more. CCI
CCI	

*Remission in total Mayo score excludes friability (Refer to Section 7.3.3).

2.2. Objectives and Endpoints during the Chronic Period

Primary Objective(s):	**Primary Endpoint(s):**
• To evaluate the safety and tolerability of PF-06651600 and PF-06700841 in subjects with moderate to severe UC in the chronic period.	• Incidence and severity of laboratory abnormalities, adverse events, serious adverse events and withdrawals due to adverse events, vital signs, 12-lead ECG in the chronic period. • Incidence of serious infections (see Section 7.2.8 for definition) in the chronic period.
Secondary Objective(s):	**Secondary Endpoint(s):**
• To evaluate the efficacy of PF-06651600 and PF-06700841 at Week 32 in subjects with moderate to severe UC.	• Total Mayo score at Week 32.
• To evaluate the efficacy of PF-06651600 and PF-06700841 for achieving remission at Week 32.	• Proportion of subjects in remission* based on total Mayo score of ≤2 with no individual subscore >1 and a rectal bleeding subscore of 0 at Week 32.
• To evaluate the efficacy of PF-06651600 and PF-06700841 in improvement of endoscopic appearance at Week 32 in subjects with moderate to severe UC.	• Proportion of subjects achieving improvement in endoscopic appearance (defined as a Mayo endoscopic subscore of ≤1) at Week 32.

	CCI
• To explore outcomes based on investigational criteria in the chronic period.	• Proportion of subjects in remission* based on modified Mayo score (Total Mayo score minus Physician's global assessment (PGA)) at Week 32. CCI
CCI	

*Remission in total Mayo score excludes friability (Refer to Section 7.3.3).

3. STUDY DESIGN

3.1. Study Overview

This is a Phase 2b, randomized, double-blind, placebo-controlled (in the induction period and not in the chronic dosing period), parallel group, multicenter study in subjects with moderate to severe active UC. The first part of the study is a screening period of up to 6 weeks followed by an 8 week double-blind induction period. The study will not be blinded across the PF-06651600 and PF-06700841 cohorts, but will be placebo-controlled during the induction phase, and double-blinded within each investigational product.

At Week 8, all subjects will be assigned to their respective treatment cohort (PF-06651600 or PF-06700841) into an additional 24 week active chronic dosing period followed by a 4 week follow up period after the last dose of investigational product for a total of 36 weeks. The chronic dosing period is in effect open label, with both subjects and Investigators aware that they have been assigned to PF-06651600 or PF-06700841, and that there is no placebo control.

3.3. Approximate Duration of Study

The study is estimated to complete in approximately 50 months, allowing for an estimated 40 months to complete enrollment with each subject remaining on study for approximately 10 months.

4. SUBJECT ELIGIBILITY CRITERIA

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

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

4.1. Inclusion Criteria

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

1. Male and/or female subjects ≥18 years to ≤75 years of age at the time of informed consent. **For subjects in Korea:** Male and/or female subjects ≥19 years to ≤75 years of age at the time of informed consent.

2. Diagnosis (endoscopic and histological) of UC for ≥3 months prior to entry into the study. A report supporting disease duration and extent (eg, proctosigmoiditis, left-sided colitis, or pancolitis) based upon prior endoscopy including a biopsy report must be available in the source documentation.

3. Subjects with moderate to severe active UC as defined by a total Mayo score of ≥6, with a rectal bleeding subscore of ≥1 and an endoscopic subscore of ≥2. Endoscopy (colonoscopy or flexible sigmoidoscopy) must be performed within 10 days of baseline, preferably 5 to 7 days prior to baseline, to allow calculation of Total Mayo Score. The endoscopic subscore assessed by the Central Reader must be available at the baseline visit and will be used to derive the total Mayo score to determine study eligibility.

4. Active disease beyond the rectum (>15 cm of active disease from the anal verge at the screening endoscopy).

5. Must have inadequate response to, loss of response to, or intolerance to at least one conventional therapy for UC:

    - Steroids;

    - Immunosuppressants (azathioprine [AZA], 6-MP, or methotrexate [MTX]);

    - Anti-TNF inhibitors (eg, infliximab, adalimumab, or golimumab);

7.2.2. Creatinine and Cystatin C

Serum creatinine is the best known standard test for monitoring renal function. However, serum creatinine based estimates of glomerular filtration rate (eGFR) may be affected by factors other than renal function, including chronic and acute illness. Cystatin C is a test that can be used either as an adjunct to or as a replacement for serum creatinine. The most reliable estimates of GFR use both test results.[5]

Cystatin C is a low molecular weight protein that is used as an alternative to serum creatinine for monitoring of renal function. It seems to correlate more closely with GFR than does serum creatinine concentration and may be a more sensitive detector of early renal dysfunction.[6,7] While use of cystatin C has been limited, its independence of demographic factors (eg, race) has made it an interesting means of determining changes in renal function in clinical settings and it is included in the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines. Estimated GFR may be calculated via the 2012 CKD-EPI creatinine, cystatin C, or creatinine-cystatin C equations.[8]

Serum creatinine will be measured and creatinine based eGFR will be calculated at times specified in the Schedule of Activities. Serum cystatin C will be measured and cystatin C based eGFR will be calculated at times specified in the Schedule of Activities.

7.2.3. Estimated Glomerular Filtration Rate

Serum creatinine and serum cystatin-C based estimated GFR (eGFR) will be calculated at times specified in the Schedule of activities, in order to facilitate calculation of eGFR at these time points. Corresponding serum creatinine and cystatin-C based eGFR will be determined to assess renal function.

The estimated GFR (eGFR) will be calculated using the 2 sets of equations developed by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), which utilize serum creatinine (SCr) and serum Cystatin C (S Cystatin C) respectively.[9]

7.2.4. Pregnancy Testing

All pregnancy tests used in this study, either urine or serum, must have a sensitivity of at least 25 mIU/mL and must be performed by a certified laboratory. For female subjects of childbearing potential, 2 negative pregnancy tests are required before receiving investigational product (1 negative pregnancy test at screening and 1 at the baseline visit immediately before investigational product administration). Following a negative pregnancy test result at screening, appropriate contraception must be commenced and the second negative pregnancy test result will then be required at the baseline visit before the subject may receive the investigational product. In the absence of regular menstrual bleeding, the study candidate should have used 2 forms of contraception for at least 1 month before the second pregnancy test. Pregnancy tests will also be repeated at all visits and at the end of the study to confirm that the subject has not become pregnant during the study. Pregnancy tests will also be done whenever 1 menstrual cycle is missed and when potential pregnancy is otherwise suspected, and may be repeated if requested by institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations. In the case of a positive

7.3.2. Subject Stool Diary

Subjects will use a diary in order to record on a daily basis the following information during the study:

- 'Normal' number of stools per day (eg, pre-UC diagnosis/when not having a flare). This question will be asked only at the screening visit.
- Number of times needed to visit the toilet to have a bowel movement (per day).
- Presence of blood in the stools (if any).
- Description of blood in the stools (if any), ONLY if presence is noted.

In order to encourage consistent diary recording, subjects should enter diary data continuously throughout the study. Instructions for completing the diary will be provided to subjects at screening and reviewed at subsequent visits.

7.3.3. Mayo Score

The Mayo Score is a tool designed to measure disease activity for UC. The Mayo scoring system ranges from 0 to 12 points and consists of 4 subscores, each graded 0 to 3 with the higher score indicating more severe disease activity (See Appendix 4).

- Stool frequency (Subscore 0-3).
- Rectal bleeding (Subscore 0-3).
- Findings on endoscopy (Subscore 0-3).
- Physician's global assessment (Subscore 0-3).

Calculation of the Mayo Score requires an assessment of the subject's stool frequency and any amount of blood in the stool. The Mayo scores will be calculated based on the subject's stool diary recorded over 3 consecutive days prior to the visit (for visits where endoscopy is not done) or endoscopy bowel preparation procedure (for visits where endoscopy is done ie, Screening, Week 8, Week 32/ET). Investigator sites will be trained on the diary usage and will train subjects on use of the diary. Diary data entered by the subject will be reviewed by the site at each visit.

If there are missing stool diary data, the average will be taken from the 3 most recently available days reported within 5 days prior to the endoscopy preparation (for visits where endoscopy is done ie, Screening, Week 8, Week 32/ET) or 5 days prior to the visit (for visits where endoscopy is not done) for calculation of Mayo score.

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7.4.5. Fecal Calprotectin

A stool sample for determination of fecal calprotectin will be obtained at the times specified in the Schedule of Activities

The study site personnel will provide appropriately labeled containers and instructions to the subject on how best to collect a sufficient fecal sample. A sample collected on the day of the visit is preferred, however if this is not possible, a sample from the day before or day after the visit should be collected, but should be **prior to the subject initiating the bowel preparation for endoscopy**.

CCI [redacted]

8.2. Definitions

8.2.1. Adverse Events

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

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

Additionally, AEs may include signs and symptoms resulting from:

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

8.2.2. Abnormal Test Findings

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

- Test result is associated with accompanying symptoms; and/or

8.3. Severity Assessment

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

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

8.4. Special Situations

8.4.1. Protocol-Specified Serious Adverse Events

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

8.4.2. Potential Cases of Drug-Induced Liver Injury

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

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

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

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

8.4.3. Potential Cases of Decreased eGFR

In the PF-06700841 FIH study B7931001, serum creatinine elevation was reported across dose levels in both healthy volunteers and psoriasis patients. The proposed mechanism for the observed serum creatinine increases in study B7931001 is inhibition of creatinine transport in the kidney (ie, transporter-mediated rather than direct nephrotoxicity) (See Section 1.4.2.1.2).

All subjects will have serum creatinine based and serum cystatin-C based eGFR calculated at times specified in the Schedule of Activities.Abnormal values in serum creatinine concurrent with absence of increase in blood urea nitrogen (BUN) that meet the below criteria, in the absence of other causes of kidney injury, are considered important medical events.

Based on these measurements, estimated GFR using serum creatinine (2009 CKD-EPI eGFR[14]) and serum cystatin C (2012 CDK-EPI eGFR[8]) will be determined at the time of elevation in serum creatinine above ULN. If an individual subject demonstrates a **CONCOMITANT serum creatinine based AND serum cystatin C based eGFR decline of ≥30% compared to the subject's baseline eGFR,** then the subject should not be further dosed and adequate, immediate, supportive measures including immediate evaluation by a nephrologist (preferably within 24 hours) with appropriate management. If the subject cannot be seen by a nephrologist within 24 hours, then the subject should be sent to a local emergency room for assessment of renal function. Results should be repeated as indicated by the nephrologist or weekly at a minimum until the eGFR returns to baseline ±15% or the renal parameters are deemed to be stable by the nephrologist and/or PI.

eGFR results will be communicated to the treating physician.

Subjects should return to the investigational site and be evaluated as soon as possible, preferably within **24 to 48 hours** from awareness of the abnormal eGFR (CONCOMITANT serum creatinine based AND serum cystatin C based eGFR decline of ≥30% compared to the subject's baseline eGFR) result for a safety follow-up visit. This evaluation should include laboratory tests, detailed history, and physical assessment. In addition to repeating serum creatinine and serum cystatin C, laboratory tests should also include: serum BUN, serum CK, serum electrolytes (including at a minimum potassium, sodium, phosphate/phosphorus, calcium), in addition to urine dipstick, urine microscopic examination, and urinary indices. All cases confirmed on repeat testing as meeting the above pre-set laboratory criteria, with no other cause(s) of laboratory abnormalities identified should be considered as important

9.5. Interim Analysis

At least one interim analysis for futility may be performed. The final number and timing of the IA(s) will be defined by the Sponsor, but a preliminarily one may be conducted approximately 6 months after the randomization of the first subject and/or after at least 50% of the planned subjects, ie, approximately 160 subjects, have completed the 8 week induction period. An active arm may be stopped for futility if the posterior probability of the given active arm being better than the placebo is less than 20%.

Further details related to the interim analysis will be outlined in the SAP.

9.6. Data Monitoring Committee

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

The E-DMC will be responsible for ongoing monitoring of the efficacy and safety of subjects in the study according to the charter. The E-DMC will review accumulating renal safety data and propose changes to the protocol as needed to ensure subject safety. The recommendations made by the E-DMC to alter the conduct of the study will be forwarded to Pfizer for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data that are not endpoints, to regulatory authorities, as appropriate.

Additional information can be obtained in the E-DMC charter.

CCI [redacted]

10. QUALITY CONTROL AND QUALITY ASSURANCE

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

Appendix 5. Inflammatory Bowel Disease Questionnaire (IBDQ)

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

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

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

    A. BOWEL MOVEMENTS AS OR MORE FREQUENT THAN THEY HAVE EVER BEEN

    B. EXTREMELY FREQUENT

    C. VERY FREQUENT

    D. MODERATE INCREASE IN FREQUENCY OF BOWEL MOVEMENTS

    E. SOME INCREASE IN FREQUENCY OF BOWEL MOVEMENTS

    F. SLIGHT INCREASE IN FREQUENCY OF BOWEL MOVEMENTS

    G. NORMAL, NO INCREASE IN FREQUENCY OF BOWEL MOVEMENTS

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

    A. ALL OF THE TIME

    B. MOST OF THE TIME

    C. A GOOD BIT OF THE TIME

    D. SOME OF THE TIME

    E. A LITTLE OF THE TIME

    F. HARDLY ANY OF THE TIME

    G. NONE OF THE TIME

G. NONE OF THE TIME

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

   A. NO ENERGY AT ALL

   B. VERY LITTLE ENERGY

   C. A LITTLE ENERGY

   D. SOME ENERGY

   E. A MODERATE AMOUNT OF ENERGY

   F. A LOT OF ENERGY

   G. FULL OF ENERGY

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

   A. ALL OF THE TIME

   B. MOST OF THE TIME

   C. A GOOD BIT OF THE TIME

   D. SOME OF THE TIME

   E. A LITTLE OF THE TIME

   F. HARDLY ANY OF THE TIME

   G. NONE OF THE TIME

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

   A. ALL OF THE TIME

   B. MOST OF THE TIME

   C. A GOOD BIT OF THE TIME

   D. SOME OF THE TIME

   E. A LITTLE OF THE TIME

   F. HARDLY ANY OF THE TIME

CCI

[redacted]

Appendix 11. Abbreviations

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

Abbreviation	Term
AA	Alopecia
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
ALT	alanine aminotransferase
ANC	Absolute neutrophil count
AST	aspartate aminotransferase
AT3	Antithrombin III
ATP	adenosine triphosphate
AUC	Area under the concentration-time profile
AUC_{tau}	Area under the concentration-time profile from time 0 to time tau (τ) the dosing interval
AUC_{24}	area under the concentration-time curve from time 0 to time 24 hours
Ae_{tau}	Cumulative amount of drug recovered unchanged in urine up to 24 hours
BA	Bioavailability
BCG	Bacillus Calmette-Guerin
BCRP	breast cancer resistant protein
CCI	[redacted]
BID	bis in die (twice daily)
BMI	Body mass index
BMX	bone marrow tyrosine kinase on chromosome X
BTK	Bruton Tyrosine Kinase
BSEP	bile salt export pump
^{14}C	Carbon-14
CD	Crohn's disease
CD8	Cluster of differentiation 8
CFB	Change from baseline
CHD	Coronary heart disease
CK	creatine kinase
CK-MB	Creatinine kinase, myocardial band
CL	Clearance
CO	Cross-Over
COE	Cross over extension
COVID-19	Corona virus disease 2019
C_{max}	maximum plasma concentration
cLDA	constrained Longitudinal Data Analysis
CL/F	Apparent clearance
CLr	Renal clearance

Abbreviation	Term
IBD	Inflammatory bowel disease
IBDQ	Inflammatory bowel disease questionnaire
ICH	International Conference on Harmonisation
IC50	50% inhibitive concentration
ID	Identification
IFN	Interferon
IGA	Immunoglobulin A
IGG	Immunoglobulin G
IGM	Immunoglobulin M
IGRA	Interferon gamma release assay
IL-6	Interleukin 6
IND	investigational new drug application
INR	international normalized ratio
IP	investigational product
IRB	institutional review board
IRT	interactive response technology
ITK	IL-2 inducible T-cell kinase
ITT	Intent to treat
IUD	intrauterine device
IUS	Intrauterine hormone-releasing system
IV	Intravenous
IWR	interactive web response
JAK	Janus kinase
KDIGO	Kidney Disease: Improving Global Outcomes
CCI [redacted]	[redacted]
LDL	Low density lipoprotein
LFT	liver function test
LLN	lower limit of normal
LLOQ	Lower limit of quantification
LOAEL	Lowest Observed Adverse Effect Level
LSLV	last subject last visit
MAD	Multiple ascending dose
MATE	multidrug and toxin extrusion
MCS	Mental component summary
MDR	Multi drug resistant
MedDRA	Medical Dictionary for Regulatory Activities
MMR	Measles, Mumps, Rubella
MnB	meningitidis serogroup B
mRNA	messenger ribonucleic acid
MRA	Magnetic Resonance Angiography
MTX	Methotrexate
N/A	not applicable