A PHASE 2B, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, PARALLEL GROUP, DOSE RANGING STUDY OF ORAL PF-06651600 AND PF-06700841 AS INDUCTION AND CHRONIC THERAPY IN SUBJECTS WITH MODERATE TO SEVERE ULCERATIVE COLITIS

Investigational Product Number:	PF-06651600, PF-06700841
Investigational Product Name:	brepocitinib, ritlecitinib
United States (US) Investigational New Drug (IND) Number:	CCI (PF-06651600) CCI (PF-06700841)
European Clinical Trials Database (EudraCT) Number:	2016-003708-29
Protocol Number:	B7981005
Phase:	2b

Document History

Document	Version Date	Summary of Changes and Rationale
Amendment 7	18 Nov 2020	• Protocol Summary: Changes made to Protocol Summary. Rationale: To align with changes made in the main protocol. C C I [redacted] • Sections 1.4.1 and 1.4.2: Summary of Clinical Experience with PF-06700841 updated. Rationale: To align with the updated Investigator Brochure. • Sections 2.1- 2.2: Corrected definition of remission based on total Mayo score per Section 7.3.3. Corrected the definition of remission based on modified Mayo Score to align with Section 7.3.3. Rationale: Clarification of endpoints. • Sections 2.2: Added PRO objective to align with the PRO endpoints for the Chronic period. Rationale: To align with the PRO objective in Induction period. • Sections 3.1: Updated to clarify placebo treatment in chronic dosing in protocol and protocol amendments prior to protocol amendment 5. Rationale: Clarification of no placebo arm in chronic dosing post-amendment 4. • Section 4.2: Exclusion criterion 34 added to exclude subjects with history of thrombotic event(s) including DVT and known inherited conditions that predispose to hypercoagulability.

		Rationale: Per regulatory request. • Section 6.5: Guidelines for Monitoring and Discontinuations updated to include discontinuation of study drug for thrombotic or thromboembolic events. Rationale: Per regulatory request. • Section 7.3.3: Added definition of endoscopic response and definition of remission based on modified Mayo Score. Removed Clinical Remission. Rationale: Definition for these endpoints was missing in the earlier version of the protocol. Definition of Clinical Remission is not applicable to the study and hence removed. • Section 7.3.4: Definition of Remission based on change in partial Mayo score is revised. Rationale: Definition corrected. • Section 9.1: Updated Type 1 error by removing adjustment for multiplicity. Rationale: Due to the reduction of the sample size (study enrollment was stopped earlier than expected) the multiplicity adjustment was removed to retain power. This flexibility was acceptable for early phase studies. • Sections 9.2.1 and 9.2.3: Clarified description of the mixed model to be used for the primary analysis. The references to the relevant literature (eg, sections of the books of Fitzmaurice, Laird and Ware (2011) and Malicrodt and Lipkovich (2017)) were added. Also clarified that the Bayesian emax model is supporting the primary analysis. Rationale: Corrected typographical errors in the earlier version and added relevant references.
Amendment 6	17 Sep 2020	• Protocol Summary and Section 1.1: Investigational product names (brepocitinib, ritlecitinib) added. Rationale: Names assigned to Investigational products. • Correction made to Document History for Amendment 5:

		Section 1.5.3 should be Section 1.5.5. Rationale: To correct the error (PACL dated 23Oct2018). • Schedule of Activities, Section 6.1, Section 7 and Section 7.3.6: Reference to Appendix 10 regarding Alternative Measures during Public Emergencies added. Rationale: To provide guidance on study conduct during public emergencies including COVID-19 (PACL dated 27Apr2020). • Section 3.1: Removed footnote from the study schematic Rationale: Footnote already explained in the text immediately below. • Schedule of Activities Footnote "d" and Section 7.2.11 updated to clarify that breast and external genitalia examination as a part of physical exam is optional, but skin examination should include a visual examination of the breast and external genitalia to assess rashes. Rationale: To ensure that rashes are detected early (PACL dated 23Oct2018). C C I [redacted] • Section 1.4: Summary of Clinical Experience updated to include additional studies (i) PF-06651600 in Crohn's disease, Alopecia Areata and Vitilligo (ii) PF-06700841 in healthy cohorts for ADME, bioavailability, QT study, skin irritation study and in plaque psoriasis. Rationale: To align with Investigator Brochure. • Section 2: Objectives and Endpoints listed separately for the Induction and Chronic dosing periods. Safety Endpoints for Induction and Chronic dosing periods updated to include laboratory abnormalites, vital signs and 12-lead ECG. Rationale: To facilitate the reporting of the induction

		and chronic periods and update safety endpoints. • Section 4.1 Inclusion criteria #6, Section 5.8.2 and Appendix 1: Updated to reference Steroid conversion table in Appendix 9. Rationale: to provide guidance on steroid conversions (PACL dated 13Mar2020). • Section 4.2: Exclusion criterion #14 updated to exclude re-testing of a positive IGRA test even though protocol states that all screening labs with abnormal results may be repeated within the screening window to confirm abnormal results. Rationale: to clarify that re-testing of positive IGRA test is not allowed (PACL dated 4Jun2019). • Section 4.3.1: Updated to indicate that the protocol specified contraception language is in alignment with the recommendations from the B7981018 study. Rationale: To align with the Investigator brochure (PACL dated 4Jun2019). • Section 5.4.2: Updated to include reference to Appendix 10 on alternative measures during public emergencies. Rationale: To provide guidance on IP preparation and dispensing during public emergencies including COVID-19 (PACL dated 27Apr2020). • Section 6.5 (Guidelines for Monitoring and Discontinuations): Added Lymphocytes $<800/mm^3$; $<0.8 \times 10^9/L$ and CK >3x ULN as additional labs to monitor. Rationale: To monitor subjects who experience decreased lymphocytes $<0.8 \times 10^9$ /L or CK >3 x ULN to ensure that these lab abnormalities are followed up in a timely manner and appropriate actions taken (PACL dated 13Mar2020). • Section 6.5 (Guidelines for Monitoring and Discontinuations): Clarified definition of serious

		infections by referencing Section 7.2.8. Rationale: To clarify definition of serious infections. • Section 7.2.6 updated to allow central lab to replace QuantiFERON®-TB Gold test (QFT-G), QuantiFERON®-TB Gold In-Tube test (QFT-GIT) and T-SPOT® TB test with other acceptable QFT tests. Rationale: To permit central lab to replace the above tests with new ones (PACL dated 4 Jun2019). • Section 7.2.12 updated to indicate that audiogram results maybe reviewed by an external audiologist. Rationale: To summarize audiology results. • Section 7.3.1: updated to indicate that a Colonoscopy should not be performed at the Early Termination (ET) visit if the previous colonoscopy was less than 8 weeks prior to this. Rationale: To avoid consecutive endoscopies if less than 8 weeks apart on early termination. C C I  • Section 7.3.3: Provided clarification on the window for stool diary to be used for MAYO score calculation at study visits (PACL dated 4Jun2019). Rationale: To provide clarification (PACL dated 4Jun2019). • Section 7.3.3: Updated to clarify the use of central versus local endoscopy scores in PGA assessment at Baseline, Week 8 and Week 32/ET visit. Rationale: to provide guidance on use of central versus

		local endoscopy scores in PGA assessment. • Section 9.1 Sample Size Determination. Rationale: To update the sample size since the study closed screening early due to business reasons. • Sections 9.2, 9.3 and 9.4: revised to describe the analyses for induction and chronic dosing periods. Rationale: To align with the the objectives and endpoints for induction and chronic dosing period in Section 2. • Section 9.7: Protocol updated to include adjudication of opportunistic infections and cardiovascular events. Rationale: Adjudication committee added based on known mechanism of acton of JAK inhibitors. • Appendix 9: Steroid conversion table Appendix 9 added. Rationale: to provide guidance on steroid conversions (PACL dated 13Mar2020). • Appendix 10 on Alternative Measures During Public Emergencies added. Rationale: To provide guidance on study conduct during public emergencies including COVID-19 (PACL dated 27Apr2020).
Amendment 5	16 August 2018	• Background and rationale in protocol summary updated. Rationale: To align with Investigator Brochure. • In the Protocol Summary, Schedule of Activities (SoA), Section 1 Introduction, Section 2 Study Objectives and Endpoints, Section 3 Study Design, Section 6 Study Procedures, and Section 9 Data Analysis/Statistical Methods, placebo treatment has been removed from the chronic dosing period. Rationale: To enable all subjects to receive active treatment after the 8 weeks double-blind induction period. • In the Protocol Summary, SoA footnote b, Section

		5.5 Administration, Section 5.9 Rescue Medication it has been clarified that subjects discontinuing early from active treatment should undergo the procedures for an Early Termination visit and then enter the follow-up period. Rationale: To provide clarification and align sections. • SoA footnote d and Section 7.2.11 Medical History, Physical Examination, Height and Weight clarifies that skin examinations should include visual inspection of the breast/and or external genitalia as part of the physical examination, even if a subject does not wish to have breast and/or external genitalia examined as part of the physical examination. Rationale: To clarify that whilst skin examination of the breasts and/or external genitalia is a requirement, the physical examination of breast and/or external genitalia is optional. • SoA footnote p and Section 7.2.4 Pregnancy testing are revised to delete the requirement of doing a second pregnancy test within 5 days after the first day of the menstrual period (counting the first day of the menstrual period as Day 1). Rationale: Two highly sensitive negative pregnancy tests at screening and at randomization are sufficient to ensure that the subject is not pregnant prior to first dose of study drug. • SoA table, Section 6.1 Screening and Section 6.2.1 Baseline amended so fecal calprotectin is measured at screening and not baseline, and aligns with stool microbiome collection. SoA footnote q, Section 7.4.5 Fecal calprotectin and Section 7.4.6 Stool Samples for Microbiome Analysis wording amended to permit some flexibility in the collection of these samples relative to bowel preparation for endoscopy. Rationale: to align fecal calprotectin and stool microbiome sample collection at screening and reduce stool sample collection frequency. The updated wording permits some flexibility in timing of collection relative to

		bowel preparation for endoscopy. • SoA footnote u and Section 7.3.1 amended to instruct that endoscopy at Weeks 8 and 32 be performed at the site visit, where possible. Rationale: To reduce the burden of visits to the site and subjects participating in the study, whilst retaining some flexibility in the event that endoscopy being performed in the week prior to visits 8 and 32 is required. • SoA footnote x and Section 5.5 Administration added clarification regarding procedures to follow in the event that a subject administers study drug the morning prior to site visit. Rationale: To provide clarification. • Section 1 Introduction and reference 3, updated Tofacitinib information. Rationale: To reflect the most recent information publicly available. • Section 1.5.1 Study Rationale updated with information on dermatological, auditory, and laboratory assessments and prohibited medication. Rationale: To give further information for the assessments being conducted in this study. CCI [redacted] • Section 1.1: Background and rationale section updated. Rationale: To align with Investigator Brochure. CCI [redacted]

		[redacted] • Section 1.4.1: Summary of clinical experience of PF-06651600 section updated. Rationale: To align with Investigator Brochure. • Section 1.4.2: Pharmacokinetics of PF-06651600 section updated. Rationale: To align with Investigator Brochure. [redacted] • Section 3.1 Study Overview schematic has been updated to reflect the removal of placebo in the chronic dosing period. Rationale: To show in the schematic that no subject in the chronic dosing period will be receiving placebo. • Section 3.3: 15 months has been added to the enrolment and total study duration. Rationale: To reflect current recruitment expectations. • Section 4.1 Inclusion criteria 1 upper age limit increased

		from 70 to 75 years old. Rationale: To allow older subjects to participate in the trial. • Section 4.1 Inclusion criteria 2 reworded and disease duration requirement lowered from 4 months to 3 months. Rationale: Reworded to simplify the language. Duration amended to allow subjects with a shorter diagnosis period to participate in the trial. • Section 4.1 Inclusion criteria 5 guidance information moved into Appendix 1. Rationale: Guidance information moved into Appendix 1 to simplify. • Section 4.2 Exclusion criteria re-ordered and consequently renumbered. Rationale: For ease of use. • Section 4.2 Exclusion Criterion 1 reworded. • Rationale: To simplify. • Section 4.2 Exclusion Criterion 25 (formerly Exclusion Criterion 28)**:** The eGFR related criterion was lowered from <80 mL/min/1.73m^2 to <60 mL/min/1.73m^2. Subsequently the exclusion of subjects with serum creatinine levels > ULN has now been removed. Reference to subjects with serum creatinine > ULN has been removed from Section 7.2.2 Creatinine and Cystatin C and Section 8.4.3 Potential Cases of Decreased eGFR. Rationale: There is no increased risk to include subjects with eGFR >60 and <80 based on available nonclinical and clinical data to date. • Section 4.2 Exclusion criteria 17 (now #15) and Section 7.2.7 Screening for Clostridium Difficile updated to permit treatment and re-testing or re-screening of subjects. Rationale: to permit subjects with appropriately resolved

		infection to enter the study. • Section 4.3.1 on contraception was updated. Rationale: to align with the Clinical Trials Facilitation Group (CTFG) European guidance of the Heads of Medicines Agencies (HMA) and TransCelerate initiative across Pharma. • Included instruction to male subjects to refrain from sperm donation for a period of 90 days after completion of active treatment. • Rationale: to be in alignment with previous Regulatory request. • Section 5.8.2 Permitted Medications now allows steroid tapering in the chronic dosing period. Rationale: To allow modification of steroid therapy. • Section 5.8.3 Prohibited Medications updated to clarify timeframe in which the listed medications are not permitted for those for which the information is not already stated. Rationale: to provide clarification and to avoid potential drug-drug interactions. • Section 11 Data Handling and Record Keeping and Section 12.3 Subject Information and Consent have been updated to comply with the European Union General Data Protection Regulation (GDPR) which became effective on 25th May 2018. Rationale: To comply with GDPR requirements. C C I [redacted] • Several additional minor editorial changes were made to protocol language for the purposes of improving clarity and readability and for maintaining consistency throughout the document.

Amendment 4	06 March 2018	• **Section 4.2: Exclusion Criterion 5:** The exclusion criterion "*Subjects with colonic dysplasia or neoplasia*" was removed and combined with the exclusion criterion 10 "*Subjects with evidence of colonic adenomas, or dysplasia*". Rationale: This change was made to remove redundancy in the protocol. • **Section 4.2: Exclusion Criterion 13:** It was clarified that subjects who have not responded to or have been intolerant of other JAK inhibitors are not permitted into the study. Rationale: Subjects who have previously been intolerant to or have been non-responders to other JAK inhibitors would not be suitable for participating in a study with PF-06651600 (a JAK 3 selective inhibitor) and PF-06700841 (dual inhibitor of TYK2 and JAK 1). • **Section 4.2: Exclusion Criterion 16:** It was clarified that subjects with repeat indeterminate IGRA results may be enrolled after a documented evaluation by appropriately qualified personnel (which may include a pulmonary or infectious disease specialist, or locally acceptable expert as defined by local guidelines), that in their opinion, the probability of reactivation is low (ie, subject would be acceptable for immunosuppressant treatment without additional action). Rationale: While the previous protocol version required those subjects with repeat indeterminate IGRA to have a consultation with a pulmonary or infectious disease specialist, it wasn't made clear that this consultation should be documented or that local guidelines should be followed. This has been clarified. • **Section 4.2: Exclusion Criterion 16:** It was clarified that subjects adequately treated (in the opinion of the appropriately qualified personnel - which may include a pulmonary or infectious disease specialist, or locally acceptable expert as defined by local guidelines) for latent and/or active tuberculosis infection may be enrolled regardless of Mantoux or IGRA results provided the treatment is well documented in the subject's medical records and/or source documentation prior to enrollment

		in the study. Rationale: For subjects who have adequately treated for latent and/or active tuberculosis infection, there is a probability of a false positive Mantoux or IGRA result. Therefore if adequate treatment is well documented in the medical records, the subject is eligible to participate in the study. • **Section 4.2: Exclusion Criterion 28 and Schedule of Activities:** Clarification was provided regarding the testing for hepatitis B and C and the following sentence was removed "*Subjects with false positive anti-HBc may be enrolled based upon consultation with hepatologist confirming no infection with hepatitis B".* Rationale: Given that reflex testing criteria can identify subjects with false positive testing for hepatitis B or C infection, this was incorporated into the protocol. • **Section 4.2: Exclusion Criterion 28:** The eGFR related criterion was lowered from <90 mL/min/1.73m^2 to <80 mL/min/1.73m^2. Rationale: This was modified to allow elderly subjects with creatinine values within normal range, but lower age adjusted eGFR to enter the study. • **Section 4.2:** The criteria to have abnormal screening lab results repeated once was removed and it was clarified that repeat testing to confirm abnormal results can be performed anytime during the screening period. Rationale: This was modified to give the opportunity to retest abnormal lab results that was considered by the investigator to be transient and/or inconsistent with the subject's clinical condition and/or past medical history. • **Section 4.2:** It was stated in this section that "*Subjects who do not meet eligibility criteria (ie, screen fail) may be re-screened once (with a new screening number) at the discretion of the investigator".* Rationale: This was added here to be consistent with what was already stated in Section 6.1 of the protocol. • **Section 7.2.6 (Interferon Gamma Release Assay**

		Tuberculin Test): It was clarified that subjects with repeat indeterminate IGRA results may be enrolled after a documented evaluation by appropriately qualified personnel (which may include a pulmonary or infectious disease specialist, or locally acceptable expert as defined by local guidelines), to rule out the possibility of low risk of infection. Rationale: This was added here to be consistent with Section 4 of the protocol. • **Section 7.2.12 Audiogram Testing:** Clarification was provided that results of the audiogram test must be available by the time of the following clinic visit. Rationale: The results of the audiogram must be available by the baseline visit to establish the baseline hearing for the subject. Following this, the reports from the audiologist must be available no later than the next visit to allow evaluation of any meaningful decline in hearing from baseline. CCI [redacted] • Several additional minor editorial changes were made to protocol language for the purposes of improving clarity and readability and for maintaining consistency throughout the document.
Amendment 3	5 April 2017	CCI [redacted] • Section 4.1, Inclusion Criterion #1, revised for subjects in

		Korea only, indicating that they must be ≥19 years to ≤70 years of age at the time of informed consent. Rationale: The lower age limit is increased to 19 years old for subjects in Korea to comply with country regulations. • Section 4.1, Inclusion Criterion #7, Section 8.1.2, Eliciting Adverse Event Information, and Section 12.3, Subject Information and Consent revised to remove all references to legally acceptable representative. Rationale: References to legally acceptable representative have been removed throughout the protocol because subjects who lack capacity to consent for themselves are not eligible to participate in this study. • Section 4.1, Inclusion Criteria, Section 5.8.2 Permitted Medications, Section 5.8.3 Prohibited Medications and Section 5.9 Rescue Medication, revised to place all washout periods relative to baseline visit and also revised to note that medications are prohibited through end of study (Week 36). Rationale: Revisions made to ensure consistency with regards to washout and timing for prohibited medications. • Section 4.2, Exclusion Criterion #13 and Section 5.8.3, Prohibited Medications, revised to exclude subjects receiving azathioprine, 6-mercaptopurine, or methotrexate within 2 weeks prior to baseline and through end of study (Week 36). Rationale: This revision is to clarify that subjects must not have treatment with azathioprine, 6-mercaptopurine, or methotrexate for at least 2 weeks prior to baseline. • Section 4.2, Exclusion Criterion #16 and Section 7.2.6, Interferon Gamma Release Assay revised to note that IGRA is tested locally *where feasible*. Rationale: This revision is made so that sites that are unable to perform IGRA at their local laboratory, will have IGRA testing performed by the central laboratory. • Section 4.2, Exclusion Criterion #18 revised to note that

		HIV is tested locally *where feasible.* Rationale: This revision is made so that sites that are unable to perform HIV at their local laboratory, will have HIV testing performed by the central laboratory. • Section 4.2, Exclusion Criterion #24 and Section 5.8.3, Prohibited Medications, revised with note excluding simvastatin or simvastatin containing products from 5 days prior to baseline and through end of study (Week 36). Rationale: Subjects receiving drugs that are substrates of CYP3A (simvastatin or simvastatin-containing products) are excluded from participation in the study to limit any potential interactions with the investigational product. • Section 5.5, Administration, revised to note that for **study visit days (ie, baseline, Weeks 2, 4, 8, 12, 16, 20, and 24)**, subjects are to be instructed to refrain from dosing at home, *bring their blister cards or bottles to the site*, and are to take the dose in the clinic *from their current blister card or bottle.* Rationale: This revision is made to highlight that on visits where dosing is at the clinic, subjects are to take the dose at the clinic and from their current blister card or bottle. • Section 6.1, Screening, Section 6.2.1, Baseline/(Week 0, Day 1), Section 7.3.1, Endoscopy and Schedule of Activities footnote w, revised to clarify that the stool frequency, rectal bleeding and centrally read endoscopy subscores from the screening endoscopy and the PGA obtained at baseline are used to determine eligibility. Rationale: This revision is made to clarify how Mayo score is calculated for eligibility. CCI [redacted]

		CCI [redacted] • Administrative changes and sentence revisions made throughout the document. Rationale: Revisions made for clarity and to correct grammatical, spelling or other errors.
Amendment 2	14 March 2017	• Section 4.1, Inclusion Criteria #5, revised definition of inadequate response to, loss of response to, or intolerance to infliximab to at least one 14-week regimen and vedolizumab to at least one 10-week regimen. Rationale: The definition of inadequate response to, loss of response to, or intolerance to infliximab and vedolizumab is revised to reflect the Summary of Product Characteristics. • Section 4.2, Exclusion Criteria #1 and Section 4.3.1, Contraception, removed *highly* when referencing highly effective contraception. Rationale: Highly has been removed when referencing highly effective contraception as not all of the methods described in the protocol are recognized as *highly* effective in all countries. • Section 5.2, Breaking the Blind is revised to state that discussion with a member of the study team in advance of unblinding is not required. Rationale: Clarification to breaking the blind is included to ensure that it is clear to investigators that they are not required to discuss unblinding plans with the Sponsor in

		advance of emergency unblinding. • Section 5.8.3, Prohibited Medications revised to prohibit any live (attenuated) vaccines from 30 days prior to baseline and through the end of study (Week 36). Rationale: The prohibition of live (attenuated) vaccines is extended from through Week 32 to through Week 36 to ensure that there is no residual investigational product on board prior to vaccinations. • Section 5.8.4, Vaccinations is added. Rationale: Vaccinations section is added to further clarify prohibition of live (attenuated) vaccines and to provide examples of such vaccines. Additionally, section is added to clarify that, current routine household contact with individuals who have been vaccinated with live vaccine components should be avoided during treatment and through the end of the study. • Section 6.5, Guidelines for Monitoring and Discontinuations revised to state that an absolute neutrophil count <1.0x 10^9/L (<1000/mm^3) or platelet count <75x 10^9/L (<75,000/mm^3) or lymphocyte count <500/mm^3 (<0.5x10^9/L) must be repeated as soon as feasible and within 3 days. Rationale: The requirement to repeat an absolute neutrophil count <1.0x 10^9/L (<1000/mm^3) or platelet count <75x 10^9/L (<75,000/mm^3) or lymphocyte count <500/mm^3 (<0.5x10^9/L) as soon as feasible and within 3 days is to ensure that these laboratory abnormalities are followed up on in a timely manner and appropriate actions taken in case of subsequent abnormal values. • Section 6.5, Guidelines for Monitoring and Discontinuations, added criteria to state that subjects who are inadequately responding to investigational product in the opinion of the investigator should be withdrawn from the study. Rationale: In order to provide additional direction to PIs and further ensure subject safety, subjects who are inadequately responding to investigational product in the opinion of the investigator should be withdrawn from the

		study. • Section 7.2.13, Electrocardiogram revised to include a statement defining QTc prolongations. Rationale: In order to provide additional guidance to investigators, QTc prolongations are defined as a QTc ≥480 msec or an absolute change in QTc ≥60 msec. • Section 9.5, Interim Analysis is revised to incorporate futility stopping guidelines and remove reference to re-estimation of sample size. Rationale: Futility stopping guidelines are incorporated for transparency. References to re-estimation of sample size is removed for internal business and operational aspects. The adjustment of the randomization ratio is no longer an option for the interim analysis.
Amendment 1	27 October 2016	• In the Schedule of Activities, Section 6 Study Procedures, and Section 7.2.12 Audiogram, added audiogram assessments at regular intervals. Rationale: Audiogram assessments are included at regular intervals to monitor for potential hearing changes. • In the Schedule of Activities and Section 6 Study Procedures, added Serum Cystatin C (and eGFR) at all time points. Rationale: Serum Cystatin C (and eGFR) assessed at all time points to facilitate interpretability of any findings in individual subjects. • In the Schedule of Activities, Section 6.5 Guidelines for Monitoring and Discontinuations, Section 7.2.2 Creatinine and Cystatin C, and Section 8.4.3 Potential Cases of Decreased eGFR, removed statement that a creatinine increase above the ULN will trigger a reflex test for serum cystatin-C in order to facilitate both serum cystatin-C based, and serum creatinine based eGFR calculation. Rationale: Serum Cystatin C (and eGFR) assessed at all time points to facilitate interpretability of any findings in individual subjects.

		• Section 7.2.2 Creatinine and Cystatin C, clarified that creatinine elevations above the ULN will be followed until resolution or baseline. Rationale: Creatinine levels above the ULN will be followed until resolution or baseline to monitor subject safety. • In the Schedule of Activities and Section 6 Study Procedures, added that the screening urinalysis will include a spot urine albumin/creatinine ratio. Rationale: Urine albumin/creatinine ratio included at screening to further ensure subject safety is fully evaluated prior to study entry. • In the Schedule of Activities, Section 5.3, Subject Compliance, Section 5.5, Administration, and Section 6, Study Procedures, removed reference to subject dosing diary. Rationale: All references to subject dosing diary have been removed as dosing compliance will be monitored by tablet counts. [redacted] • Section 4.1, Inclusion Criteria, added definition of intolerance to anti-TNF inhibitors. Rationale: Definition of anti-TNF inhibitors added to clarify criteria for inclusion to ensure appropriate study

		population is enrolled. • Section 4.1, Inclusion Criteria, Section 4.2 Exclusion Criteria, Section 5.8.2, Permitted Medications, and Section 5.8.3, Prohibited Medications, increased the dosage of prednisone permitted to <25 mg/day. Rationale: Prednisone dose increased to 25 mg/day to more closely identify with clinical practice as well as help with study recruitment. • Section 4.2, Exclusion Criteria, added the following exclusions: subjects with active renal disease, including recent kidney stones and subjects with severe hepatic impairment (defined as Child-Pugh C). Rationale: Subjects with active renal disease, including recent kidney stones and subjects with sever hepatic impairment (defined as Child-Pugh C) are excluded from participation to ensure subject safety is fully evaluated prior to study entry. • Section 4.2, Exclusion Criteria, added exclusion of subjects with current or recent history of clinically significant severe, progressive hearing loss or auditory disease. Rationale: Subjects with current or recent history of clinically significant severe, progressive hearing loss or auditory disease are excluded from participation to exclude subjects in whom any further reduction in hearing ability would have the greatest impact. • Section 4.2, Exclusion Criteria and Section 5.8.3, Prohibited Medications, added exclusion of subjects receiving strong P-gp inhibitors and subjects receiving drugs that are substrates of MDRI (eg, digoxin), OCT2 or MATE (dofetilide) which have a narrow therapeutic index. Rationale: Subjects receiving strong P-gp inhibitors and drugs that are substrates of MDRI (eg, digoxin), OCT2 or MATE (dofetilide) are excluded from participation in the study to limit any potential interactions with the investigational product. • Section 4.2, Exclusion Criteria, modified the lymphocyte

		count and hemoglobin criteria for study entry and added an exclusion subjects with ≥3+ proteinuria. Rationale: The lymphocyte count and hemoglobin criteria are modified and exclusion of subjects with ≥3+ proteinuria is added to ensure that subjects entering the study are not put at additional risk of experiencing CTCAE Grade 3 adverse events by entering the study with these laboratory values on the lower end of the normal range. • Section 5.8.1, Oral Corticosteroids, removed requirement for subject to record oral corticosteroids on a daily diary. Rationale: To eliminate duplication of effort and for ease of subject, there is no need for daily diary collection of corticosteroids. This data will be captured on the CRF. • Section 6.5, Guidelines for Monitoring and Discontinuations, added that treatment with investigational product will be discontinued and the subject withdrawn from the study if they have symptomatic anemia and a hemoglobin of <7 g/dL or any anemia requiring a blood transfusion. Rationale: Subjects with symptomatic anemia and a hemoglobin of <7 g/dL or any anemia requiring a blood transfusion will be discontinued from the study to further evaluate subject safety and feasibility of continuation based on emerging data. • Section 6.5, Guidelines for Monitoring and Discontinuations, added that treatment with investigational product will be discontinued and subject withdrawn from the study if there is an AST or ALT elevation ≥3 times the upper limit of normal with an INR >1.5. Rationale: Subjects who develop an AST or ALT elevation ≥3 times the upper limit of normal with an INR >1.5 will be discontinued from the study to further evaluate subject safety and feasibility of continuation based on emerging data. • Section 6.5, Guidelines for Monitoring and Discontinuations, added that any clinically meaningful, treatment related decline in hearing from baseline will result in the subject being discontinued from treatment with investigational product and withdrawn from the

		study. Rationale: Subjects who develop a clinically meaningful, treatment related decline in hearing from baseline will be discontinued from treatment and withdrawn from the study to further evaluate subject safety. • Section 7.2.11 Medical History, Physical Examination, Height and Weight, clarified that both complete and targeted physical examinations include full body skin examinations. Additionally, clarified that skin examinations should include visual inspection of the breasts and external genitalia. Rationale: Full body skin examinations, including the breast and external genitalia are required to ensure subject safety and monitor for any dermatological adverse events. • Section 9.6 Data Monitoring Committee, added a statement that the E-DMC will review accumulating renal safety data and propose changes to the protocol as needed to ensure subject safety. Rationale: The E-DMC will review accumulating renal safety data and propose changes to the protocol as needed to ensure subject safety on an ongoing basis and amend the protocol as requiring based on emerging safety data. • Minor administrative changes and sentence revisions made throughout the document. Rationale: Revisions made for clarity and to correct minor grammatical or spelling errors.
Original Protocol	29 August 2016	Not applicable (N/A)

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and institutional review boards (IRBs)/ethics committees (ECs).

TABLE OF CONTENTS

LIST OF TABLES

APPENDICES

PROTOCOL SUMMARY

Background and Rationale:

The Janus kinase (JAK) family kinases mediate signal transduction via interactions with type I and type II cytokine receptors. Upon binding of the cytokine to its receptor, the associated JAKs are activated, and phosphorylate each other and the receptor. The phosphorylated receptors serve as docking sites for the signal transducers and activators of transcription (STAT) family (STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, and STAT6) of transcription factors. The STATs are then phosphorylated by the co-localized JAKs, which stabilize homo- or heterodimeric STAT complexes that translocate the nucleus where they bind to specific gene promoters and activate transcription of a range of target genes.

PF-06651600 (ritlecitinib) is an orally bioavailable small molecule that selectively inhibits JAK3 by irreversibly blocking the adenosine triphosphate (ATP) binding site without significantly inhibiting the other three JAK isoforms (JAK1, JAK2, and TYK2). PF-06651600 also inhibits irreversibly the tyrosine kinase expressed in hepatocellular carcinoma (TEC kinase) family (BTK, bone marrow tyrosine kinase on chromosome X (BMX), (interleukin-2-inducible T-cell kinase) ITK, TEC, and tyrosine kinase expressed in T cells (TXK)), with high selectivity over the broader kinome. The selective inhibition of JAK3 will lead to modulation of γ-common chain cytokine pathways, such as IL-7, IL-9, IL-15 and IL-21, which have been implicated in the pathophysiology of ulcerative colitis (UC). Furthermore, *in vivo* PF-06651600 will spare signaling of key immunoregulatory cytokines, such as IL-10, IL-27 and IL-35, which have been shown to be critical to maintain immune homeostasis in the digestive tract. Finally, TEC kinase inhibition will impact cluster of differentiation 8 *(*CD8)+ T and natural killer (NK) cells cytotoxic functions, which play a role in the pathogenesis of Inflammatory Bowel Disease (IBD). Taken together, it is hypothesized that PF-06651600 could be efficacious in the treatment of UC.

PF-06700841 (brepocitinib) is an orally bioavailable, small molecule, potent dual inhibitor of human tyrosine-protein kinase 2 (TYK2) and JAK1. JAK1 inhibition will impact the signaling of pro-inflammatory cytokines such as interferon (IFN)-gamma and cytokines signaling through the γ-common chain receptor such as IL-7, IL-9, IL-15 and IL-21, while the inhibition of TYK2 will block the production of pro-inflammatory cytokines interferon-gamma and IL-17 through upstream inhibition of the IL-12/Th1 and IL-23/Th17 pathways. Taken together, it is hypothesized that dual inhibition of both TYK2 and JAK1 could be efficacious in the treatment of UC.

Both PF-06651600 and PF-06700841 are under development as induction and chronic therapy for the treatment of inflammatory bowel disease (IBD).

Objectives and Endpoints:

Objectives and Endpoints during the Induction period.

Primary Objective(s):	**Primary Endpoint(s):**
• To evaluate the efficacy of PF-06651600 and PF-06700841 at Week 8 in subjects with moderate to severe UC.	• Total Mayo score at Week 8.
Secondary Objective(s):	**Secondary Endpoint(s):**
• To evaluate the safety and tolerability of PF-06651600 and PF-06700841 in subjects with moderate to severe UC in induction.	• Incidence and severity of laboratory abnormalities, adverse events, serious adverse events and withdrawals due to adverse events, vital signs, 12-lead ECG in the induction period. • Incidence of serious infections (see Section 7.2.8 for definition) in the induction period.
• 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):**
CCI [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. CCI [redacted] • Change from baseline in hematological values including reticulocytes, hemoglobin, neutrophils, platelets, CCI [redacted].
• 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 [redacted]
CCI [redacted]	[redacted]

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

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.
Tertiary/Exploratory Objective(s):	**Tertiary/Exploratory Endpoint(s):**
C C I [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. C C I [redacted] • Change from baseline at Week 32 in total Mayo score.
• C C I [redacted]	[redacted]

	CCI [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].
• 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 [redacted]
CCI [redacted]	[redacted]

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

Study Design and Treatments:

This is a Phase 2b, randomized, double-blind, placebo-controlled (for induction period and not for chronic dosing (ie, chronic therapy)), 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. At Week 8, all subjects will continue within 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. Total duration of the study will be approximately 42 weeks, including screening. 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. 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 dose levels (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 drug:placebo ratios of 2:2:2:1 for each drug at Week 8. See Section 3.1.

During the chronic dosing period, all subjects from the induction period PF-06651600 cohort (including subjects who received placebo) will receive 50 mg of PF-06651600, while all subjects from the induction period PF-06700841 cohort (including subjects who received placebo) will receive 30 mg of PF-06700841 for 24 weeks. After completion of the chronic dosing period, subjects will enter the 4-week follow up period.

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.

Statistical Methods:

The primary efficacy analysis will be conducted on total Mayo score at Week 8.

Analysis will include data from all active arms and combined placebo.

Analysis details will be outlined in statistical analysis plan.

The primary analysis at Week 8 will be based on constrained Longitudinal Data Analysis (cLDA) using Total Mayo score. Other statistical analysis methods will include fitting bayesian emax model for dose-response estimation after conducting Bayesian predictive checks on monotonicity.

The primary analysis will be conducted on the intention-to-treat (ITT) population, defined as all randomized subjects who received at least one dose of investigational product or placebo. Sensitivity analysis handling of the missing values (including subjects who are missing due to COVID-19) will be outlined in the statistical analysis plan (SAP).

SCHEDULE OF ACTIVITIES

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

The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities table, in order to conduct evaluations or assessments required to protect the well-being of the subject. Refer to Appendix 10 for Alternative Measures During Public Emergencies if applicable.

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**
Informed consent	X										
Medical history[c]	X										
Complete physical examination[d]	X	X			X					X	
Targeted physical examination[d]			X	X		X	X	X	X		X
Audiogram	X				X[e]		X[e]			X[e]	
Vital signs & temperature[f]	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG[f]	X				X					X	
Height[g]	X										
Weight[g]	X									X	
Chest radiograph[h]	X										
Laboratory											
Hematology	X	X	X	X	X	X	X	X	X	X	X
Serum chemistry	X	X	X	X	X	X	X	X	X	X	X
HbA_{1C}	X										
Fasting Lipid Panel[i]	X	X	X	X	X	X	X	X	X	X	X
Cystatin C (and eGFR)		X	X	X	X	X	X	X	X	X	X
Urinalysis[j]	X[k]	X	X	X	X	X	X	X	X	X	X
Stool microbiology[l]	X										
(HBsAg, HBcAb, HBsAb, HCV Ab, HCV RNA)[m]	X										
HIV serology	X										
FSH[n]	X										

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	

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.

h. If not performed within the 12 weeks prior to screening. Copy of the report must be available in the source document if previously performed. 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 (see Section 7.2.14).

i. Includes fasting cholesterol, triglycerides, HDL, and LDL.

j. Dipstick in all cases; 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.

k. Screening urinalysis will include spot urine albumin/creatinine ratio.

l. Stool microbiology (stool culture for enteric pathogens, ova and parasites, and Clostridium difficile toxin test), if not performed within 6 weeks prior to screening, should be prior to administration of any bowel prep for endoscopy.

m. Subjects who are HBsAg negative and HBcAb positive will be reflex tested for HBsAb. Subjects who are HCV Ab positive require further testing with HCV RNA. See Section 4.2 for details.

n. To be done in postmenopausal females only (females who are amenorrheic for at least 12 consecutive months).

o. Only for women of childbearing potential. If serum pregnancy test is borderline positive, the central lab will run a FSH test to confirm menopause.

p. If not performed within 12 weeks prior to screening (see Assessments Section 7.2.5 for details).

q. Collection of stool for [redacted] fecal calprotectin analyses should be prior to administration of any bowel prep for endoscopy.

[redacted]

s. At each biopsy collection time point, the 7 biopsies should be taken for the analyses described: 6 from abnormally inflamed colonic mucosa and 1 from normal appearing colonic mucosa (if possible) in a targeted manner from the most affected area 15-30 cm from the anal verge in the colon. [redacted]

t. For subject at risk for colorectal cancer, a colonoscopy is required instead of flexible sigmoidoscopy if not performed within the specified time period (see Section 4.2). Only one endoscopy (either colonoscopy or flexible sigmoidoscopy) needs to be done for a subject within 10 days prior to baseline visit. This should preferably be done within 5 to 7 days prior to baseline to allow stool data collection for Mayo score calculation and also to obtain endoscopic subscore report from the central reader. The centrally read endoscopic subscore will be used to determine eligibility.

u. Week 8 and Week 32/early withdrawal endoscopy to be performed at the Week 8 and Week 32/early withdrawal visit to site, but may be performed up to -7 days prior if necessary (see Section 7.3.1). Colonoscopy should be performed at the Early Termination (ET) visit unless the previous colonoscopy was less than 8 weeks prior to this.

v. Bowel movement diary instructions will be provided at screening. The bowel movement diary to collect BM frequency and rectal bleeding should be collected daily beginning approximately 2 weeks prior to screening endoscopy.

w. Mayo score at Week 0 will be calculated based on stool frequency, rectal bleeding, and centrally read endoscopic subscores for the endoscopy performed during the screening period and the PGA obtained at baseline.

[redacted]

C
C
I

[redacted]

1. INTRODUCTION

IBD is a chronic inflammatory condition of the gastrointestinal tract that affects five million people worldwide. IBD presents as one of two major forms, UC or Crohn's disease (CD). UC is characterized by continuous inflammation that is localized to the colon. CD is characterized by discontinuous inflammation that can affect the entire gastrointestinal tract from mouth to anus and may be associated with long-term debilitating sequelae, such as fistulae and intestinal strictures.

The incidence of UC reported in the past 20 years varies by location. Reported rates in North America range from about 8-19, in South America from 1.5-2.6, in Asia and the Middle East from 0.6-4.4, in Western Europe from 2.3-17.5, in Eastern Europe from 0.8-5.9, and in Australia/New Zealand, from 7.6-17.4 per 100,000 person-years. The prevalence of UC in the same time period, by geographic region, ranged from 155.8-248.6 in North America, was 76.1 in a single report from South America, from 4.9-168.3 in Asia and the Middle East, from 4.9-294 in Northern and Western Europe, from 2.42-101 in Eastern Europe and 145 in Australia and New Zealand per 1,000,000 persons. Globally there does not appear to be a gender difference in incidence of UC.[1]

Although UC can occur at any age, the incidence peaks between 15 to 25 years with a second peak between 55 to 65 years.[2] UC is a lifelong condition with a serious effect on the quality of life.

Current IBD treatments include aminosalicylates, corticosteroids, immunosuppressants, and monoclonal antibodies against tumor necrosis factor (TNF)-α or α4β7 integrin. Despite multiple therapies being available, limitations remain in the treatment of IBD, and patients continue to have symptoms or develop intolerance to or side effects from their treatment regimens. Because of the significantly reduced risk for immunogenicity and the potential for oral administration, small molecule inhibitors have emerged as an attractive therapeutic modality. Tofacitinib is a JAK inhibitor with broad specificity, mainly targeting JAK1 and JAK3, with lesser effects on JAK2, and therefore affects multiple cytokine signaling pathways. Tofacitinib has been approved for use in rheumatoid arthritis and has demonstrated significant differences in clinical response and remission in comparison to placebo in subjects with UC.[3] Pfizer's plan is to test multiple selective kinase inhibitor assets simultaneously in the UC disease setting, which in this trial will include a JAK3-specific inhibitor and a TYK2/JAK1-specific inhibitor in the context of a single clinical study. Each arm of the study will address a biologically distinct question. The JAK3-specific arm will address the involvement of cytokines that signal through JAK3 in UC, and the TYK2/JAK1-specific arm will address the involvement of cytokines that signal through TYK2 and JAK1 in UC.

Both PF-06651600 and PF-06700841 avoid specific targeting of JAK2, thus reducing the risks of undesired side effects, such as anemia.

1.1. Background and Rationale

The JAK family kinases mediate signal transduction via interactions with type I and type II cytokine receptors. Upon binding of the cytokine to its receptor, the associated JAKs are activated, and phosphorylate each other and the receptor. The phosphorylated receptors serve as docking sites for the STAT family (STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, and STAT6) of transcription factors. The STATs are then phosphorylated by the co-localized JAKs, which stabilize homo- or heterodimeric STAT complexes that translocate the nucleus where they bind to specific gene promoters and activate transcription of a range of target genes.

PF-06651600 (ritlecitinib) is a potent, JAK 3 selective, covalent inhibitor. It is an orally bioavailable small molecule that selectively inhibits JAK3 by irreversibly blocking the ATP binding site without significantly inhibiting the other three JAK isoforms (JAK1, JAK2, and TYK2). PF-06651600 also inhibits irreversibly the TEC kinase family (BTK, bone marrow tyrosine kinase on chromosome X (BMX), ITK, TEC, and tyrosine kinase expressed in T cells (TXK)), with high selectivity over the broader kinome. The selective inhibition of JAK3 will lead to modulation of γ-common chain cytokine pathways, such as IL-7, IL-9, IL-15 and IL-21, which have been implicated in the pathophysiology of UC. Furthermore, in vivo PF-06651600 will spare signaling of key immunoregulatory cytokines, such as IL-10, IL-27 and IL-35, which have been shown to be critical to maintain immune homeostasis in the digestive tract. Finally, TEC kinase inhibition will impact CD8+T and NK cells cytotoxic functions, which play a role in the pathogenesis of IBD. Taken together, it is hypothesized that PF-06651600 could be efficacious in treatment of UC.

PF-06700841 (brepocitinib) is an orally bioavailable, small molecule, potent dual inhibitor of human TYK2 and JAK 1. JAK1 inhibition will impact the signaling of pro-inflammatory cytokines such as IFN-gamma and cytokines signaling through the γ-common chain receptor such as IL-7, IL-9, IL-15 and IL-21, while the inhibition of TYK2 will block the production of pro-inflammatory cytokines interferon-gamma and IL-17 through upstream inhibition of the IL-12/Th1 and IL-23/Th17 pathways. Taken together, it is hypothesized that dual inhibition of both TYK2 and JAK1 could be efficacious in the treatment of UC.

Both PF-06651600 and PF-06700841 are under development as induction and chronic therapy for the treatment of inflammatory bowel disease (IBD).

1.2. Non-Clinical Pharmacokinetics and Metabolism

CCI [redacted]

CCI 

CCI

[redacted]

CCI

CCI

[redacted]

CCI [redacted]

1.3. Non-Clinical Safety Studies

CCI [redacted]

CCI [redacted]

[redacted]

[redacted]

1.3.2. Non-Clinical Safety Studies with PF-06700841

CCI [redacted]

CCI [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

1.4. Summary of Clinical Experience

1.4.1. Summary of Clinical Experience of PF-06651600

PF-06651600 has been explored in seven completed Phase 1 trials in healthy subjects and in two Phase 2 trials in subjects with RA (B7981006) and AA (B7931005). There are 3 ongoing studies in AA (B7981015, B7981032, B7981037), and 1 each in vitiligo (B7981019), CD (B7981007), and RA (B7921023).

1.4.1.1. Summary of Clinical Safety of PF-06651600

1.4.1.1.1. Study B7981001

B7981001 was a Phase 1, randomized, double-blind, third-party open, placebo-controlled, single- and multiple-dose escalation, parallel group study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of PF-06651600 in healthy subjects. This single ascending dose (SAD) and multiple ascending dose (MAD) study was the first evaluation of PF-06651600, a JAK3/TEC inhibitor, in humans. During the SAD period, a total of 64 subjects were randomized and received doses of 5, 20, 50, 100, 200, 400 or 800 mg of PF-06651600 or placebo in a dose escalation format. During the MAD period, a total of 51 subjects were randomized and received doses of 50 mg QD, 100 mg BID (twice a day), 200 mg QD, 400 mg QD, or 200 mg BID or placebo for 14 days.

CCI

[redacted]

CCI

[redacted]

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.

CCI [redacted]

CCI

[redacted]

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

CCI

[redacted]

CCI

[redacted]

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.

CCI

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]

1.4.1.1.7. Study B7981019

B7981019 is an ongoing Phase 2b, randomized, double-blind, parallel group, multicenter, placebo-controlled, dose-ranging study to investigate different dose/dose regimens of PF-06651600 in active non-segmental vitiligo with a partially blinded extension period. The study has a maximum duration of approximately 60 weeks. This includes an up to 4-week Screening period, a 24-week dose ranging period, an up to 24-week extension period, and a 8-week follow-up period. The 24-week dose ranging period is comprised of a

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.

CCI

[redacted]

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).

CCI

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

1.4.2. Summary of Clinical Experience with PF-06700841

1.4.2.1. Summary of Clinical safety of PF-06700841

This section consists of safety information for PF-06700841 in 7 completed Phase 1 studies (Studies B7931001, B7931009, B7931010, B7931014 and B7931029), and 2 completed Phase 2 studies (B7931004 and B7931005), Two Phase 1 studies (B7931019 and B7931033) have completed enrollment (clinical study report is under preparation) and draft data from these small studies are included in the IB. Data have not been pooled for the studies conducted with brepocitinib. Safety and efficacy data are presented separately for each study.

Adverse events (AE) may be reported as all-causality or treatment-related. Treatment-related adverse events are those events considered related to the study treatment at least by the investigator. See IB for adverse events that have been further evaluated and determined by the sponsor to be expected adverse reactions (ie, events for which there is a reason to conclude that the drug caused the event[s]).

1.4.2.1.1. Study B7931001

The B7931001 study was a Phase 1, within cohort, randomized, double-blind, third party open, placebo-controlled, parallel group study with single and multiple dose escalation in healthy adult subjects, and multiple dosing in subjects with chronic plaque psoriasis. In addition, the bioavailability (BA) of a tablet formulation relative to the first in human (FIH) solution/suspension formulation, as well as the effect of a high fat meal on the BA of the tablet formulation, was determined in a 3 -way crossover study design.

Of the 96 subjects randomized into study B7931001, 74 subjects have received at least one active dose of oral PF-06700841, 41 healthy subjects in the single and multiple ascending dose period of the trial, 12 healthy subjects in BA and 21 subjects with chronic plaque psoriasis.

In the SAD/MAD period, 41 healthy subjects received doses of 1, 3, 10, 30, 100, or 200 mg of PF-06700841 during the SAD period, and doses of 10, 30, 100, or 175 mg QD for 10 days during the MAD period. Subjects participating in the 100 mg multiple dose cohort returned for a third period to receive 50 mg PF-06700841 BID for 10 days. Thirty subjects with moderate to severe chronic plaque psoriasis were also randomized into study B7931001 to receive once daily placebo (n=9), 30 mg (n=14), or 100 mg (n=7) PF-06700841 for 28 days. In the BA period, 12 healthy subjects were randomized and received PF-06700841.

1.4.2.1.1.1. Adverse Events

PF-06700841 was generally safe and well tolerated in all cohorts in the Phase 1 clinical study B7931001. There were no deaths in the study. Subjects reported 11 TEAEs in the SAD phase, 22 TEAEs in the MAD phase, 39 TEAEs in the psoriasis phase, and 3 TEAEs in the BA phase. All AEs were mild or moderate in severity; there were no severe or serious adverse events, or serious infections in any of the 4 study groups cohorts. Of the 7 healthy volunteers who prematurely discontinued the MAD cohort, 3 discontinuations were due to AEs. Of the 13 patients in the psoriasis cohort who discontinued prematurely, 7 of the

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.

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]

CCI

[redacted]

[redacted]

1.4.2.1.4. Study B7931019

This study was designed to determine the effect of PF-06700841 on QTc interval in healthy participants. This was a Phase 1, 3-way crossover, 3-treatment, 6-sequence, sponsor-open study, in which, each participant received single oral doses of PF-06700841 200 mg, placebo and moxifloxacin 400 mg, according to one of the treatment sequences they were randomly assigned. Treatment assignments to PF-06700841 and placebo were blinded to the participants and investigator but moxifloxacin treatment was unblinded.

CCI

[redacted]

[redacted]

1.4.2.1.5. Study B7931029

This is a Phase 1, single center, randomized, vehicle and white petrolatum controlled, evaluator blinded study to assess the skin irritation potential with a range of concentrations of PF-06700841 cream including vehicle and empty patch with white petrolatum under occlusive conditions in adult Japanese healthy participants.

CCI

[redacted]

All participants had 6 application sites on the back where 6 patches of investigational

CCI

[redacted]

1.4.2.1.6. Study B7931033

This was a Phase 1, open-label, fixed-sequence, 2-period study to investigate the effect of multiple oral doses of itraconazole on a single oral dose of brepocitinib PK in healthy participants at a single center. Approximately 12 healthy participants were enrolled in the study. The study has completed enrollment; however, the clinical study report has not been finalized as of the time of this IB update, and these summarized results are in draft stage.

CCI

[redacted]

1.4.2.1.7. Study B7931010

This was an open-label, single dose, 2-period, 2-sequence crossover study in 8 healthy participants to characterize the PF-06700841 pharmacokinetic (PK) profile and bioavailability following single oral dose formulation of immediate release (IR) tablets and modified release (MR) tablets each administered as 30 mg dose in the fasted state.

CCI

[redacted]

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.

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.

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

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]

[redacted]

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.

CCI [redacted]

[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.

Table 4. Summary of Steady Sate Plasma and Urine PF-06700841 Pharmacokinetic Parameters Following Multiple Dose Administration (10 Days), Study B7931001

	PF-06700841 Parameter Summary Statistics[a] by Treatment				
Parameter, units	10 mg (QD)	30 mg (QD)	100 mg (QD)	50 mg (BID)	175 mg (QD)
N, n	5, 5	3, 3	6, 6	4, 4	4, 4
AUC_{τ}, ng.hr/mL	422.8 (41)	1880 (52)	6089 (38)	3560 (35)	16180 (15)
C_{max}, ng/mL	63.4 (11)	286.6 (17)	734.1 (29)	522.0 (31)	2091 (28)
T_{max}, hr	1.0 (1.0-1.0)	1.00 (1.00-1.00)	1.5 (1.0-2.0)	1.0 (1.0-2.0)	0.98 (0.50-2.0)
CL/F, L/hr	23.7 (41)	16.0 (51)	16.4 (38)	14.0 (35)	10.8 (16)
t½, hr	5.93 ± 3.33	4.86 ± 1.93	10.67 ± 1.84	9.13 ± 2.26	7.46 ± 2.16
V_z/F, L	177.6 (30)	106.2 (12)	249.4 (45)	180.9 (30)	112.4 (18)
Ae_{τ}%	11.1 (45)	9.3 (57)	NR	15.5 (57)	8.9 (44)
CLr, L/hr	2.619 (18)	1.486 (15)	NR	2.179 (31)	0.9629 (58)

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 was determined; NR = Not reported.
AUC_{τ}, = Area under the concentration-time curve from zero to 24 hours (QD) or zero to 12 hours (BID) postdose at steady state; QD = Once daily; BID = Twice daily; C_{max} = Peak plasma concentration; CL/F = apparent total body clearance; V_z/F = apparent volume of distribution; Ae_{τ}% = Percent of dose recovered unchanged in urine over the dosing interval τ; CLr = Renal clearance.

Urinary recovery of PF-06700841 was low, with approximately <16% of the dose recovered unchanged in urine on Day 10 across all doses (geometric mean Ae_{τ}% of 8.9% to 15.5%). Renal clearance ranged from 0.96 L/hr to 2.62 L/hr.

The relative BA (B7931001) of 100 mg PF-06700841 tablets compared to 100 mg oral suspension was 96.2% for AUC_{inf} and 94.3% for C_{max}. Both of the 90% CIs for the ratio were within the 80% to 125% equivalence interval. When the 100 mg tablets were administered under fed conditions, T_{max} was delayed with a median value of 4.0 hours, compared to a median T_{max} 0.5 hours under fasted conditions. For 100 mg tablets fed vs. fasted, the ratio (90% CI) of adjusted geometric means for AUC_{inf} and C_{max} was 82.3% (73.5%, 92.3%) and 64.3% (56.0%, 73.8%), respectively. Tablets will be administered with no requirement regarding food in the current study.

Listed in Table 5 are the PK parameters following multiple-dose administration of PF-06700841 to psoriasis subjects. PF-06700841 was absorbed rapidly with median T_{max} of 1 hour to 2 hours post dose. Mean terminal t½ was 16 hours in the 30 mg group and 6 hours in the 100 mg group. The mean t½ value in the 30 mg group included a reported t½ value of 87.5 hours for one subject with an anomalous data point at 216 hours postdose: all other subjects in the dose group had concentrations below the lower limit of quantitation (LLOQ) after 24 hours, and t½ values of 6.48 hours or less.

Table 5. Summary of Plasma Steady State PF-06700841 Pharmacokinetic Parameters Following Multiple Dose Administration (28 Days) in Psoriasis Subjects, Study B7931001

	Parameter Summary Statistics[a] by Treatment	
Parameter, units	PF-06700841 30 mg QD (P)	PF-06700841 100 mg QD (P)
N, n	7, 7	5, 5
AUC_{τ}, ng.hr/mL	990.0 (103)	7672 (43)
C_{max}, ng/mL	204.7 (43)	924.2 (13)
T_{max}, hr	1.00 (0.983-2.00)	2.00 (1.00-2.00)
CL/F, L/hr	30.30 (103)	13.04 (43)
MRT, hr	6.072 (92)	8.534 (36)
PTF	3.414 (44)[b]	2.654 (42)
$t_{½}$, hr	16.01 ± 31.58	6.032 ± 1.712
V_z/F, L	245.4 (206)	109.6 (18)

[a] Geometric mean (geometric %CV) for all except: median (range) for T_{max}; arithmetic mean ± SD for $t_{½}$.
[b] 4 subjects contributing to the mean in this group.
N = Number of subjects in the treatment group and contributing to the mean; n= number of subjects where $t_{½}$, Vz/F and MRT were determined.

In general, dose normalized exposure was higher in the 100 mg group than in the 30 mg group although the highest individual dose normalized values for both AUC_{τ} and C_{max} were observed in one subject in the 30 mg group. Note that the subject in the 30 mg group with the highest C_{max} and AUC_{τ} values was not the same subject with the anomalous 87.5 hour $t_{½}$ value.

1.5. Rationale

1.5.1. Study Rationale

This multicenter, multiple-arm, dose ranging, placebo-controlled study (in the induction period and not the chronic dosing period) will be the first determination of safety and efficacy of PF-06651600 and PF-06700841 in subjects with moderate to severe UC. The objectives of this study are to evaluate the efficacy (based on total Mayo score), safety, tolerability, CCI and PD of 20, 70, and 200 mg of PF-06651600 and 10, 30, and 60 mg of PF-06700841 dosed once daily during an induction period of 8 weeks, followed by a chronic dosing period at doses of 50 mg and 30 mg of PF-06651600 and PF-06700841, respectively for 24 weeks (Section 2). The current non-clinical toxicology packages support treatment duration ≥6 months.

Dermatologic rashes have been observed in the Phase 1 PF-06651600 studies. As the more severe rashes were associated with twice a day administration, dosing has been limited to once a day in this study. The availability of dermatology consultation in this study is purely a precautionary measure.

CCI [redacted] Periodic audiogram monitoring is being implemented to detect any clinically-meaningful changes in hearing that might occur. The availability of audiology consultation in this study is purely a precautionary measure.

Changes in lipid profile linked to Interleukin-6 (IL-6) inhibition have been observed with JAK inhibitors. Therefore, lipid profiles will be assessed in this study.

Simvastatin is highly metabolized in the gut and modeling based on in vitro data suggests that PF-06651600 may exhibit time dependent inhibition of CYP3A which could result in a clinically relevant increase in simvastatin plasma levels. Thus, simvastatin use with PF-06651600 is currently prohibited. Since PF-06651600 is metabolized by CYP3A, moderate to potent inhibitors and inducers of CYP3A are prohibited.

Increases in serum creatinine have been observed in the Phase 1 PF-06700841 studies. However, nonclinical data suggest that this could be due to inhibition of creatinine transport in the proximal tubule of the nephron rather than being an indication of renal toxicity. Parallel cystatin C assessments in the Phase 1 studies were consistent with this hypothesis. The availability of nephrology consultation in this study is purely a precautionary measure.

By including two investigational drugs in a single study, the respective placebo groups can be combined, resulting in fewer subjects being exposed to placebo and smaller overall study size. The inclusion of these two investigational drugs is appropriate as the target population for both is identical, as are the efficacy outcome measures.

Though clinical remission based on total Mayo score has traditionally been used as a primary endpoint in the UC population, total Mayo score at Week 8 is used in this study to maximize the value of the information from the statistical inference perspective. The two scores are highly correlated, with total Mayo score being a good predictor of the remission rates, but utilization of the total Mayo score in an appropriate model setting allows for a sample size reduction, while not compromising the statistical power.

All endoscopies will be read by a Central Reader who will be blinded to study treatment.

CCI [redacted]

1.5.2. Dose Rationale

The dose selection strategy was designed to balance pharmacology and safety for this study with an 8 week induction period followed by a 24 week chronic dosing period in subjects with moderate to severe UC. A population PK model was developed using the data from the FIH study for PF-06651600 (Study B7981001) and similarly for PF-06700841 (Study B7931001). PK was assumed to be similar between healthy subjects and subjects with moderate to severe UC. The activity of the JAK inhibitors was assessed by measurement of various PD markers and markers of safety that were collected in the FIH studies and analyzed using indirect response modeling. The magnitude of change in these markers required for efficacy and/or safety is poorly understood.

1.5.3. PF-06651600 Dose Rationale

The predicted PK parameters for PF-06651600 based on simulations using the global PK model are provided in Table 6.

Table 6. Summary of Predicted Geometric Mean Steady State Total Plasma PF-06651600 Pharmacokinetic and Pharmacodynamic Parameters During the Induction and Chronic Periods of Multiple Dose Administration

Dose mg QD	Total C_{max} ng/mL	CCI	Total AUC_{tau} ng.hr/mL	CCI	IP-10 % Reduction from Baseline
			Induction		
20	91.3 (3.3)		209.8 (17)		11 (42)
70	381.0 (3.5)		1015 (21)		23 (35)
200	1254 (2.1)		3712 (14)		42 (19)
			Chronic		
50	259.5 (3.4)		662.0 (20)		18 (39)

AUC_{tau} = Area under the concentration-time curve from zero to 24 hours postdose at steady state; C_{max} = Peak plasma concentration; QD = Once daily; ( ) = Coefficient of variation expressed as a percent; human unbound fraction (fu) = 0.86; 1 ng/mL= 3.504 nM.

CCI

In human whole blood lymphocytes, PF-06651600 inhibited JAK1/JAK3 dependent STAT5 and STAT3 phosphorylation by IL-15 and IL-21 respectively, with IC_{50} values of 56.5 ng/mL and 103 ng/mL, respectively. All other pathways were inhibited at IC_{50} values >571 ng/mL. The inhibition (11-42%) of IP-10 is indicative of modulation of interferon gamma. The predicted average percent IL-15 and IL-21 in vitro signaling inhibition in

human whole blood based on human PK for the selected induction and chronic dosing periods are provided in Table 7.

Table 7. Summary of the Predicted Average Percent In Vitro Signaling Inhibition Following Multiple Dose Administration

Cytokine	Average Percent Signaling Inhibition			
	20 mg	50 mg	70 mg	200 mg
IL-15	20	44	55	81
IL-21	12	30	39	71

Pharmacological modulation of the target can be inferred from the predictions in Table 7.

1.5.4. PF-06700841 Dose Rationale

The predicted PK parameters for PF-06700841 based on simulations using the global PK model are provided in Table 8.

Table 8. Summary of Predicted Geometric Mean Steady State Total Plasma PF-06700841 Pharmacokinetic and Pharmacodynamic Parameters During the Induction and Chronic Periods of Multiple Dose Administration

Dose mg QD	Total C_{max} ng/mL	CCI	Total AUC_{tau} ng.hr/mL	CCI	Percent Reduction from Baseline			
					hsCRP	IP-10	Neutrophils	Reticulocytes
Induction								
10	56.6 (36)	CCI	435.7 (40)	CCI	69 (24)	30 (39)	10 (59)	13 (41)
30	206.7 (27)		1619 (44)		80 (7.5)	44 (29)	23 (66)	33 (40)
60	433.3 (27)		3797 (43)		84 (6.4)	51 (21)	32 (70)	50 (34)
Chronic Dosing								
30	202 (30)		1499 (44)	C	81 (9.6)	45 (29)	28 (50)	34 (40)

AUC_{tau} = Area under the concentration-time curve from zero to 24 hours postdose at steady state; C_{max} = Peak plasma concentration; QD = Once daily; ( ) = Coefficient of variation expressed as a percentage

[redacted]

In study B7931001, mechanistic biomarkers of efficacy, hsCRP and interferon gamma-induced protein 10 (IP-10) related to IL-6 and IFN-gamma, respectively, were measured in healthy subjects. Based on indirect response modeling, the predicted percent reductions in the hsCRP levels ranged between 69% and 84% over the dose range 10-60 mg. Similarly, the reduction of IP-10 levels ranged between 30% and 51% over the same dose range. Modeling and simulations predicted maximum reductions during the induction period in neutrophils and reticulocytes of 32% and 50%, respectively.

Subjects with moderate to severe psoriasis received doses of 30 mg or 100 mg QD or placebo for 28 days (B7931001). Efficacy was measured by placebo adjusted psoriasis area and severity index (PASI) change from baseline. Significant psoriasis disease modification (change >-9) at 30 mg and 100 mg was observed in the patients.

Overall, the doses selected for this study are expected to demonstrate clinically relevant efficacy in subjects with moderate to severe UC.

1.5.5. Summary of Benefits and Risks

IBD is a serious and potentially life threatening disease.

The completed Phase 1 study B7981001 was a randomized, double blind, third party open, placebo controlled, single and multiple dose escalation, parallel group study in healthy adult subjects. Based on this study, PF-06651600 appeared to be generally safe and well-tolerated. No clinically significant changes in vital signs, electrocardiogram or laboratory data were observed. No dose limiting adverse events (AEs) were reported and no subjects met the protocol prescribed individual stopping rules. There were no deaths in the study.

The completed RA Phase 2a study was a randomized double-blind, parallel group, placebo controlled, multi-center study to assess the efficacy and safety profile of 200 mg QD dose of PF-06651600 compared to placebo after 8 week treatment in seropositive subjects with moderate to severe active RA and an inadequate response to methotrexate. PF-06651600 appeared to be generally safe and well tolerated in this study. No deaths or SAEs were reported. TEAEs were numerically higher in the active group compared to placebo and were generally mild in severity. The most common TEAEs by SOC were Infections and Infestations, Skin and Subcutaneous Tissue Disorders, Blood and Lymphatic System Disorders and Gastrointestinal Disorders. There was one mild case of herpes simplex in the PF-06651600 group that was considered to be treatment related with no cases in the placebo group.

The Phase 2a study in subjects with AA is ongoing. However, draft data from an interim analysis at 24 weeks has been reported in this IB. The study is a Phase 2a, randomized, double-blind, placebo-controlled, multi-center study with an extension period to evaluate the efficacy and safety profile of PF-06651600 and PF-06700841 in subjects with moderate to severe active AA. PF-06651600 appeared generally safe and well tolerated. There were no deaths in the study. There were no subjects with SAEs in the PF-06651600 group. The number of AEs was higher in the placebo group relative to the PF-06651600 group. The most common AEs were in the Infections and Infestations, Gastrointestinal Disorders, and Skin and Subcutaneous Tissue Disorders categories, and the majority of events were mild. No serious infections or cases of herpes zoster were reported in the study. Hematological changes were observed in both active groups during the induction and maintenance periods, but were not associated with clinically relevant adverse events.

The safety profile observed during the Phase 1 program for PF-06700841 appears to be acceptable at dosages up to 175 mg administered orally as multiple doses over 10 days. A longer dosing duration was explored in psoriasis patients, who received the maximum PF-06700841 dose level of 100 mg daily for 28 days. No serious or severe AEs were reported in the Phase 1 study. However, there was one AE of herpes zoster infection in a psoriasis subject treated with 100 mg PF-06700841 for 4 weeks. As with other immunomodulators, the risk of infection is potential concern due to the immunosuppressive effects of PF-06700841. To limit this risk, a maximum daily dose below 100 mg (the dose associated with infection in the Phase 1 study B7931001) will be used in this Phase 2 trial. A chronic therapy dose of 30 mg was selected since this dose has demonstrated anti-inflammatory activity resulting in clinical efficacy in patients with psoriasis.

Additional information for these compounds may be found in the single reference safety document (SRSD), which for this study is the individual IB for each compound.

CCI

[redacted]

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives and Endpoints during the Induction Period

Primary Objective(s):	**Primary Endpoint(s):**
• To evaluate the efficacy of PF-06651600 and PF-06700841 at Week 8 in subjects with moderate to severe UC.	• Total Mayo score at Week 8.
Secondary Objective(s):	**Secondary Endpoint(s):**
• To evaluate the safety and tolerability of PF-06651600 and PF-06700841 in subjects with moderate to severe UC in induction.	• Incidence and severity of laboratory abnormalities, adverse events, serious adverse events and withdrawals due to adverse events, vital signs, 12-lead ECG in the induction period. • Incidence of serious infections (see Section 7.2.8 for definition) in the induction period.

• 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]

	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.

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]

	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	

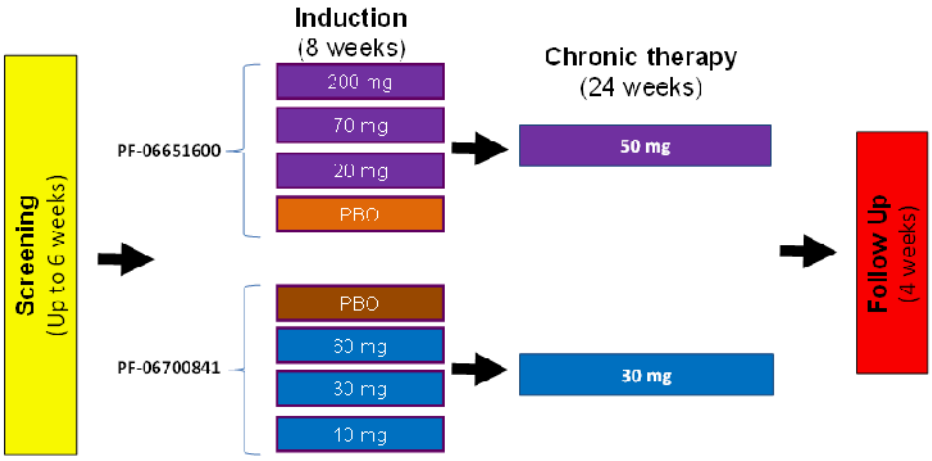
*Remission in total Mayo score excludes friability (Refer to Section 7.3.3).

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.



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.

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);

- Anti-integrin inhibitors (eg, vedolizumab).

See Appendix 1 for guidance only. Local standards of care, as well as investigator assessment should be considered in any assessment.

6. Subjects currently receiving the following treatment for UC are eligible providing they have been on stable doses as described below:

   - Oral 5-ASA or sulfasalazine stable dose for at least 4 weeks prior to baseline. If oral 5-ASA treatment has been recently discontinued, it must have been stopped for at least 2 weeks prior to baseline.

   - Oral corticosteroids (dose equivalent to prednisone up to 25 mg/day; budesonide up to 9 mg/day; See Appendix 9) stable dose for at least 2 weeks prior to baseline. If oral corticosteroids have been recently discontinued, they must have been stopped at least 2 weeks prior to baseline. Decreases in steroid use due to AEs are allowed.

7. Evidence of a personally signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study.

8. Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

9. Female subjects of childbearing potential (Women of child-bearing potential: WOCBP) must test negative for pregnancy at screening visit and baseline visit.

10. Female subjects considered to be of non-childbearing potential must meet at least 1 of the following criteria:

    a. Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; status may be confirmed with a serum follicle-stimulating hormone (FSH) level confirming the postmenopausal state;

    b. Have undergone a documented hysterectomy and/or bilateral oophorectomy;

    c. Have medically confirmed ovarian failure.

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

4.2. Exclusion Criteria

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

1. Female subjects who are pregnant or wish to become pregnant; breastfeeding female subjects; male subjects with partners currently pregnant; male subjects able to father children and female subjects of childbearing potential who are unwilling or unable to use 2 effective methods of contraception (at least 1 highly effective method) as outlined in this protocol for the duration of the study and for at least 28 days after the last dose of investigational product.

2. Presence of indeterminate colitis, microscopic colitis, ischemic colitis, infectious colitis, radiation colitis, and diverticular disease associated with colitis, or clinical findings suggestive of Crohn's disease (eg, fistulae, granulomas on biopsy).

3. Subjects with known colonic stricture and subjects with history of colonic or small bowel obstruction or resection.

4. Subjects with significant trauma or major surgery within 4 weeks of screening.

5. Subjects considered in imminent need for surgery or with elective surgery scheduled to occur during the study.

6. Subjects with a history of bowel surgery within 6 months prior to baseline.

7. Subjects displaying clinical signs of fulminant colitis or toxic megacolon.

8. Subjects with primary sclerosing cholangitis.

9. Subjects with history of colonic or small bowel stoma.

10. Subjects with evidence of colonic dysplasia, adenomas or neoplasia. However, subjects with adenomatous polyps identified on screening endoscopy will be eligible if the polyps have been completely removed and follow-up surveillance per local guidelines is negative.

11. Subjects who meet either of the 2 criteria below are considered at risk for colorectal cancer and must have a colonoscopy prior to randomization. The colonoscopy and pathology reports (if biopsies obtained) must be available in the source documentation:

    - If the subject is ≥50 years of age, a colonoscopy within 10 years of screening is required to exclude adenomatous polyps. Subjects with adenomatous polyps identified on screening endoscopy will be eligible after complete polypectomy and follow-up surveillance per local guidelines is negative.

- If the subject has had extensive (ie, greater than left sided) colitis for ≥8 years or disease limited to left side of colon (ie, distal to splenic flexure) for ≥10 years, regardless of age, a colonoscopy within 1 year of screening visit is required to survey for dysplasia. Subjects with dysplasia or cancer identified on biopsies will be excluded.

12. Subjects receiving the following therapies within the time period described below or expected to receive any of these therapies during the study period:

    - >9 mg/day of oral budesonide or >25 mg/day of prednisone or equivalent oral systemic corticosteroid dose within 2 weeks prior to baseline.

    - IV, IM (parenteral), or topical (rectal) treatment of 5-ASA or corticosteroid enemas/suppositories within 2 weeks prior to baseline.

    - Azathioprine, 6-mercaptopurine, or methotrexate within 2 weeks prior to baseline.

    - Anti-TNF inhibitors (or biosimilars thereof) as described below:

        - Infliximab within 8 weeks prior to baseline;

        - Adalimumab within 8 weeks prior to baseline;

        - Golimumab within 8 weeks prior to baseline;

        - Anti-integrin inhibitors (eg, vedolizumab) within 8 weeks prior to baseline.

    - Interferon therapy within 8 weeks prior to baseline.

    - Subjects with prior treatment with lymphocyte-depleting agents/therapies within 1 year prior to baseline (eg, CamPath® [alemtuzumab], alkylating agents [eg, cyclophosphamide or chlorambucil], total lymphoid irradiation, etc).

      Subjects who have received rituximab or other selective B lymphocyte-depleting agents within 1 year prior to baseline.

    - Subjects previously receiving leukocyte apheresis, including selective lymphocyte, monocyte, or granulocyte apheresis, or plasma exchange within 6 months prior to baseline.

    - Other marketed immunosuppressants or biologics with immunomodulatory properties within 3 months prior to baseline.

    - Other investigational procedures(s) or product(s), such as immunosuppressants used in transplantation (eg, mycophenolate mofetil, cyclosporine, rapamycin, or tacrolimus) or live (attenuated) vaccine within 30 days prior to baseline.

- Other JAK inhibitors within 3 months prior to baseline. Subjects who have not responded to or have been intolerant of other JAK inhibitors.

- Participation in other studies involving investigational drug(s) within 30 days, or 5 half-lives of investigational product (IP) (whichever is greater), prior to study entry and/or during study participation.

13. Abnormal findings on the chest x-ray film such as presence of tuberculosis (TB), general infections, heart failure, or malignancy. Chest x-ray examination may be performed up to 12 weeks prior to screening. Documentation of the official reading must be located and available in the source documentation. If a subject had a CT scan of the chest (with or without IV contrast) up to 12 weeks prior to screening, the CT scan results can substitute for the chest radiograph results.

14. Any history of either untreated or inadequately treated latent or active TB infection, current treatment for active or latent TB infection, evidence of currently active TB by chest x-ray, or residing with or frequent close contact with individual(s) with active TB. Subjects who have a positive Mantoux (PPD) tuberculin skin test or a positive Interferon Gamma Release Assay (IGRA to be tested at the site's local lab where feasible) during screening or within 12 weeks prior to randomization, except as noted below:

    - An IGRA is preferred for subjects with a prior BCG vaccination (to be tested by a site's local lab when feasible), but may be used for any subject. Documentation of IGRA product used and the test result must be in the subject's source documentation.

        - If the results of the IGRA are positive, the test must not be repeated.

        - If the results of the IGRA are indeterminate, the test may be repeated, and if a negative result is obtained, enrollment may proceed. A positive test on repeat is exclusionary.

        - Subjects with repeat indeterminate IGRA results may be enrolled after a documented evaluation by appropriately qualified personnel (which may include a pulmonary or infectious disease specialist, or locally acceptable expert as defined by local guidelines), that in their opinion, the probability of reactivation is low (ie, subject would be acceptable for immunosuppressant treatment without additional action).

    - Subjects adequately treated (in the opinion of the appropriately qualified personnel - which may include a pulmonary or infectious disease specialist, or locally acceptable expert as defined by local guidelines) for latent and/or active tuberculosis infection may be enrolled regardless of Mantoux or IGRA results provided the treatment is well documented in the subject's medical records and/or source documentation prior to enrollment in the study.

Note:

- A positive Mantoux tuberculin skin test is defined as ≥5 mm of induration (or as defined by country specific or local standards) at 48-72 hours without consideration of prior Bacillus Calmette-Guerin (BCG) vaccination. Documentation of the dose and product used for the Mantoux tuberculin test as well as the official test reading must be obtained and available in the subject's source documentation.

- The following are acceptable assays: QuantiFERON® - TB Gold test (QFT-G), QuantiFERON® - TB Gold In-Tube test (QFT-GIT) and T-SPOT® - TB test during screening or within 12 weeks prior to screening.

15. Presence of active enteric infections (positive stool culture and sensitivity performed at screening or 6 week prior to the screening visit). The presence of *Clostridium difficile* infection (reference C. diff section) or pseudomembranous colitis. Known active invasive fungal infections such as histoplasmosis or parasitic infections. Subject with *Clostridium difficile* infection may be treated and re-tested or re-screened at the discretion of the Investigator.

16. Known history of human immunodeficiency virus (HIV) based on documented history with positive serological test, or positive HIV serologic test at screening, tested at the site's local lab (when feasible).

17. Subjects with Hepatitis B or Hepatitis C viruses.

    - For Hepatitis B, all subjects will undergo testing for Hepatitis B Surface Antigen (HBsAg) and Hepatitis B Core Antibody (HBcAb) during Screening. Subjects who are HBsAg positive are not eligible for the study. Subjects who are HBsAg negative and HBcAb positive will be reflex tested for Hepatitis B Surface Antibody (HBsAb) and if HBsAb is positive, may be enrolled in the study; if HBsAb is negative, the subject is not eligible for the study.

    - For Hepatitis C, all subjects will undergo testing for Hepatitis C antibody (HCVAb) during Screening. Subjects with positive HCV Ab tests will be reflex tested for HCV ribonucleic acid (HCV RNA). Only subjects with negative HCV Ab or HCV RNA will be allowed to enroll in the study.

18. Clinically significant infections within 6 months of baseline (eg, those requiring hospitalization or parenteral antimicrobial therapy, or opportunistic infections), or a history of any infection otherwise judged by the investigator to have the potential for exacerbation by participation in the study.

19. Cancer or history of cancer or lymphoproliferative disease within the previous 5 years (with the exception of subjects with adequately treated or excised non-metastatic basal cell or squamous cell carcinoma of the skin or cervical carcinoma in situ).

20. Presence of transplanted organ; skin grafts are allowed.

21. Have a history (single episode) of disseminated herpes zoster or disseminated herpes simplex, or a recurrent (more than one episode of) localized dermatomal herpes zoster.

22. Have current or recent history of clinically significant severe or progressive hearing loss or auditory disease. Subjects with hearing aids will be allowed to enter the study provided their hearing impairment is considered controlled/clinically stable.

23. Significant concurrent medical condition at the time of screening or baseline visit, including but not limited to the following:

    - Any major illness/condition or evidence of an unstable clinical condition (eg, renal, hepatic, hematologic, gastrointestinal, endocrine, pulmonary, immunologic [eg, Felty's syndrome], or local active infection/infectious illness) that, in the investigator's judgment will substantially increase the risk to the subject if he or she participates in the study.

    - Active renal disease and/or recent kidney stones.

    - Severe hepatic impairment (defined as Child-Pugh C).

    - Acute coronary syndrome (eg, myocardial infarction, unstable angina pectoris) and any history of cerebrovascular disease within 24 weeks before screening.

24. Prior evidence of liver injury or toxicity due to methotrexate.

25. Abnormality in hematology and/or chemistry profiles during screening:

    - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels ≥1.5 times the upper limit of normal (ULN).

    - Total bilirubin level ≥1.5 times the ULN; subjects with a history of Gilbert's syndrome may have a direct bilirubin measured and would be eligible for this study provided the direct bilirubin in ≤ ULN.

    - Hemoglobin level ≤90 g/L (9.0 g/dL).

    - Platelet count ≤100 x 10^9/L (100,000 cells/mm^3) or ≥1000 x 10^9/L (1,000,000 cells/mm^3).

    - White blood cell (WBC) count ≤3.0 x 10^9/L (3000 cells/mm^3) or absolute neutrophil count (ANC) <1200 cells/mm^3 or absolute lymphocyte count of <0.8 x 10^9/L (<800 cells/mm^3).

    - eGFR <60 mL/min/1.73m^2 based on the age appropriate calculation.

- Proteinuria ≥3+.
- Glycosylated hemoglobin (HbA_{1C}) >10%.
    - Subjects with HbA_{1C} > ULN without a diagnosis of diabetes mellitus should be evaluated prior to randomization for confirmation of diagnosis.

26. Subjects with any condition possibly affecting oral drug absorption (eg, gastrectomy, clinically-significant diabetic gastroenteropathy, or certain types of bariatric surgery such as gastric bypass). Procedures such as gastric banding that simply divide the stomach into separate chambers are NOT exclusionary.

27. Subjects receiving prohibited concomitant medications, including moderate to potent CYP3A inducers or inhibitors (See Appendix 2) in the time periods described below:

    - For moderate to potent CYP3A inducers, within 28 days or 5 half-lives, whichever is longer, prior to baseline.
    - For moderate to potent CYP3A inhibitors, within 7 days or 5 half-lives, whichever is longer, prior to baseline.

    Note: Simvastatin or simvastatin-containing products from 5 days prior to baseline.

28. Subjects receiving strong P-gp inhibitors (eg, quinidine) within 5 half-lives prior to baseline.

29. Subjects receiving narrow therapeutic index substrates of MDR1 (eg, digoxin), OCT2 or MATE (eg, dofetilide) within 5 half-lives prior to baseline.

30. Donation of blood in excess of 500 mL within 8 weeks prior to baseline.

31. History of alcohol or drug abuse with less than 6 months of abstinence prior to baseline.

32. Investigator site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or subjects who are Pfizer employees, including their family members, directly involved in the conduct of the study.

33. Other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.

34. History of thrombotic event(s), including deep venous thrombosis (DVT), and known inherited conditions that predispose to hypercoagulability.

Screening laboratory tests with abnormal results (if considered by the investigator to be transient and inconsistent with the subject's clinical condition) may be repeated within the screening window to confirm abnormal results. If results return to protocol acceptable limits within the screening period, the subject may enter the study.

Subjects who do not meet eligibility criteria (ie, screen fail) may be re-screened **once** (with a new screening number) at the discretion of the investigator.

4.3. Lifestyle Requirements

4.3.1. Contraception

CCI [redacted]

Subjects who are, in the opinion of the investigator, sexually active and at risk for pregnancy with their partner(s) must agree to use 2 methods of effective contraception (at least 1 highly effective method) throughout the study and for at least 28 days after the last dose of investigational product. The investigator or his or her designee, in consultation with the subject, will confirm that the subject has selected 2 appropriate methods of contraception for the individual subject and his/her partner(s) from the list of permitted contraception methods (see below) and will confirm that the subject has been instructed in their consistent and correct use. At time points indicated in the Schedule of Activities, the investigator or designee will inform the subject of the need to use 2 methods of effective contraception (at least 1 highly effective method) consistently and correctly and document the conversation, and the subject's affirmation, in the subject's chart. In addition, the investigator or designee will instruct the subject to call immediately if 1 or both of the selected contraception methods is discontinued or if pregnancy is known or suspected in the subject or partner.

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

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.

2. Intrauterine device (IUD).

3. Intrauterine hormone-releasing system (IUS).

4. Bilateral tubal occlusion.

5. Vasectomized partner.

- Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.

6. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:

   - Oral;
   - Intravaginal;
   - Transdermal;
   - Injectable.

7. Progestogen-only hormone contraception associated with inhibition of ovulation:

   - Oral;
   - Injectable.

8. Sexual abstinence:

   - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

Effective method:

1. Male condom or female condom.

All sexually active male subjects must agree to prevent potential transfer to and exposure of partner(s) to drug through ejaculate by using a condom consistently and correctly, beginning with the first dose of investigational product and continuing for at least 28 days after the last dose of investigational product. Male subjects must refrain from donating sperm during the study and for 90 days after the last dose of investigational product.

CCI [redacted]

4.3.2. Dietary Restriction

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

4.4. Sponsor's Qualified Medical Personnel

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

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

5. STUDY TREATMENTS

For the purposes of this study, and per International Conference on Harmonisation (ICH) guidelines, investigational product is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference/comparator in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (ICH E6 1.33).

For this study, the investigational product(s) are PF-06651600 and PF-06700841 tablets.

5.1. Allocation to Treatment

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

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

5.2. Breaking the Blind

The study will be Sponsor, subject, and investigator blinded during the induction phase.

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

5.3. Subject Compliance

IP accountability and compliance will be assessed by the site at each clinic visit starting at the visit after the baseline visit up through Week 32. Subject compliance will be verified by the accounting of investigational product at each visit. When investigational product is administered at the research facility, it will be administered under the supervision of study personnel.

Compliance of the IP will be monitored by delegated site personnel by the accounting of unused IP returned by the subject at study visits. Compliance will be documented on the CRF and source document. Non-compliance is defined as taking less than 80% or more than 120% of IP during the double-blind study treatment (induction) and/or chronic dosing period(s) and as directed by the dosing instructions, regardless of reason. Subjects are to bring the blister cards and/or bottles with any remaining study drug to each visit for review. The investigator has the discretion to withdraw any subject from the study for reasons of non-compliance with the dosing regimen. Investigators should indicate on appropriate CRF page non-compliance with study treatment and provide an explanation. Inventory control of all IP must be rigorously maintained throughout the duration of the study until all IP has been accounted for and/or returned to the sponsor. Any discrepancies noted between drug dispensing records and drug inventory must be reported to Pfizer.

5.4. Investigational Product Supplies

5.4.1. Dosage Form(s) and Packaging

Blinded PF-06651600, PF-06700841 and matching placebos will be provided as tablets in blister cards for oral administration during the induction period of the study. For the chronic dosing period, PF-06700841 tablets will be supplied in bottles, PF-06651600 tablets will be supplied as tablets in blister cards. The designation “PF-06651600-15” and “PF-06700841-15” may appear on labeling and indicates a salt. They are equivalent to “PF-06651600” and “PF-06700841” with regard to this protocol. The PF-06651600 10 mg and 50 mg tablets and their matching placebos will be supplied in separate blister cards and labeled according to local regulatory requirements. The PF-06700841 5 mg and 25 mg tablets and their matching placebos will be supplied in separate blister cards and labeled

according to local regulatory requirements. Blinding occurs within investigational products, not across investigational products and only for the induction phase.

5.4.2. Preparation and Dispensing

The investigational product will be dispensed using an IRT drug management system at each visit from baseline visit through Week 24. A qualified staff member will dispense the investigational product via unique container numbers in the blister cards or bottles provided, in quantities appropriate for the study visit schedule. The subject should be instructed to maintain the product in the blister cards or bottles provided throughout the course of dosing and return the blister cards or bottles to the site at the next study visit. Refer to Appendix 10 for investigational drug dispensing during public emergencies if applicable.

5.5. Administration

PF-06651600 and PF-06700841 tablets and matching placebo for oral administration will be dispensed in blister cards or bottles as described above in Section 5.4.1. Subjects will be dispensed an appropriate number of blister cards or bottles sufficient for administration until the next dispensing visit and given clear dosing instructions.

Sites will be trained on how subjects should take tablets at home through an IP manual and/or other vehicle(s). Sites are responsible for communicating this information and site staff **should review the dosing instructions with subjects at every study visit** through Week 24.

Subjects should take the IP orally for 8 weeks during the induction period and an additional 24 weeks during the chronic dosing period for a total of 32 weeks. Subjects should swallow the tablets with ambient temperature water to a total volume of approximately 240 mL. Subjects should swallow the IP whole, and will not manipulate or chew the IP prior to swallowing. **Subjects will be instructed to take the IP in the morning after breakfast whenever possible** even though IP may be taken with or without food; however, for **study visit days (ie, baseline, Weeks 2, 4, 8, 12, 16, 20, and 24)**, subjects are to be instructed to refrain from dosing at home, bring their blister cards or bottles to the site. **Subjects are to take the dose in the clinic from their current blister card or bottle**. If a subject administers the morning dose prior to the visit, the subject may be rescheduled within the permitted window or the visit may be conducted CCI [redacted]

If a dose is missed and the interval to the next dose is less than 8 hours, the missed dose should not be administered.

During the induction phase, if subjects require discontinuation of investigational product for medically mandated reasons (eg, following instructions from investigator) for more than 7 consecutive days at any time during the study, they will be discontinued from treatment and 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 before entering the follow-up period, and will not be permitted to enter the chronic dosing period. During the chronic dosing period, if dosing is missed for more than 7 consecutive days, the subject should be considered for discontinuation following consultation with the Sponsor.

5.6. Investigational Product Storage

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

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

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

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

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

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

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

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

5.7. Investigational Product Accountability

The investigator site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies. All investigational products will be accounted for using a drug accountability form/record.

All blister cards and/or bottles of study drug must be returned to the investigator by the subject at every visit.

5.7.1. Destruction of Investigational Product Supplies

The sponsor or designee will provide guidance on the destruction of unused investigational product (eg, at the site). If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer, and all destruction must be adequately documented.

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

5.8. Concomitant Treatment(s)

All concomitant medication(s) and treatment(s) administered/taken during the study must be recorded with indication, daily dose, and start and stop dates of administration. All subjects will be questioned about concomitant medication at each site visit.

A subject who is receiving metformin as concomitant medication must allow at least two hours after taking either medication and before taking investigational product.

Medication(s) administered/taken following the first dose of IP will be documented as concomitant medication(s).

Treatments taken within 42 days before the first dose of study drug will be documented as prior treatment. Treatments taken after the first dose of study drug will be documented as concomitant treatment.

5.8.1. Oral Corticosteroids

Any oral corticosteroids taken during the screening and treatment periods of the study will be captured on the appropriate CRF.

5.8.2. Permitted Medications

Subjects will be allowed to use the following medications as detailed below:

- Concomitant use of oral 5-ASA or sulfasalazine. Dose must be stable for at least 4 weeks prior to baseline and through end of study (Week 36). If oral 5-ASA treatment has been recently discontinued, it must have been stopped for at least 2 weeks prior to baseline.

- A stable dose of oral corticosteroids (dose equivalent to prednisone up to 25 mg/day; budesonide up to 9 mg/day; See Appendix 9) for at least 2 weeks prior to baseline and through end of the induction period (Week 8, except for the case of subjects undergoing optional steroid tapering in the chronic dosing period).

- If oral corticosteroids have been recently discontinued, they must have been stopped at least 2 weeks prior to baseline. Rectal steroids are prohibited. Decreases in steroid use due to AEs are allowed.

- Upon a subject achieving remission during the chronic dosing period, steroids may be slowly tapered per local guidelines. Steroid tapering is allowed only in the chronic dosing period. Subjects may reduce the daily dose of prednisone or equivalent by 2.5 to 5 mg weekly (based on their symptoms) until the dose of prednisone or equivalent is 10 mg/day, then reduce the daily dose of prednisone or equivalent by 2.5 mg weekly until the dose is 0 mg. If a subject experiences worsening of UC symptoms during the corticosteroid taper that in the opinion of the investigator are attributable to the corticosteroid taper, then the investigator may instruct the subject to revert back to the preceding dose in the taper schedule (ie, "step up"). The signs or symptoms leading to this change (eg, increased stool frequency, increased rectal bleeding) must be recorded on the CRF. Study subjects with signs or symptoms attributed to corticosteroid taper are permitted to step up their corticosteroid dosage one time during study participation and then resume corticosteroid taper to achieve steroid-free status. See Appendix 9 for guidance on steroid equivalency.

5.8.3. Prohibited Medications

The following medications are prohibited for the specified time periods as described below:

- Oral budesonide (>9 mg/day) or prednisone (>25 mg/day) or equivalent oral systemic corticosteroid within 2 weeks prior to baseline and through end of study (Week 36).

- IV, IM (parenteral), or topical (rectal) treatment of 5-ASA or corticosteroid enemas/suppositories within 2 weeks prior to baseline and through end of study (Week 36).

- Azathioprine, 6-mercaptopurine, or methotrexate within 2 weeks prior to baseline and through end of study (Week 36).

- Biologics including anti-TNF inhibitors (eg, infliximab, adalimumab, golimumab), or biosimilars thereof, within 8 weeks prior to baseline and through end of study (Week 36).

- Anti-integrin inhibitors (eg, vedolizumab) within 8 weeks prior to baseline and through end of study (Week 36).

- Interferon therapy within 8 weeks prior to baseline and through end of study (Week 36).

- Lymphocyte-depleting agents/therapies within 1 year prior to baseline and through end of study (Week 36).

- Leukocyte apheresis including selective lymphocyte, monocyte, or granulocyte apheresis, or plasma exchange within 6 months prior to baseline and through end of study (Week 36).

- Rituximab or other selective B lymphocyte-depleting agents within 1 year prior to baseline and through end of study (Week 36).

- Other marketed immunosuppressants or biologics with immunomodulatory properties within 3 months prior to baseline and through end of study (Week 36).

- Use of immunosupressants used in transplantation (eg, mycophenolate mofetil, cyclosporine, rapamycin, or tacrolimus) within 30 days prior to baseline and through end of study (Week 36).

- Any live (attenuated) vaccines from 30 days prior to baseline and through the end of study (Week 36).

- Anti-motility agents for control of diarrhea (eg, diphenoxylate hydrochloride with atropine sulfate or loperamide) from 5 days prior to baseline through end of study (Week 36).

- Moderate to potent CYP3A inducers or inhibitors as listed in Appendix 2 through end of the study (Week 36) (unless as in an emergency as outlined in Appendix 2).

- Simvastatin or simvastatin-containing products from 5 days prior to baseline and through end of study (Week 36).

- Strong P-gp inhibitors (eg, quinidine) within 5 half-lives prior to baseline and through end of study (Week 36).

- Narrow therapeutic index substrates of MDR1 (eg, digoxin), OCT2 or MATE (eg, dofetilide) within 5 half-lives prior to baseline and through end of study (Week 36).

5.8.4. Vaccinations

Vaccination with live virus, attenuated live virus, or any live viral components is prohibited within the 30 days prior to the first dose of study drug and through the end of the study (Week 36). Similarly, current routine household contact with individuals who have been vaccinated with live vaccine components should be avoided during treatment and through the end of the study.

Such vaccines include but are not limited to FluMist® (intranasal influenza vaccine), attenuated rotavirus vaccine, varicella (chickenpox) vaccine, attenuated typhoid fever vaccine, oral polio vaccine, MMR (measles, mumps, rubella) vaccine and vaccinia (smallpox) vaccine. Following vaccination with live component vaccines, the virus may be

shed in bodily fluids, including stool, and there is a potential risk that the virus may be transmitted.

5.9. Rescue Medication

Subjects requiring rescue medication prior to the end of study (Week 36) visit will be discontinued from treatment 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 then enter the follow up period. Subjects requiring rescue medication after the Week 32 visit should complete the follow-up visit.

6. STUDY PROCEDURES

Refer to Appendix 10 for Alternative Measures During Public Emergencies if applicable.

6.1. Screening

After informed consent has been obtained, subjects have up to 6 weeks of a screening period to complete all of the screening procedures. Subject's eligibility for the study will be evaluated during this period based on medical history, physical examination, laboratory values, bowel movement diary data and additional tests. To prepare for study participation, subjects will be instructed on the use of Lifestyle Requirements (see Section 4.3) and Concomitant Medications (see Section 5.8).

Screening laboratory tests with abnormal results may be repeated to confirm abnormal results; the last value will be used to determine eligibility. If results return to protocol accepted limits within the 6-week screening period, the subject may enter the study.

Subjects who do not meet eligibility criteria (ie, screen fail) may be re-screened **once** (with a new screening number) at the discretion of the investigator.

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

The following procedures will be performed:

- Informed consent and Eligibility Assessment.
- Complete medical history including:
  - History of UC, including duration of disease, extent of disease, extra-intestinal manifestations, duration of current flares, number of flares in the preceding year, and UC related hospitalizations;
  - History of chicken pox and shingles;

  - History of skin rash, skin infection and any abnormalities that may predispose the subject to infection;
  - Reasons for previous UC medication intolerance (eg, discontinuation of medication due to an AE as determined by the investigator);
  - History of previous vaccinations, specifically influenza, pneumococcal, varicella, and zoster;
  - History of illegal drug use;
  - Smoking status;
  - Average weekly alcohol consumption;
  - Family history of premature coronary heart disease (CHD). Premature coronary heart disease is defined as CHD in a male first-degree relative first observed at <55 years or CHD in female first-degree relative first observed <65 years;
  - Family history of colorectal cancer.
- Assessment of prior concomitant medications, including a complete history of all therapies for UC received since diagnosis (including treatment response), and detailed UC medications (including dose, frequency, and route) taken within 3 months prior to the screening visit. Complete history of all drugs (including nonprescription drugs, vitamins, and dietary or herbal supplements), taken within 4 weeks prior to screening procedures.
- Complete physical examination (including height and weight).
- Vital signs including temperature.
- 12-lead electrocardiogram (ECG).
- Audiogram.
- Laboratory tests including (see Section 7):
  - Hematology;
  - Serum chemistry;
  - Fasting lipid panel (at least 8 hour fast);
  - HbA_{1C};

- HBsAg, HBcAb, HCVAb. Subjects who are HCV Ab positive require further testing with HCV RNA;
- HIV-1/HIV-2 serology;
- β-hCG blood test will be performed for women of childbearing potential;
- Urinalysis, including spot urine albumin/creatinine ratio;
- FSH should be done in postmenopausal women (females who are amenorrheic for at least 12 consecutive months);
- Stool microbiology (stool culture for enteric pathogens, ova and parasites, and Clostridium difficile toxin test), if not performed within 6 weeks prior to screening, should be prior to administration of any bowel prep for endoscopy.
- Tuberculosis Screening (Refer to Sections 7.2.5 and 7.2.6).

- Chest radiograph (posteroanterior and lateral), if not performed and documented within 12 weeks prior to screening. Negative results must be documented prior to Baseline (Day 1) randomization.
- Stool sample for fecal calprotectin analysis (should be prior to initiation of any bowel preparation for endoscopy).

C
C
I

[redacted]

- Subjects will be instructed on daily collection of bowel movement diary data. The bowel movement diary to collect BM frequency and rectal bleeding should be collected daily beginning approximately 2 weeks prior to screening endoscopy.
- Endoscopy:

  Colonoscopy is required for the following subjects:

  - Who are at least 50 years old and have not had a colonoscopy performed within 10 years; OR
  - Who have extensive colitis for ≥8 years or disease limited to left side of colon for ≥10 years and have not had a colonoscopy within 1 year.

  Flexible sigmoidoscopy: All other subjects may undergo a flexible sigmoidoscopy at the discretion of the investigator. Subjects who undergo colonoscopy do not require a separate sigmoidoscopy.

- 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 stool diary data collection for Mayo score calculation and to obtain endoscopic subscore report from the central reader. 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.

  CCI [redacted]

- Contraception check (Refer to Section 4.3).

- Serious and non-serious adverse event monitoring.

6.2. Study Period (Induction)

6.2.1. Baseline/(Week 0/Day 1)

Subjects are required to fast (no food or drink except water) for at least 8 hours prior to the baseline visit. This is required for fasting lipid profile and fasting glucose sample collection.

Eligibility assessment will be performed based on all available data collected during the screening period and at baseline visit.

The following procedures will be performed:

- Review study data collected during screening and perform initial eligibility assessment before proceeding to the other procedures below.

- Assessments (Bowel Movement and CCI [redacted] IBDQ, SF-36, EQ-5D-3L, EQ-5D-VAS).

- Complete physical examination.

- Vital signs including temperature.

- Laboratory tests including:

  - Hematology;

  - Serum chemistry;

  - Lipid profile (fasting);

  - hsCRP;

  CCI [redacted]

- Cystatin C (and eGFR);
- [redacted]
- Urinalysis;
- Urine pregnancy test for women of childbearing potential.

- Prior/concomitant medication assessment.
- Serious adverse event and adverse event monitoring.
- Contraception check.
- Mayo (total and partial) scores at Week 0 will be calculated based on stool frequency, rectal bleeding, and centrally read endoscopic subscores for the endoscopy performed during the screening period and the PGA obtained at baseline.
- [redacted]
- Assessment of eligibility.
- Randomization.
- [redacted]
- Study drug dispensing.
- Administration of the first dose of IP.
- Provide and review dosing instruction.

6.2.2. Week 2 (±2 Days)

There is a ±2 day window for this study visit.

Subjects are required to fast (no food or drink except water) for at least 8 hours prior to the visit. This is required for fasting lipid profile and fasting glucose sample collection.

The following procedures will be performed:

- Assessments (Bowel Movement and CCI Partial Mayo score).
- Targeted physical examination (consisting of examination of skin, heart, lungs, abdomen, and examination of body systems where there are symptom complaints by the subject).
- Vital signs including temperature.
- Laboratory tests including:
  - Hematology;
  - Serum Chemistry;
  - Fasting lipid panel;
  - Cystatin C (and eGFR);
  - CCI
  - Urinalysis;
  - Urine pregnancy test for women of childbearing potential;
  - CCI
- Administration of one dose of IP.
- Provide and review dosing instruction.
- IP accountability and dispensing.
- Serious adverse event and adverse event monitoring.
- Concomitant medication assessment.

- Contraception check.

6.2.3. Week 4 (±2 Days)

There is a ±2 day window for this study visit.

Subjects are required to fast (no food or drink except water) for at least 8 hours prior to the visit. This is required for fasting lipid profile and fasting glucose sample collection.

The following procedures will be performed:

- Assessments (Bowel Movement and CCI [redacted] Partial Mayo score, IBDQ, SF-36, EQ-5D-3L, EQ-5D-VAS).
- Targeted physical examination (consisting of examination of skin, heart, lungs, abdomen, and examination of body systems where there are symptom complaints by the subject).
- Vital signs including temperature.
- Laboratory tests including:
  - Hematology;
  - Serum Chemistry;
  - Fasting lipid panel;
  - Cystatin C (and eGFR);
  - hsCRP;
  - CCI [redacted]
  - Urinalysis;
  - Urine pregnancy test for women of childbearing potential;
  - Stool sample for fecal calprotectin analysis;
  - CCI [redacted]
- Provide and review dosing instruction.

- Administration of one dose of IP.
- [redacted]
- IP accountability and dispensing.
- Serious adverse event and adverse event monitoring.
- Concomitant medication assessment.
- Contraception check.

6.2.4. Week 8 (±2 Days)

There is a ±2 day window for this study visit.

Subjects are required to fast (no food or drink except water) for at least 8 hours prior to the visit. This is required for fasting lipid profile and fasting glucose sample collection.

The following procedures will be performed:

- Assessments (Bowel Movement and [redacted] IBDQ, SF-36, EQ-5D-3L, EQ-5D-VAS).
- Complete physical examination.
- Audiogram.
- Vital signs including temperature.
- 12-lead ECG.
- Laboratory tests including:
  - Hematology;
  - Serum Chemistry;
  - Fasting lipid panel;
  - hsCRP;
  - [redacted]
  - Cystatin C (and eGFR);
  - [redacted]

[redacted]

- Urinalysis;
- Urine pregnancy test for women of childbearing potential;
- Stool sample for fecal calprotectin analysis;

[redacted]

- Administration of one dose of IP.
- Provide and review dosing instruction for the chronic dosing period.

[redacted]

- Endoscopy (colonoscopy or flexible sigmoidoscopy):

[redacted]

- Mayo score.

[redacted]

- Partial Mayo Score calculation.
- Re-Randomization to chronic dosing period.
- IP accountability and dispensing.
- Serious adverse event and adverse event monitoring.
- Concomitant medication assessment.
- Contraception check.

6.3. Study Period (Chronic Therapy)

Subjects will begin the chronic dosing period after assessments at week 8 are complete.

6.3.1. Week 12 (±4 Days)

There is a ±4 day window for this study visit.

Subjects are required to fast (no food or drink except water) for at least 8 hours prior to the visit. This is required for fasting lipid profile and fasting glucose sample collection.

The following procedures will be performed:

- Assessments (Bowel Movement and CCI [redacted] Partial Mayo score).
- Targeted physical examination (consisting of examination of skin, heart, lungs, abdomen, and examination of body systems where there are symptom complaints by the subject).
- Vital signs including temperature.
- Laboratory tests including:
  - Hematology;
  - Serum Chemistry;
  - Fasting lipid panel;
  - Cystatin C (and eGFR);
  - Urinalysis;
  - Urine pregnancy test for women of childbearing potential;
  - C [redacted]
- Administration of one dose of IP.
- Provide and review dosing instruction.
- IP accountability and dispensing.
- Serious adverse event and adverse event monitoring.
- Concomitant medication assessment.
- Contraception check.

6.3.2. Week 16 (±4 Days)

There is a ±4 day window for this study visit.

Subjects are required to fast (no food or drink except water) for at least 8 hours prior to the visit. This is required for fasting lipid profile and fasting glucose sample collection.

The following procedures will be performed:

- Assessments (Bowel Movement and CCI Partial Mayo score).
- Targeted physical examination (consisting of examination of skin, heart, lungs, abdomen, and examination of body systems where there are symptom complaints by the subject).
- Audiogram.
- Vital signs including temperature.
- Laboratory tests including:
  - Hematology;
  - Serum Chemistry;
  - Fasting lipid panel;
  - Cystatin C (and eGFR);
  - hsCRP;
  - CCI
  - Urinalysis;
  - Urine pregnancy test for women of childbearing potential;
  - Stool sample for fecal calprotectin analysis;
  - CCI
- Administration of one dose of IP.
- Provide and review dosing instruction.
- IP accountability and dispensing.

- Serious adverse event and adverse event monitoring.
- Concomitant medication assessment.
- Contraception check.

6.3.3. Week 20 (±4 Days)

There is a ±4 day window for this study visit.

Subjects are required to fast (no food or drink except water) for at least 8 hours prior to the visit. This is required for fasting lipid profile and fasting glucose sample collection.

The following procedures will be performed:

- Assessments (Bowel Movement and CCI [redacted] Partial Mayo score).
- Targeted physical examination (consisting of examination of skin, heart, lungs, abdomen, and examination of body systems where there are symptom complaints by the subject).
- Vital signs including temperature.
- Laboratory tests including:
  - Hematology;
  - Serum Chemistry;
  - Fasting lipid panel;
  - Cystatin C (and eGFR);
  - Urinalysis;
  - Urine pregnancy test for women of childbearing potential;
  - C [redacted]
- Administration of one dose of IP.
- Provide and review dosing instruction.
- IP accountability and dispensing.
- Serious adverse event and adverse event monitoring.
- Concomitant medication assessment.

- Contraception check.

6.3.4. Week 24 (±4 Days)

There is a ±4 day window for this study visit.

Subjects are required to fast (no food or drink except water) for at least 8 hours prior to the visit. This is required for fasting lipid profile and fasting glucose sample collection.

The following procedures will be performed:

- Assessments (Bowel Movement and CCI [redacted] Partial Mayo score).
- Targeted physical examination (consisting of examination of skin, heart, lungs, abdomen, and examination of body systems where there are symptom complaints by the subject).
- Vital signs including temperature.
- Laboratory tests including:
  - Hematology;
  - Serum Chemistry;
  - Fasting lipid panel;
  - Cystatin C (and eGFR);
  - hsCRP;
  - Urinalysis;
  - Urine pregnancy test for women of childbearing potential;
  - Stool sample for fecal calprotectin analysis;
  - C [redacted]
- Administration of one dose of IP.
- Provide and review dosing instruction.
- IP accountability and dispensing.
- Serious adverse event and adverse event monitoring.
- Concomitant medication assessment.

- Contraception check.

6.3.5. Week 32 (±4 Days)/Early Termination Visit

For subjects who discontinue early during the chronic dosing period (after Week 8 and prior to Week 32 visit), the procedures scheduled for Week 32 will be performed on the last day the subject takes the investigational product or as soon as possible thereafter.

There is a ±4 day window for this study visit.

Subjects are required to fast (no food or drink except water) for at least 8 hours prior to the visit. This is required for fasting lipid profile and fasting glucose sample collection.

The following procedures will be performed:

- Assessments (Bowel Movement and CCI Diary Data, IBDQ, SF-36, EQ-5D-3L, EQ-5D-VAS).
- Complete physical examination (including weight).
- Audiogram.
- Vital signs including temperature.
- 12-lead ECG.
- Laboratory tests including:
  - Hematology;
  - Serum Chemistry;
  - Fasting lipid panel;
  - Cystatin C (and eGFR);
  - hsCRP;
  - [redacted]

[redacted]

- Urinalysis;
- Urine pregnancy test for women of childbearing potential;
- Stool sample for fecal calprotectin analysis;

[redacted]

- Administration of final dose of IP.
- Endoscopy (colonoscopy or flexible sigmoidoscopy):

[redacted]

- Mayo score.

[redacted]

- Partial Mayo Score calculation.
- IP accountability.
- Serious adverse event and adverse event monitoring.
- Concomitant medication assessment.
- Contraception check.

6.3.6. Follow-up Visit (Week 36±7 Days)

There is a ±7 day window for this study visit.

Follow-up contact will be completed at least 28 calendar days, and up to 35 calendar days after the last administration of the investigational product to capture any potential adverse events (see Section 8.1.4) and to confirm appropriate contraception usage (see Section 4.3.1).

Subjects are required to fast (no food or drink except water) for at least 8 hours prior to the visit. This is required for fasting lipid profile and fasting glucose sample collection.

The following procedures will be performed:

- Targeted physical examination (consisting of examination of skin, heart, lungs, abdomen, and examination of body systems where there are symptom complaints by the subject).
- Vital signs including temperature.
- Laboratory tests including:
  - Hematology;
  - Serum Chemistry;
  - Fasting lipid panel (at least 8 hours fast);
  - Cystatin C (and eGFR);
  - Urinalysis;
  - Urine pregnancy test for women of childbearing potential.
- Serious adverse event and adverse event monitoring.
- Concomitant medication assessment.
- Contraception check.

6.4. Subject Withdrawal

6.4.1. Withdrawal of Consent

Subjects who request to discontinue receipt of study treatment will remain in the study and continue to be followed for protocol specified follow-up procedures; the follow-up visit should occur 4 weeks after their last dose whenever possible. The procedures scheduled for Week 32 will be performed on the last day the subject takes the investigational product or as soon as possible thereafter. The only exception to this is when a subject specifically withdraws consent for any further contact with him or her or persons previously authorized by the subject to provide this information. Subjects should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of investigational product or also from study procedures and/or post treatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

6.4.2. Lost to Follow-up

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

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety (see also the Withdrawal From the Study Due to Adverse Events section) or behavioral reasons, or the inability of the subject to comply with the protocol-required schedule of study visits or procedures at a given study site.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. All attempts to contact the subject and information received during contact attempts must be documented in the subject's medical record. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request that the subject return all unused investigational product(s), request that the subject return for a final visit, if applicable, and follow up with the subject regarding any unresolved adverse events (AEs).

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

Subjects who withdraw from the study may be replaced at the discretion of the investigator upon consultation with the sponsor.

6.5. Guidelines for Monitoring and Discontinuations

The following laboratory abnormalities require monitoring and re-testing ideally within 3-5 days, except as noted below when a shorter re-testing period is required:

- Absolute neutrophil counts $<1.2 \times 10^9/L$ ($<1200/mm^3$).
- Hemoglobin <9.0 g/dL.

- Platelet counts <100 x 10^9/L (<100,000/mm^3).
- Lymphocytes <800/mm^3; <0.8 x 10^9/L.
- CK > 3x ULN.
- Any single AST and/or ALT elevation ≥3 times the upper limit of normal (repeat laboratory testing should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, GGT, PT [prothrombin time] with INR [international normalized ratio], and alkaline phosphatase), regardless of the total bilirubin. (Please note that 3 times the upper limit of normal increases in ALT, AST need confirmation on separate blood draw before undertaking thorough evaluation for liver injury).
- For women of child-bearing potential with any positive urine β-hCG test, the subject will have study drug interrupted and a serum sample submitted to the central laboratory for β-hCG testing.

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

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

- Serious infections (See Section 7.2.8).
- Two sequential absolute neutrophil counts <1.0 x 10^9/L (<1000/mm^3); repeat testing must be performed as soon as feasible and within 3 days of the initial absolute neutrophil count <1.0 x 10^9/L (<1000/mm^3).
- Two sequential platelet counts <75 x 10^9/L (<75,000/mm^3); repeat testing must be performed as soon as feasible and within 3 days of the initial platelet count <75 x 10^9/L (<75,000/mm^3).
- Two sequential lymphocyte counts <500/mm^3; <0.5x10^9/L; repeat testing must be performed as soon as feasible and within 3 days of the initial lymphocyte count <500/mm^3; <0.5x10^9/L.
- Two sequential hemoglobin values of <8.0 g/dL; <4.96 mmol/L; <80 g/L.
- Symptomatic anemia with hemoglobin <7.0 g/dL; <70 g/L or any anemia requiring a blood transfusion.

- If an individual subject demonstrates **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 dosed further and adequate, immediate supportive measures including evaluation by a nephrologist (preferably within 24 hours) for 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 principal investigator (PI).

- AST or ALT elevation >8 times the upper limit of normal.

- Two sequential AST or ALT elevation ≥3 times the upper limit of normal with at least one total bilirubin value ≥2 times the upper limit of normal.

- Two sequential AST or ALT elevation ≥3 times the upper limit of normal accompanied by signs or symptoms consistent with hepatic injury.

- Two sequential AST or ALT elevation ≥5 times the upper limit of normal, regardless of total bilirubin or accompanying signs or symptoms.

- AST or ALT elevation ≥3 times the upper limit of normal with an INR >1.5.

In each of the 5 cases above, there is a need for additional investigations, such as review of ethanol, recreational drug and dietary supplement consumption; testing for acute hepatitis A, B or C infection and biliary tract imaging should be promptly discussed with the Pfizer medical monitor or designee.

- Female subjects found to be pregnant during the study.

- At the discretion of the PI, initiation of any new treatment for UC for disease progression.

- Subjects who are inadequately responding to investigational product in the opinion of the investigator.

- Surgery for UC.

- Clinically meaningful, treatment related decline in hearing from baseline.

- Thrombotic or thromboembolic event occurs(even if not categorized as serious or severe in intensity), unless clearly unrelated to study drug.

- Other treatment related serious or severe AEs, after consultation with the Pfizer medical monitor or designee.

7. ASSESSMENTS

Every effort should be made to ensure that the protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside of the control of the investigator that may make it unfeasible to perform the test. In these cases the investigator will take all steps necessary to ensure the safety and well-being of the subject. When a protocol-required test cannot be performed, the investigator will document the reason for this and any corrective and preventive actions that he or she has taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely manner.

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

Refer to Appendix 10 for Alternative Measures During Public Emergencies if applicable.

7.1. Blood Volume

Total planned blood sampling for an individual subject that completes all currently scheduled assessments through the Week 36 visit is approximately 430 mL. Additional blood samples may need to be collected at times not specified in the protocol (eg, replacement of clotted or compromised specimens or repeat of clinically significant out of range laboratory results).

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.

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

confirmed pregnancy, the subject will be withdrawn from administration of investigational product but will remain in the study in follow-up.

7.2.5. Mantoux/Purified Protein Derivative (PPD) Tuberculin Test

Subjects may be screened for TB using the PPD Tuberculin Test per local guidelines. The test consists of an intracutaneous injection of 5 Tuberculin Units (5 TU) PPD in 0.1 mL of solution on the volar aspect of the forearm, using a short beveled 26- or 27- gauge needle (Mantoux test). After the tuberculin test is administered, the test area will be evaluated by a qualified healthcare professional, per local guidelines, 48 to 72 hours later. The test is positive if the induration diameter is ≥5 mm at 48 to 72 hours post injection.

To be eligible for this study, a negative test response is required during screening unless the test was performed and documented negative within 12 weeks prior to screening. If a subject had a CT scan of the chest (with or without contrast) within 12 weeks prior to screening, the CT scan results can substitute for chest radiograph results. Subjects with suspected false positive PPD results, eg, results from suspected BCG vaccination, should be further tested with an Interferon Gamma Release Assay (IGRA) assay during screening.

7.2.6. Interferon Gamma Release Assay Tuberculin Test

Subjects may be screened for TB using an IGRA per local guidelines. IGRA will be tested locally (where feasible) during screening or within 12 weeks prior to screening. The following are acceptable assays: QuantiFERON®-TB Gold test (QFT-G), QuantiFERON®-TB Gold In-Tube test (QFT-GIT) and T-SPOT® TB test. Central lab used for the study may replace these tests with other acceptable QFT tests. Blood sampling may include 3 mL up to 10 mL of blood. Site personnel should follow the processing and analyses steps based on the assay chosen. Ensure incubation steps are followed as appropriate.

An IGRA is preferred for subjects with a prior BCG vaccination, but may be used for any subject. Documentation of IGRA product used and the test result must be in the subject's source documentation.

If the results of the IGRA are indeterminate, the test may be repeated, and if a negative result is obtained, enrollment may proceed. A positive test on repeat is exclusionary.

Subjects with repeat indeterminate IGRA results may be enrolled after a documented evaluation by appropriately qualified personnel (which may include a pulmonary or infectious disease specialist, or locally acceptable expert as defined by local guidelines), to rule out the possibility of low risk of infection (ie, subject would be acceptable for immunosuppressant treatment without additional action).

Subjects adequately treated (in the opinion of the appropriately qualified personnel - which may include a pulmonary or infectious disease specialist, or locally acceptable expert as defined by local guidelines) for latent and/or active tuberculosis infection may be enrolled regardless of Mantoux or IGRA results provided the treatment is well documented in the subject's medical records and/or source documentation prior to enrollment in the study.

The sample(s) will be analyzed by the site's local laboratory. Refer to local lab for any additional processing information and shipping instructions.

7.2.7. Screening for *Clostridium Difficile*

C.difficile testing is performed at screening (if not performed 6 weeks prior to screening) and during the study when there is a suspected disease flare or gastroenteritis. *C. difficile* infection in these settings requires treatment as determined by the PI. Subjects with *Clostridium difficile* infection may be treated and re-tested or re-screened at the discretion of the Investigator.

Highly sensitive screening tests, with high negative predictive value, should be employed in evaluating subjects for eligibility for the study. The detection of *C. difficile* by toxigenic stool culture (stool culture followed by detection of toxin) is considered the gold standard for the diagnosis of the colonization or infection with pathogenic *C. difficile*. Comparable sensitivity may be achieved by direct testing of stool via point of use rapid membrane enzyme immunoassay card for both *C. difficile* toxin A and B and glutamate dehydrogenase (GDH) antigen on a card. Use of the card for point of care screening is encouraged where permitted by local regulation. Molecular techniques such as polymerase chain reaction (PCR) for detection of toxin RNA are also acceptable alternatives.

Refer to the lab manual for further guidance and instruction for *C. difficile* screening.

7.2.8. Infections

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

Treated infections are infections that:

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

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

- Require parenteral antimicrobial therapy and present with positive pre-treatment culture;

AND EITHER

- Require hospitalization for treatment;

OR

- Meet other criteria that require the infection to be classified as a SAE.

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

Subjects who experience non-serious infections that require treatment may have their study drug temporarily discontinued during treatment at the investigator's discretion. Consultation with the Pfizer medical monitor is available. Temporary discontinuation of study drug should be recorded in the CRF.

CCI [redacted]

7.2.10. Vital Signs (Blood Pressure, Pulse Rate, and Temperature)

Single sitting blood pressure (BP), pulse rate, and temperature will be measured at times specified in the Schedule of Activities. Additional collection times or changes to collection times will be permitted, as necessary to ensure appropriate collection of safety data.

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

Sitting blood pressure will be measured with the subject's arm supported at the level of the heart, and recorded to the nearest mmHg. It is preferred that the same arm (preferably the dominant arm) be used throughout the study.

The same size BP cuff, which has been properly sized and calibrated, will be used to measure BP each time. The use of automated devices for measuring BP and pulse rate is acceptable, although, when done manually, pulse rate will be measured in the brachial/radial artery for at least 30 seconds. When the timing of these measurements coincides with a blood collection, it is preferred that vital signs be obtained prior to the nominal time of blood collection.

It is preferred that body temperature be collected using tympanic, oral, or axillary methods and that the same method be used consistently throughout the study.

7.2.11. Medical History, Physical Examination, Height and Weight

Medical history, including UC history, history of illegal drug, alcohol, tobacco use, skin rash, skin infection, and any abnormalities that may predispose the subject to infection will be collected at the Screening visit. Smoking status and average weekly alcohol consumption (units/week) will also be collected.

Complete physical examinations must be performed by the investigator, sub-investigator, or a qualified healthcare professional per local guidelines. Complete physical examinations consist of assessments of general appearance; skin, head, eyes, ears, nose and throat (HEENT); heart, lungs; breast (optional); abdomen; and external genitalia (optional); extremities; neurologic function; back; and lymph nodes.

Targeted physical examinations must be performed by the investigator, sub-investigator, or a qualified healthcare professional per local guidelines and should include skin, heart, lungs, abdomen and examination of body systems where there are symptom complaints by the subject.

Both full and targeted physical examinations must include a full body skin examination. Skin examinations should include a visual inspection of the breasts and external genitalia to assess for rashes, even if a subject does not wish to have examination of the breast and/or external genitalia (these are optional) done as a part of the physical examination.

Complete and Targeted physical examinations are performed at specified timepoints (See Schedule of Activities).

Height and weight will be measured without the subject wearing shoes. Height (inches or centimeters) will be measured and recorded at the Screening visit only and weight (lbs or kg) will be measured and recorded at various timepoints (See Schedule of Activities).

7.2.11.1. Dermatology/Skin

As part of the physical examination, all subjects will have a dermatological full body exam at times specified in the Schedule of Activities. Skin lesions will be evaluated as defined in the National Cancer Institute Common Toxicity Criteria for Adverse Events v4.0 (See Appendix 3, for Dermatology/Skin Category) and managed as shown below.

Table 9. Management of Dermatological Events

Dermatologic Event (CTCAE v 4.0)*	Course of Management
Acne/Acneiform Rash/Maculopapular Rash	
Grade ½	1. Investigator's discretion for withdrawing IP. 2. Execute reasonable monitoring. 3. Consider treatment with topical agents such as clindamycin or corticosteroids.
Grade 3	1. Discontinue IP. 2. Monitor to resolution (defined as a Return to Baseline status). 3. Consider treatment with topical agents such as clindamycin or corticosteroids.
Pruritus	
Grade 1 Mild or localized	1. Investigator's discretion for withdrawing IP. 2. Execute reasonable monitoring. 3. Consider treatment with topical agents such as clindamycin or corticosteroids.
Grade 2 Intense or widespread	1. Discontinuation of the IP may not be required unless condition is sustained >4 days or at the investigator's discretion. 2. Execute reasonable monitoring. 3. Consider treatment with topical agents such as clindamycin or corticosteroids.
Grade 3 Intense or widespread and interfering with activities of daily living	1. Permanently discontinue IP. 2. Monitor to resolution (Return to Baseline). 3. Consider treatment with topical agents such as clindamycin or corticosteroids.

* Refer to Appendix 3 for clarification.

All reports of potential drug-related rash will be followed up until resolution or clinically stable or following agreement with Pfizer.

Upon resolution of a Grade 1 or 2 rash/pruritus, including confirmed herpes zoster, subjects **may** be re-challenged with IP at the discretion of the investigator. Re-challenge is not permitted with Grade 3 rash/pruritus.

All events of rash should be treated according to International and local guidelines for the treatment of rash, eg, where appropriate, topical corticosteroids and/or agents such as antibiotics or antivirals could be prescribed.

CCI [redacted] Also, a swab (for microbiological assessment) of the affected area will be taken for culture and sensitivity to assess for any bacterial or fungal pathogens. CCI [redacted]

Investigators will complete a questionnaire and take appropriate photographs of the rash in order to provide information necessary for a dermatologist's assessment of the event.

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.

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.

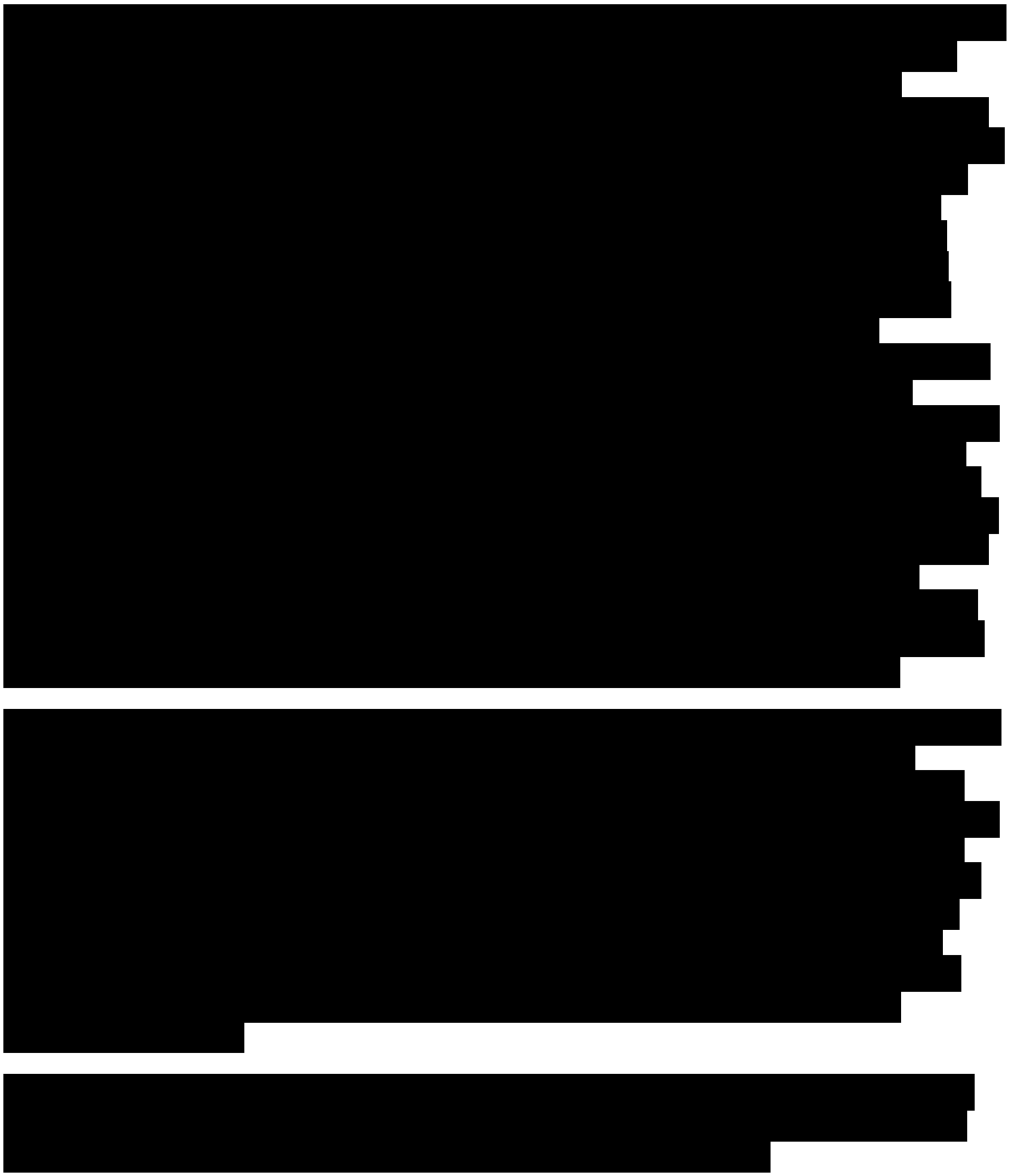
The endoscopic subscore by the Central Reader must be available at the baseline visit. The assessment by the Central Reader will be used to derive the total Mayo score for study eligibility. The stool frequency, rectal bleeding and centrally-read endoscopic subscores for the endoscopy performed during 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

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



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.

If there only 2 available days reported within the 5 days prior to the study 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), the average will be taken from the limited available data unless there is no diary data reported within 5 days. In this case, stool frequency and rectal bleeding subscores will be considered as missing.

Note that if there is 1 day of diary data or no diary data recorded prior to the baseline endoscopy preparation, then the patient cannot be randomized into the study.

Values used for Mayo score calculation should exclude any day when a bowel prep or endoscopy is performed.

The endoscopic appearance will be read by the Central Reader.

The physician's global assessment (PGA) acknowledges the other three criteria, the subject's abdominal discomfort and sense of general well-being. In addition, the investigator should consider other observations (eg, physical findings) and subject's performance status when making the PGA assessment. In consequence, the PGA should be recorded after all other components of the Mayo score and relevant interval medical history and physical examination have been completed. The PGA assessment should take into account the centrally read endoscopy score at baseline, Week 8, and Week 32/early withdrawal visits, however the locally read endoscopy score is an acceptable alternative at Week 8 and Week 32/early withdrawal visits when the endoscopic subscore by the Central Reader are not available prior to the conduct of the Week 8 or Week 32/ET PGA collection timepoint. It is preferred that the same physician performs all such assessment for a given subject throughout the study.

The Mayo score at the screening visit must be ≥6 with an endoscopic subscore of ≥2 and rectal bleeding subscore ≥1 and meet all other eligibility criteria to be eligible for the study. The duration of the time between the Mayo endoscopic subscore assessment and baseline should not exceed 10 days.

Endpoints based on the total Mayo scores are defined below:

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

- Clinical response: decrease from baseline in total Mayo score of at least 3 points and at least 30%, with an accompanying decrease in the subscore for rectal bleeding of at least 1 point or absolute subscore for rectal bleeding of 0 or 1.

- Deep remission: total Mayo score of 2 points or lower, with no individual subscore exceeding 1 point and a 0 on both endoscopic and rectal bleeding subscore.

- Symptomatic remission: total Mayo score of 2 points or lower, with no individual subscore exceeding 1 point, and both rectal bleeding and stool frequency subscores of 0.

- Improvement in endoscopic appearance: endoscopic subscore of 0 or 1.
- Endoscopic remission: endoscopic subscore of 0.
- Endoscopic response is defined by a decrease from baseline in the endoscopic subscore of 1 point or more.

Remission* based on modified Mayo score (Total Mayo score minus PGA): endoscopic subscore = 0 or 1 AND stool frequency = 0 or 1 AND rectal bleeding = 0.

7.3.4. Partial Mayo Score

A partial Mayo Score (Mayo Score without endoscopic subscore, ranging from 0 to 9) will be assessed at the times specified in the Schedule of Activities. On dosing days, the partial Mayo Score should be assessed prior to administration of investigational product. Response based on change in partial Mayo score is defined as a decrease from baseline of at least 2 points, while remission is defined as an absolute value of partial Mayo score <2 points with no individual subscore >1.[10]

CCI [redacted]

7.3.6. Patient Reported Outcomes (PRO) for Health Outcomes Assessment

Patient reported outcomes (PRO) assessments are self-administered during the study. Refer to Appendix 10 for Alternative Measures During Public Emergencies if applicable.

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

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

- Inflammatory Bowel Disease Questionnaire (IBDQ).
- Short Form-36, version 2, acute (SF-36).

- 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]

CCI [redacted]

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]

CCI

[redacted]

CCI

[redacted]

CCI [redacted]

8. ADVERSE EVENT REPORTING

8.1. Requirements

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

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

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

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

For each event, the investigator must pursue and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE (see the Serious Adverse Events section below). In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

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

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

8.1.1. Additional Details on Recording Adverse Events on the CRF

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

8.1.2. Eliciting Adverse Event Information

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

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

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

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

8.1.4. Time Period for Collecting AE/SAE Information

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

8.2. Definitions

8.2.1. Adverse Events

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

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

Additionally, AEs may include signs and symptoms resulting from:

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

8.2.2. Abnormal Test Findings

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

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

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

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

8.2.3. Serious Adverse Events

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

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

Or that is considered to be:

- An important medical event.

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

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

8.2.4. Hospitalization

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

Hospitalization does not include the following:

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

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

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

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

8.3. Severity Assessment

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

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

8.4. Special Situations

8.4.1. Protocol-Specified Serious Adverse Events

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

8.4.2. Potential Cases of Drug-Induced Liver Injury

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

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.

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

medical event irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal serum creatinine.

All relevant test results will be forwarded to Pfizer immediately by the PI.

This requirement applies to all subjects, all cohorts.

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

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

8.4.4.1. Exposure During Pregnancy

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

- A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the investigational product:
    - An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).
- A male has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

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

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP supplemental form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural

integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

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

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

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

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

8.4.4.2. Exposure During Breastfeeding

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

8.4.4.3. Occupational Exposure

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

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

8.4.5. Medication Errors

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

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

8.4.5.1. Medication Errors

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

Medication errors include:

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

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

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

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

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

9. DATA ANALYSIS/STATISTICAL METHODS

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

The information from the two placebo arms in the induction stage will be combined for the statistical analysis. It will be further combined with the historical database using Bayesian statistical methodology. The historical study data base will include the data obtained from Phase 3 tofacitinib trials available to the Sponsor. The integration details and historical data

specifications will be detailed in the SAP. The integration with historical data will involve application of statistical procedures attempting maximization of the commensurability between the current trial and the subgroup of the historical data used for synthesizing the prior distribution.

9.1. Sample Size Determination

The primary endpoint for the study is based on total Mayo score at Week 8. The study is powered for the induction stage.

The study will enroll approximately 318 subjects with the expected number of completers of 286 assuming an estimated drop out rate of ~10%. The table below represents the approximate number of expected completers per arm in the induction phase:

PF-06651600 Placebo	PF-06651600 200 mg	PF-06651600 70 mg	PF-06651600 20 mg	PF-06700841 Placebo	PF-06700841 60 mg	PF-06700841 30 mg	PF-06700841 10 mg
11	44	44	44	11	44	44	44

For induction phase analysis purposes, the combined placebo group is thus expected to have approximately 22 completers.

Using a between-group comparison at Week 8 (end of induction), assuming estimated standard deviation of the total Mayo score equal to 3, Type 1 error = 10% (2-sided)) and assuming a true difference between drug and placebo to be 2.1, planned sample size of 44 completers in the active and 22 completers in the placebo will provide 84.3% power. The delta of 2.1 is based on what has been seen in Tofacitinib Phase 3 studies for this endpoint.

9.2. Efficacy Analysis

9.2.1. Analysis of the Primary Endpoint During Induction Period

Primary efficacy analysis will be conducted based on total Mayo score at Week 8.

The primary analysis at Week 8 will be based on constrained Longitudinal Data Analysis (cLDA) model[15,16] using Total Mayo score. The constraint in cLDA is that the expected baseline values of Total Mayo score are identical in all of the treatment groups as a result of randomization. The model will include baseline and week 8 values of the Total Mayo Score as the response vector. The model will include treatment (6 active dose and pooled placebo), visit (baseline and Week 8) and treatment by visit interaction as fixed effects. An unstructured variance-covariance matrix will be allowed. Other statistical analysis methods will include fitting bayesian emax model for dose-response estimation after conducting Bayesian predictive checks on monotonicity. The Bayesian emax model will estimate the dose response and will be supportive to the primary analysis.

The primary analysis will be conducted on the intention-to-treat (ITT) population, defined as all randomized subjects who received at least one dose of investigational product or placebo. Sensitivity analysis handling of the missing values (including subjects who are missing due to COVID-19) will be outlined in the SAP.

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.

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.

During study conduct and/or after study completion, the investigator site may be subject to review by the IRB/EC, and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

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

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

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

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

A CRF is required and should be completed for each included subject. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer. The investigator shall ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to prevent access by unauthorized third parties.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

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

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

11.2. Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to the ICH guidelines, according to local regulations, or as specified in the clinical study agreement (CSA), whichever is longer. The investigator must ensure that the records continue to be stored securely for so long as they are retained.

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

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

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

12. ETHICS

12.1. Institutional Review Board/Ethics Committee

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

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

12.2. Ethical Conduct of the Study

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

12.3. Subject Information and Consent

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of subject personal data. Such measures will include omitting subject names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws.

The personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, when study data are compiled for transfer to Pfizer and other authorized parties, subject names will be removed and will be replaced by a single specific numerical code based on a numbering system defined by Pfizer. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, subject-specific code. The investigator site will maintain a confidential list of subjects who participated in the study, linking each subject's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subjects' personal data consistent with the Clinical Study Agreement and applicable privacy laws.

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

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

The investigator must ensure that each study subject is fully informed about the nature and objectives of the study, the sharing of data relating to the study and possible risks associated with participation, including the risks associated with the processing of the subject's personal data. The investigator further must ensure that each study subject is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

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

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

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

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

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in a Member State

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

13.2. End of Trial in All Other Participating Countries

End of trial in all other participating countries is defined as last subject last visit (LSLV).

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or investigational product safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of PF-06651600 and/or PF-06700841 at any time.

If a study is prematurely terminated, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating subjects and the hospital pharmacy (if applicable) within 28 days. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

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

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

www.clinicaltrials.gov

Pfizer posts clinical trial US Basic Results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a Pfizer product, regardless of the geographical location in which the study is conducted. US Basic Results are submitted for posting within 1 year of the primary completion date (PCD) for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

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

EudraCT

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

www.pfizer.com

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

15.2. Publications by Investigators

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

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

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

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

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

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

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

16. REFERENCES

1. Molodecky NA, Soon IS, Rabi DM, Ghali WA, Ferris M, Chernoff G, et al. "Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review." Gastroenterology. 2012:142(1):46-54 e42: quiz e30.

2. Basson, MD, Ulcerative Colitis [http://emedicine, Medscape Web site]. June 28, 2010. Available at http://emedicine.medscape.com/article/183084- overview.

3. Sandborn WJ, et. al. Tofacitinib as induction and maintenance therapy for Ulcerative Colitis. NEJM 2017 376:1723-1736.

4. Olaharski, A.J., et al. (2009) "Identification of a kinase profile that predicts chromosome damage induced by small molecule kinase inhibitors." PLoS computational biology 5:e1000446.

5. Hoek FJ, Kemperman FA, Krediet RT. A comparison between cystatin C, plasma creatinine and the Cockcroft and Gault formula for the estimation of glomerular filtration rate. Nephrol Dial Transplant. 2003;18(10):2024-31.

6. Newman DJ, Thakkar H, Edwards RG, Wilkie M, White T, Grubb AO, et al. Serum cystatin C measured by automated immunoassay: a more sensitive marker of changes in GFR than serum creatinine. Kidney international. 1995;47(1):312-8.

7. Dharnidharka VR, Kwon C, Stevens G. Serum cystatin C is superior to serum creatinine as a marker of kidney function: a meta-analysis. Am J Kidney Dis. 2002;40(2):221-6.

8. Inker LA, Schmid CH, Tighiouart H, Eckfeldt JH, Feldman HI, Greene T, et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. N Engl J Med. 2012;367(1):20-9.

9. Zhu Y, Ye X, Zhu B, et al. Comparisons between the 2012 New CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) Equations and Other Four Approved Equations. PLoS ONE 9(1): e84688. doi: 10.1371/journal.pone.0084688.

10. Lewis JD, Chuai S, Nessel L, et al. Use of the Non-invasive Components of the Mayo Score to Assess Clinical Response in Ulcerative Colitis. Inflammatory Bowel Disease 2008 December; 14(12): 1660-1666. doi 10.1002/ibd20520.

11. Irvine EJ, Feagan B, Rochon J, Archambault A, Fedorak RN, Groll A, Kinnear D, Saibil F, McDonald JW. Quality of life: a valid and reliable measure of therapeutic efficacy in the treatment of IBD. Canadian Crohn's Relapse Prevention Trial Study Group. Gastroenterology 1994; 106:287-296.

12. Feagan B, Reinisch, W Rutgeerts P, et al. The Effects of Infliximab Therapy on Health-Related Quality of Life in Ulcerative Colitis Patients. American Journal of Gastroenterology 2007; 102:794-802.

13. Konig HH, Ulshofer A, Gregor M, et al. Validation of the EuroQol questionnaire in patients with inflammatory bowel disease. European Journal of Gastroenterology & Hepatology 2002, 14:1205-1215.

14. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009 May 5; 150(9):604-12.

15. Fitzmaurice GM, Laird NM, Ware JH Applied Longitudinal Data Analysis, Second Edition, 2011, Published by John Wiley and Sons, 2011, section 5.7, pp.156-162.

16. Mallinckrodt C, Lipkovich I Analyzing Longitudinal Clinical Trials Data. A Practical Guide. CRC Press, 2017, pp. 100-110.

Appendix 1. Supplementary information for Inclusion Criteria 5

Note: The information below is provided for guidance only. Local standards of care, as well as investigator assessment should be considered in any assessment.

Inadequate response to, loss of response to, or intolerance to corticosteroid treatment (See Appendix 9 for steroid equivalency) may be defined as one or more of the following:

- Steroid refractory: Persistent symptoms of active disease despite treatment with at least one 4-week induction regimen that included a dose equivalent to ≥30 mg prednisone (oral) daily for at least 2 weeks or IV for at least 1 week within the previous 5 years;

- Steroid dependent: Two failed attempts to taper steroids below a dose equivalent to 10 mg prednisone (oral) daily;

- Steroid intolerant: History of intolerance to corticosteroids (including but not limited to Cushing's syndrome, osteopenia/osteoporosis, hyperglycemia, insomnia, infection) within the previous 5 years.

Inadequate response to, loss of response to, or intolerance to prior immunosuppressant treatment is defined by one or more of the following:

- Persistent signs and symptoms of active disease despite a history of at least one 12-week regimen of oral AZA (≥2-2.5 mg/kg/day) or 6-MP (≥1-1.5 mg/kg/day) and/or MTX (≥25 mg/week) within the previous 5 years;

- History of intolerance to AZA, 6-MP, or MTX (including but not limited to nausea/vomiting, abdominal pain, pancreatitis, liver function testing (LFT) abnormalities, lymphopenia, TPMP [thiopurine methyltransferase] genetic mutation, infection) within the previous 5 years.

Inadequate response to, loss of response to, or intolerance to prior anti-TNF inhibitors and anti-integrin inhibitors (within the previous 5 years) is defined as one or more of the following:

- Persistent signs and symptoms of active disease despite at least one 8-week regimen of adalimumab (subcutaneous doses of 160 mg at Week 0 and 80 mg at Week 2 followed by a dose of ≥40 mg every 2 weeks) or golimumab (subcutaneous doses of 200 mg at Week 0 and 100 mg at Week 2, followed by 50 mg or 100 mg every 4 weeks), or one 14-week regimen of infliximab (3 intravenous doses ≥5 mg/kg), or one 10-week regimen of vedolizumab (intravenous doses of 300 mg at Weeks 0, 2, and 6).

- Intolerance is defined as: Clinically significant side effect(s) [including hypersensitivity (eg, signs/symptoms including rash, flushing, anaphylaxis, serum sickness) and development of anti-drug antibodies] to at least 1 treatment regimen with an anti-TNF inhibitor.

Appendix 2. Prohibited Concomitant Medications

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

Moderate to Potent CYP3A Inhibitors*	**Moderate to Potent CYP3A Inducers****
Amprenavir	Avasimibe#
Amiodarone	Bosentan
Aprepitant	Barbiturates
Atazanavir	Carbamazepine#
Boceprevir	Efavirenz
Casopitant	Etravirine
Cimetidine	Mitotane#
Ciprofloxacin	Modafinil
Clarithromycin#	Nafcillin
Cobicistat#	Phenobarbital#
Conivaptan#	Phenytoin#
Darunavir	Rifabutin#
Diethyldithiocarbamate	Rifampin #
Diltiazem	St. John's Wort#
Dronedarone	Talviraline
Elvitegravir#	
Erythromycin	
Fluconazole	
Fluvoxamine	
Imatinib	
Indinavir#	
Itraconazole#	
Ketoconazole#	
Lopinavir#	
Mibefradil#	
Mifepristone (RU486)	
Nefazodone#	
Nelfinavir#	
Norfloxacin	
Posaconazole#	
Ritonavir#	
Saquinavir#	
Schisandra sphenanthera	
Telaprevir	
Telithromycin#	
Tipranavir#	
Tofisopam	
Troleandomycin#	
Verapamil	
Voriconazole#	

* All prohibited drugs that are CYP3A inhibitors require at least a 7 day or 5 half-lives (whichever is longer) washout prior to the first dose of study drug. Note: Amiodarone requires discontinuation at least 290 days (~5 half-lives, half-life averages ~58 days) prior to the first dose of study drug.

** All prohibited drugs that are CYP3A inducers require at least a 28 day or 5 half-lives (whichever is longer) washout prior to the first dose of study drug.

Noted as potent inhibitors or inducers.

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

In a situation where appropriate medical care of a subject requires the use of a prohibited CYP3A inhibitor or inducer:

Moderate to potent inhibitors and inducers of CYP3A are not permitted in the study EXCEPT in emergency situations requiring no more than one day of administration. ***Note: Amiodarone and mitotane are not permitted for any duration due to their long half-lives.*** Topical (including skin or mucous membranes) application of antimicrobial and antifungal medications is permitted.

Appendix 3. Common Terminology Criteria for Adverse Events v4.0 (CTCAE)-Dermatology

The NCI Common Terminology Criteria for Adverse Events v4.0 is a descriptive terminology that can be utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term. One page of the Dermatology/Skin Category is presented, which contains listings for Pruritus, Rash/Desquamation, and Rash: Acne/acneiform.

Skin and subcutaneous tissue disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Pruritus	Mild or localized; topical intervention indicated	Intense or widespread; intermittent; skin changes from scratching (eg, edema, papulation, excoriations, lichenification, oozing/crusts); oral intervention indicated; limiting instrumental ADL	Intense or widespread; constant; limiting self-care ADL or sleep; oral corticosteroid or immunosuppressive therapy indicated	-	-
Definition: A disorder characterized by an intense itching sensation.					
Purpura	Combined area of lesions covering <10% BSA	Combined area of lesions covering 10 - 30% BSA; bleeding with trauma	Combined area of lesions covering >30% BSA; spontaneous bleeding	-	-
Definition: A disorder characterized by hemorrhagic areas of the skin and mucous membrane. Newer lesions appear reddish in color. Older lesions are usually a darker purple color and eventually become a brownish-yellow color.					
Rash acneiform	Papules and/or pustules covering <10% BSA, which may or may not be associated with symptoms of pruritus or tenderness	Papules and/or pustules covering 10 - 30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL	Papules and/or pustules covering >30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; limiting self-care ADL; associated with local superinfection with oral antibiotics indicated	Papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated; life- threatening consequences	Death
Definition: A disorder characterized by an eruption of papules and pustules, typically appearing in face, scalp, upper chest and back.					

Skin and subcutaneous tissue disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Rash maculo-papular	Macules/papules covering <10% BSA with or without symptoms (eg, pruritus, burning, tightness)	Macules/papules covering 10 - 30% BSA with or without symptoms (eg, pruritus, burning, tightness); limiting instrumental ADL	Macules/papules covering >30% BSA with or without associated symptoms; limiting self-care ADL	-	-
Definition: A disorder characterized by the presence of macules (flat) and papules (elevated). Also known as morbillform rash, it is one of the most common cutaneous adverse events, frequently affecting the upper trunk, spreading centripetally and associated with pruritus.					

Rash/desquamation and erythema multiforme progressing to Grade 2, acne/acneiform rash or pruritus progressing to Grade 3 are the severity levels for permanently discontinuing a subject from IP.

Pruritus progressing to Grade 2 sustained (>4 days) is cause to permanently discontinue IP.

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.

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

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

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

G. NONE OF THE TIME

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

   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

10. How often during the last 2 weeks have you felt generally unwell? 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

11. How often during the last 2 weeks have you been troubled because of fear of not finding a washroom? Please choose an option from:

    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

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

    A. A GREAT DEAL OF DIFFICULTY; ACTIVITIES MADE IMPOSSIBLE

    B. A LOT OF DIFFICULTY

    C. A FAIR BIT OF DIFFICULTY

    D. SOME DIFFICULTY

    E. A LITTLE DIFFICULTY

    F. HARDLY ANY DIFFICULTY

    G. NO DIFFICULTY; THE BOWEL PROBLEMS DID NOT LIMIT SPORTS OR LEISURE ACTIVITIES

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

    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

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

    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

15. How often during the last 2 weeks have you felt depressed or discouraged? 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

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

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

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

A. A MAJOR PROBLEM

B. A BIG PROBLEM

C. A SIGNIFICANT PROBLEM

D. SOME TROUBLE

E. A LITTLE TROUBLE

F. HARDLY ANY TROUBLE

G. NO TROUBLE

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

A. A MAJOR PROBLEM

B. A BIG PROBLEM

C. A SIGNIFICANT PROBLEM

D. SOME TROUBLE

E. A LITTLE TROUBLE

F. HARDLY ANY TROUBLE

G. NO TROUBLE

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

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

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

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

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

A. NONE OF THE TIME

B. A LITTLE OF THE TIME

C. SOME OF THE TIME

D. A GOOD BIT OF THE TIME

E. MOST OF THE TIME

F. ALMOST ALL OF THE TIME

G. ALL OF THE TIME

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

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

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

    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

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

    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

25. How much of the time during the last 2 weeks have you felt tearful or upset? 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

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

    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

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

    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

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

    A. NO SEX AS A RESULT OF BOWEL DISEASE

    B. MAJOR LIMITATION AS A RESULT OF BOWEL DISEASE

    C. MODERATE LIMITATION AS A RESULT OF BOWEL DISEASE

    D. SOME LIMITATION AS A RESULT OF BOWEL DISEASE

    E. A LITTLE LIMITATION AS A RESULT OF BOWEL DISEASE

    F. HARDLY ANY LIMITATION AS A RESULT OF BOWEL DISEASE

G. NO LIMITATION AS A RESULT OF BOWEL DISEASE

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

    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

30. How much of the time during the last 2 weeks have you felt irritable? 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

31. How often during the past 2 weeks have you felt a lack of understanding from others? 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

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

A. VERY DISSATISFIED, UNHAPPY MOST OF THE TIME

B. GENERALLY DISSATISFIED, UNHAPPY

C. SOMEWHAT DISSATISFIED, UNHAPPY

D. GENERALLY SATISFIED, PLEASED

E. SATISFIED MOST OF THE TIME, HAPPY

F. VERY SATISFIED MOST OF THE TIME, HAPPY

G. EXTREMELY SATISFIED, COULD NOT HAVE BEEN MORE HAPPY OR PLEASED

Appendix 6. Short Form -36, version 2, acute (SF-36)

Please answer every question. Some questions may look like others, but each one is different. Please take the time to read and answer each question carefully by filling in the bubble that best represents your response.

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.
Thank you for completing this survey!

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. <u>Compared to one week ago</u>, how would you rate your health in general <u>now</u>?

Much better now than one week ago	Somewhat better now than one week ago	About the same as one week ago	Somewhat worse now than one week ago	Much worse now than one week ago
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a. <u>Vigorous activities</u>, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b. <u>Moderate activities</u>, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c. Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d. Climbing <u>several</u> flights of stairs	☐ 1	☐ 2	☐ 3
e. Climbing <u>one</u> flight of stairs	☐ 1	☐ 2	☐ 3
f. Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g. Walking <u>more than a mile</u>	☐ 1	☐ 2	☐ 3
h. Walking <u>several hundred yards</u>	☐ 1	☐ 2	☐ 3
i. Walking <u>one hundred yards</u>	☐ 1	☐ 2	☐ 3
j. Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

4. During the past week, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. Were limited in the kind of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. Had difficulty performing the work or other activities (for example, it took extra effort)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. During the past week, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. Did work or other activities less carefully than usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

6. During the past week, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. How much bodily pain have you had during the past week?

None	Very mild	Mild	Moderate	Severe	Very severe
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

8. During the past week, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

9. These questions are about how you feel and how things have been with you during the past week. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past week…

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Did you feel full of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Have you been very nervous?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e. Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f. Have you felt downhearted and depressed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g. Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h. Have you been happy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i. Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

10. During the past week, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

11. How TRUE or FALSE is each of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a. I seem to get sick a little easier than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

Appendix 7. Euro Quality of Life Questionnaire 5 Dimensions 3 Levels and Visual Analog Scale (EQ-5D-3L & VAS)

By placing a checkmark in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ❑

I have some problems in walking about ❑

I am confined to bed ❑

Self-Care

I have no problems with self-care ❑

I have some problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

Usual Activities *(eg, work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ❑

I have some problems with performing my usual activities ❑

I am unable to perform my usual activities ❑

Pain/Discomfort

I have no pain or discomfort ❑

I have moderate pain or discomfort ❑

I have extreme pain or discomfort ❑

Anxiety/Depression

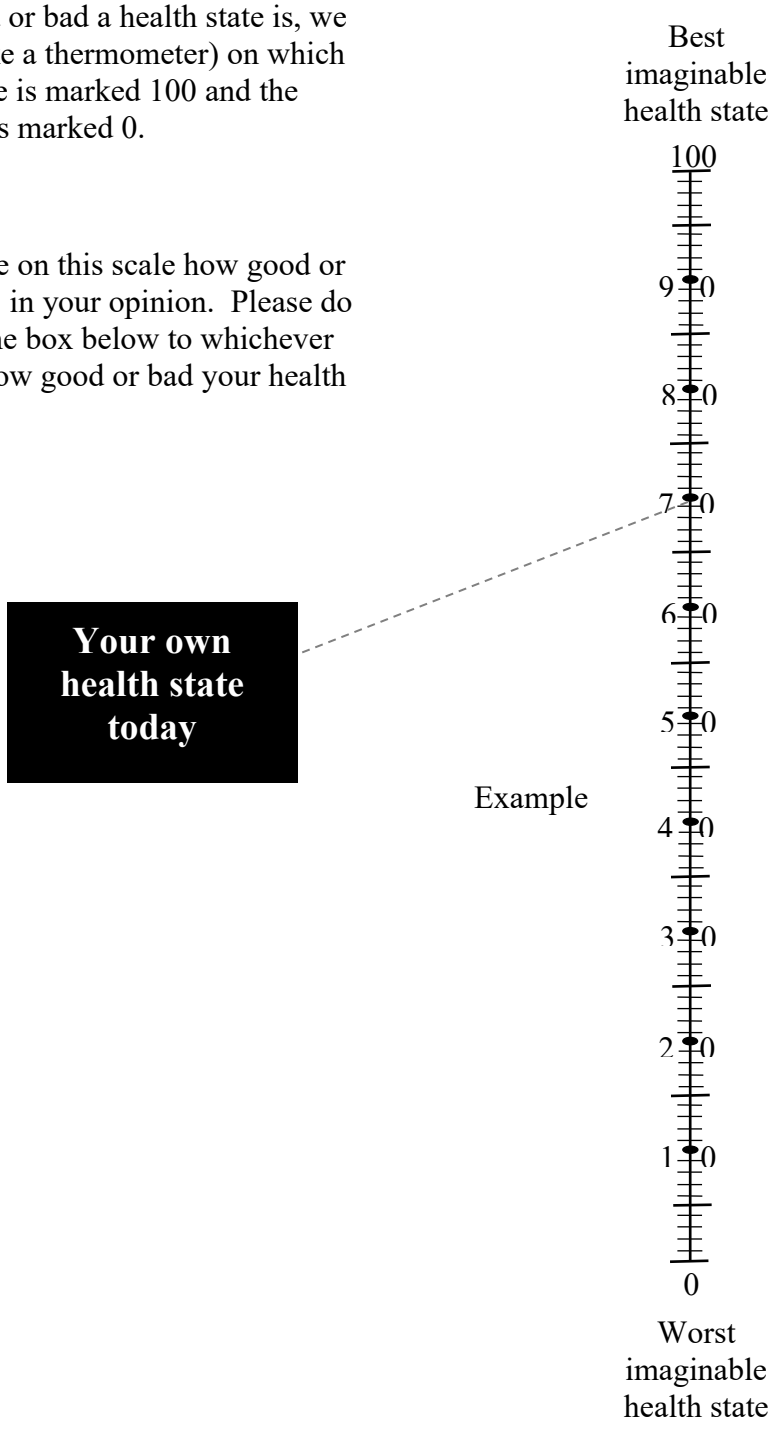
I am not anxious or depressed ❑

I am moderately anxious or depressed ❑

I am extremely anxious or depressed ❑

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.



CCI

[redacted]

Appendix 9. Summary of corticosteroid equivalents

Compound	Equivalent Dose (mg)
Prednisone	10
Prednisolone	10
6α-methylprednisolone	8
Triamcinolone	8
Betamethasone	1.2
Dexamethasone	1.5
Hydrocortisone	40
Cortisone	50
Deflazacort	12
Cloprednol	5
Prednylidene	12

Appendix 10. Alternative Measures During Public Emergencies

The alternative study measures described in this section are to be followed during public emergencies, including the COVID-19 pandemic. This appendix applies for the duration of the COVID-19 pandemic globally and will become effective for other public emergencies only upon written notification from Pfizer.

Use of these alternative study measures are expected to cease upon the return of business as usual circumstances (including the lifting of any quarantines and travel bans/advisories).

All procedures should be performed per protocol Schedule of Activities to monitor the safety of the partcipant.

If the sponsor determines that the impact of COVID-19 on protocol visits and procedures and associated timeframe needs to be reported on a CRF, this will be requested.

In situations where participants are quarantined, self-isolating or unable to visit the study site, the participant verbal consent must be documented in the site's source documents prior to performing any protocol procedures or shipping study intervention.

Appendix 10.1. Eligibility

Not Applicable.

Appendix 10.2. TeleHealth Visits

In the event that in-clinic study visits cannot be conducted, every effort should be made to follow up on the safety of study participants at scheduled visits per the Schedule of Activities or unscheduled visits.

Telehealth visits may be used to continue to assess participant safety and collect data points, (if permitted by law or local guidance). Telehealth includes the exchange of healthcare information and services via telecommunication technologies (eg, audio, video, video-conferencing software) remotely, allowing the participant and the investigator to communicate on aspects of clinical care, including medical advice, reminders, education, and safety monitoring. The following assessments must be performed during a telehealth visit.

- Review and record any AEs and SAEs since the last contact. Refer to Section 8.
- Review and record any new concomitant medications or changes in concomitant medications since the last contact.
- Review and record contraceptive method and results of pregnancy testing. Confirm that the participant is adhering to the contraception method(s) required in the protocol. Refer to Section 4.3.1 and Section 7.2.4.

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.

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
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

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

Abbreviation	Term
NADPH	nicotinamide adenine dinucleotide phosphate
NK	Natural Killer
NOAEL	No observed adverse effect level
OAT	organic anion transporting
OATP	organic anion transporting polypeptide
OCT	Organic cation transporter
PCD	primary completion date
PCOA	Patient-Centered Outcome Assessments
PCS	Physical component summary
PD	Pharmacodynamics(s)
PFS	prefilled syringe
P-gp	P-glycoprotein
PGA	Physician's global assessment
PGx	Pharmacogenomics(s)
PI	principal investigator
PK	Pharmacokinetic
PO	Oral
PPD	Purified protein derivative
PRO	Patient reported outcome
PT	prothrombin time
QD	Once daily
QFT-G	QuantiFERON-TB Gold
QFT-GIT	QuantiFERON-TB Gold In-Tube
RA	Rheumatoid Arthritis
R_{ac}	Observed accumulation ratio
R_{ss}	Steady state accumulation ratio
RNA	ribonucleic acid
rGST	Recombinant Glutatione-S-Transferase
SAD	Single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SBE	Single-Blind Extension Period
SLE	Systemic Lupus Erythematosus
SC	Subcutaneous
SCr	Serum creatinine
SF-36	Short form 36
SOC	System organ class
SOP	standard operating procedure
SRSD	single reference safety document
STAT	signal transducers and activators of transcription
SUSAR	suspected unexpected serious adverse reaction
CCI	[redacted]

Abbreviation	Term
T-cell	T lymphocyte
$t_{1/2}$	Terminal half life
TB	Tuberculosis
TBili	total bilirubin
TEAE	Treatment emergent adverse event
TEC	tyrosine kinase expressed in hepatocellular carcinoma (TEC)
T_{max}	Time at which C_{max} occurred
TNF	Tumor necrosis factor
TPMP	thiopurine methyltransferase
TXK	tyrosine kinase expressed in T cells
TYK	tyrosine-protein kinase
UC	Ulcerative colitis
CCI	[redacted]
UDP	uridine 5'-diphospho
ULN	upper limit of normal
URI	upper respiratory tract infection
US	United States
UV	Ultraviolet
V_{ss}	volume of distribution at steady state
Vz/F	Apparent volume of distribution
WBC	White blood cells
WOCBP	Women of child bearing potential