A PHASE 2A, MULTICENTER, SINGLE ARM, OPEN-LABEL, TWO-STAGE, STUDY TO EVALUATE THE EFFICACY, SAFETY, TOLERABILITY AND PHARMACOKINETICS OF PF-06480605 IN SUBJECTS WITH MODERATE TO SEVERE ULCERATIVE COLITIS

Compound:	PF-06480605
Compound Name:	Not Applicable (N/A)
United States (US) Investigational New Drug (IND) Number:	129188
European Clinical Trials Database (EudraCT) Number:	2016-001158-16
Protocol Number:	B7541002
Phase:	2a

[redacted]

Document History

Document	Version Date	Summary of Changes and Rationale
Amendment 2	12 Jan 2017	• Throughout the protocol, clarified that serum total sTL1A (soluble TL1A) will be analyzed. Rationale: To clarify the specific serum TL1A test to be performed for this study. • Schedule of Activities: Footnote 'k' modified to indicate that hepatitis testing (HBsAg, total HBcAb, HCVAb confirmed by HCV RNA) analysis will be performed by the central laboratory. Rationale: To clarify that testing and analysis for hepatitis will be performed by the central laboratory. • Sections 1.2.2, 3.1, 4.1, 4.3, and 7.2.2: Results of the preliminary embryo, fetal, and developmental (pEFD) toxicity study added and applicable protocol text modified accordingly Rationale: Addition of non-clinical safety information for investigators and regulators. CCI [redacted] Rationale: To correct typographical error and clarify the endpoint. • Section 4.1, inclusion criteria #1, removed the phrase "or a legally acceptable representative". Rationale: Adult subjects that lack the capacity to consent for the study themselves will not be enrolled. • Section 4.1, inclusion criteria #3, increased upper age limit of subjects for study inclusion from age 65 to age 75.

		Rationale: Upper age limit for study participation increased to 75 years old to help with study recruitment. • Section 4.1 inclusion criteria #4 and Section 4.3, notation added that for subjects in France, women of childbearing potential (WOCBP) are NOT eligible for this study. Rationale: Country-specific requirement. • Section 4.1, inclusion criteria #8, notation added that there is no specific requirement for a subject to "washout" of a current treatment and that no patient should be actively removed from prohibited medications in order to meet study inclusion/exclusion criteria, and Section 6.1, removed the phrase "(eg, washout of prohibited medications)". Rationale: There is no protocol-required washout included in this study. • Section 4.1, inclusion criteria #8, modified inclusion criteria for subjects in The Netherlands only, indicating that subjects must have inadequate response to, loss of response to, or intolerance to at least one biological therapy, such as an anti-TNF inhibitor. Rationale: Revision made to comply with country-specific ethics committee requirement. • Sections 4.2, exclusion criteria #10, and Sections 6.1 and 7.2.4, clarified that IGRA testing to be performed at site's local laboratory **where feasible.** Rationale: Sites that are unable to perform IGRA at their local laboratory will have IGRA testing performed by the central laboratory. • Section 4.2, exclusion criteria #17, modified criteria for subjects in France only indicating that subjects must not have received any biologic treatment for at least 5 half-lives prior

		to first dose of PF-06480605. (eg, infliximab: 47.5 days, adalimumab: 70 days, golimumab: 70 days, vedolizumab: 125 days). Rationale: Revision made to comply with country-specific requirement. • Section 5.4, added clarification that the end of infusion stop time should be recorded when the end of infusion saline flush is complete. Rationale: Information provided for clarity. • Section 5.9, added clarification that subjects are free to 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. Also, if a subject requires initiation of a new therapy for ulcerative colitis, the subject should be withdrawn from the study and appropriate treatment should be administered at the discretion of the investigator. Rationale: Information provided for clarity that if rescue medication is determined to be appropriate for a subject, the subject should be withdrawn from the study. • Section 6.2, added suggested order for completion of post-dose procedures. Rationale: Information provided for clarity and as additional guidance for investigators and site personnel. • Section 7.1, modified the total planned blood volume provided by an individual subject who completes all scheduled assessments through Week 26, per protocol, from approximately 550 mL to approximately 613 mL. Rationale: Total blood volume changed based on recalculation utilizing central vendor blood volume requirements. • Section 7.3.2, sentence added to clarify that for all tissue biopsies collected, the colonic

		segment and approximate distance from the anal verge should be notated for each sample in the source documents. Rationale: Addition made for clarity. • Appendix 3, addition of appendix to capture operational items not included in the mandatory contract format for France (ie, French "Contrat Unique"). Rationale: France requirement. • Minor administrative changes and sentence revisions made throughout the document. Rationale: Revisions made for clarity and to correct minor grammatical or spelling errors.
Amendment 1	18 May 2016	• Throughout the protocol, endoscopy requirements were modified to remove the option that allows flexible sigmoidoscopy. Rationale: All subjects will require a colonoscopy to assess the entire affected area(s) of the colon to enable appropriate efficacy assessments in the study. • Throughout the protocol, the requirement for subjects to enter their corticosteroid usage via e-Diary has been removed, and this information will only need to be collected by the site in the appropriate CRF, as required for all prior and concomitant medication usage. Rationale: To eliminate duplication of effort and for ease of subject e-Diary requirements, there is no need for e-Diary collection of this information. • Throughout the protocol, the subject observation period following PF-06480605 administration has been increased to a minimum of 2 hours after infusion has ended. Rationale: Subject observation period increased to 2 hours to monitor subject safety and to

		provide a consistent and minimum monitoring time frame, based on results from the first-in-human study. • In the schedule of activities and Section 6.2.12, clarification made that subjects with AEs as a result of positive ADA/NAbs may be requested to return for additional follow up for up to 3 months after the follow up/EOS visit and will have PK samples collected in addition to ADA/NAb samples. Also added clarification that other assessments may also be performed during these visits as appropriate depending upon the actual AE that is experienced. • Rationale: Additional text added to clarify specific requirements during these potential additional visits. In the schedule of activities and Section 6.2.2, addition of ADA/NAb and ADA epitope/affinity sample collection at Visit 2 (Week 2, Day 15). Rationale: Sample added to collect potential early immunogenicity response. • Section 1.3.1: Statement added that historical internal data may be utilized to compare with the safety data from this study in order to place the safety findings in context given this is a single arm study. Rationale: To provide additional clarity for evaluation of safety data. • Section 2.1.2, revised secondary objective to reflect that remission will be evaluated at Week 14, defined as a total Mayo score of ≤2 with no individual subscore >1. Rationale: To clearly define how remission will be evaluated. • Section 2.1.2, addition of secondary objective: "To evaluate the efficacy of PF-06480605 in induction of endoscopic remission at Week 14

		(defined as Mayo endoscopic subscore of 0) in subjects with moderate to severe UC." Rationale: To enable evaluation of endoscopic remission. CCI [redacted] • Sections 2.1 and 2.2, revised primary objective and primary endpoint text from "mucosal healing" to "endoscopic improvement", and added that endoscopic improvement would be defined as Mayo endoscopic subscore of 0 or 1, "and without friability". Rationale: Endoscopic improvement can be derived from the Mayo endoscopic subscore alone, whereas mucosal healing would require a validated histologic assessment of the mucosa. Definition further clarifies evaluation of endoscopic improvement. • Section 2.2, addition of secondary endpoint: "Remission at Week 14 (defined as a total Mayo score ≤2 with no individual subscore >1)." Rationale: This will enable comparison with legacy data. CCI [redacted] C [redacted]

[redacted]

		CCI [redacted] CCI [redacted] • In the protocol summary and Section 3.1, individual stopping rules and overall study stopping criteria has been added: 1) If ≥2 subjects receiving PF-06480605 develop the same adverse laboratory event with Common Terminology Criteria for Adverse Events (CTCAE V4.03) Grade 3 or higher, or if 1 subject develops a laboratory adverse event with a CTCAE Grade 4 or higher, then the study may be terminated. 2) If ≥2 subjects experience an ECG abnormality defined as a prolonged QTcF of >500 msec over baseline assessment, then the study may be terminated. If a single subject experiences a prolonged QTcF of >500 msec over baseline assessment, then this subject will be discontinued from the study. Rationale: Individual stopping rules and overall study stopping rules added to further evaluate safety and feasibility of study continuation based on emerging data. • Section 3.1, modified text to indicate that early PK readout of PF-06480605 will be conducted after at least 6 subjects have completed the Week 4 visit to confirm that the predicted exposures of PF-06480605 in active UC

		patients are consistent with expected values, based on the healthy subject PK data. Also added that following this early PK readout analysis, dose may be modified to match the exposures observed in healthy volunteers receiving 500 mg/kg IV (Study B7541001). Rationale: This analysis will now be mandatory, rather than optional. • Section 3.4, removed the sentence indicating that approximately 40 subjects would be enrolled to ensure that 36 evaluable subjects complete the study with colonoscopy at Week 14. Rationale: If futility criteria are not met, recruitment will continue until at least 36 evaluable subjects complete the study with a final colonoscopy at Week 14, which is required for analysis. • Section 4.1, inclusion criteria #3 modified to delete the phrase "or adult age". Rationale: This phrase was removed to avoid enrolling subjects who are younger than 18 years of age but consider themselves to be adults. • Section 4.1 and 4.2, inclusion criteria #4 was modified and (former) exclusion criteria #1 was removed to clarify that women of childbearing potential (WOCBP) will be eligible for the study while pEFD toxicology are ongoing provided these women use two highly effective methods of contraception throughout the study and until the Week 26 visit (or 98 days after the last dose of IP), as outlined in Section 4.3. Rationale: WOCBP need not be excluded from the study while pEFD toxicology studies are ongoing as long as they comply with contraception requirements. • Section 4.1, inclusion criteria #8 modified to

		specify objective criteria to define failure of each listed conventional therapy, including dose and duration that must have been utilized. Rationale: To provide consistent specific parameters to define treatment failure. • Section 4.2, exclusion criteria #14 modified to add that subjects with current, or a history of QT prolongation would be excluded. Rationale: Clarification made for patient safety. • Section 5.2.1, criteria for interruption or stopping infusion related to potential immunogenicity related adverse events has been added. Additional clarification on specific signs and symptoms that may be observed has been added. Rationale: Infusion reactions are generally not well defined and may encompass a wide range of clinical events. Appropriate guidance and reporting of these events may mitigate risk to subjects. • Section 6.1, Section 7.2.1, and Schedule of Activities, screening HbA1c added to table of laboratory tests. Rationale: This test was inadvertently omitted from the list previously. • In Section 6.2.1, the requirement for fasting at least 8 hours on Day 1 prior to administration of PF-06480605 has been removed. Rationale: Fasting requirement removed since there is no data to support this requirement. • In Section 7.3.2, tissue biopsy collections were clarified in terms of number and type of tissue samples to be collected during the colonoscopy procedure. Text related to sample processing has been removed from protocol. Rationale: To provide clarity and to better

		specify requirements for appropriate tissue sample analysis. Information on sample processing will be provided in the central laboratory vendor procedure manual. • In Section 7.3.3, additional information provided on how Mayo scores will be calculated utilizing patient reported diary data and handling of missing data. Rationale: Additional clarification provided for Mayo score calculation and how missing data will be managed. • 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	14 March 2016	• Not applicable (N/A)

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

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APPENDICES

PROTOCOL SUMMARY

Background and Rationale:

The investigational product (IP), PF-06480605, is currently being developed for the treatment of inflammatory bowel disease (IBD).

PF-06480605 is a fully human neutralizing antibody against Tumor Necrosis Factor-like Ligand 1A (TL1A), a member of the tumor necrosis factor (TNF) family of cytokines. PF-06480605 contains three mutations in the Fc region to reduce effector function. Its mechanism of action is to neutralize the binding and subsequent signaling of TL1A to its functional receptor Death Receptor 3 (DR3).

The TL1A/DR3 pathway has been implicated in the regulation of pathogenic Th1, Th2, Th9 and Th17 T-cells, and of NK and NK-T cell responses, in immune-mediated diseases. The TL1A expression on antigen presenting cells (monocytes, macrophages, dendritic cells) and DR3 expression on effector cells (ILC2, T-cells, NK and NK-T cells) is highly dependent on pro-inflammatory conditions. Moreover, data from nonclinical species and humans implicate TL1A in the pathophysiology of IBD.[1]

This multicenter, single arm (non-placebo controlled), two-stage study will be the first use of PF-06480605 in subjects with moderate to severe ulcerative colitis (UC). The objectives of this study are to evaluate the safety, tolerability, pharmacokinetics (PK) and efficacy (based on Mayo endoscopic subscore) of PF-06480605.

The current non-clinical toxicology package available will support a 12 week treatment period. To mitigate the need for a placebo arm, endoscopic improvement, a more objective endpoint, with lower placebo rates than clinical disease activity scores, was selected as the primary endpoint. All colonoscopies will be read by a Central Reader who will be blinded to study treatment. An induction period (12 weeks of dosing with primary endpoint at Week 14) greater than the traditional 8 weeks was chosen to increase the likelihood of achieving endoscopic improvement.

Objectives and Endpoints

Primary Objectives

- To evaluate the safety and tolerability of PF-06480605 in subjects with moderate to severe UC.
- To evaluate the efficacy of PF-06480605 in induction of endoscopic improvement (as assessed by Mayo endoscopic subscore) at Week 14 in subjects with moderate to severe UC.

Secondary Objectives

- To evaluate the efficacy of PF-06480605 in induction of remission at Week 14 (defined as a total Mayo score ≤2 with no individual subscore >1) in subjects with moderate to severe UC.
- To evaluate the efficacy of PF-06480605 in induction of endoscopic remission at Week 14 (defined as a Mayo endoscopic subscore of 0) in subjects with moderate to severe UC.
- To describe the PK of PF-06480605 in subjects with moderate to severe UC.
- To evaluate the immunogenicity of PF-06480605 in subjects with moderate to severe UC.
- To evaluate disease and pathway related biomarkers (ie, high sensitivity C-reactive protein [hsCRP] and fecal calprotectin), and serum total soluble TL1A (sTL1A).

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Primary Endpoints

- Safety and tolerability of PF-06480605: treatment emergent adverse events (TEAEs), withdrawal due to adverse events (AEs), and serious adverse events (SAEs) will be reported.
- Endoscopic improvement at Week 14 (defined as a Mayo endoscopic subscore of 0 or 1, and without friability).

Secondary Endpoints

- Remission at Week 14 (defined as a total Mayo score ≤2 with no individual subscore >1).
- Endoscopic remission at Week 14 (defined as a Mayo endoscopic subscore of 0).
- PF-06480605 plasma concentrations.
- Incidence of development of anti-drug antibodies (ADAs) and neutralizing antibodies (NAbs).
- Change from baseline in fecal calprotectin.
- Change from baseline in hsCRP.
- Change from baseline in serum total sTL1A.

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CCI [redacted]

Study Design and Treatments

This is a Phase 2a, single arm, two-stage study in subjects with moderate to severe UC. Subjects will receive 500 mg of PF-06480605 intravenously every 2 weeks (Q2W) for a total of 7 doses. At the end of the first stage (12 evaluable subjects with a Week 14 colonoscopy), an interim analysis (IA) will be performed for an early efficacy assessment. Enrollment in the second stage will be stopped if the futility criteria are met and any ongoing subjects in the second stage will be moved to the follow-up period. Otherwise, the study will continue to enroll additional subjects in the second stage for final efficacy assessment. CCI [redacted]

The duration of participation for eligible subjects will be approximately 8 months, including a screening period of up to 6 weeks, a 12 week treatment period, and a follow-up period ending 14 weeks after the last dose of IP. Subjects with AEs as a result of positive ADA/NAbs may be requested to return for additional follow-up for up to 3 months after the follow-up/end of study (EOS) visit. During the treatment period, subjects will visit the site every 2 weeks (±3 days) for IP administration (7 visits), and then will return to the site every 4 weeks (±7 days) through Week 24 and again at Week 26, for follow-up visits (5 visits).

Stopping Rules

In addition, individual stopping rules will be implemented to further evaluate safety and feasibility of study continuation, as described below:

- If ≥2 subjects receiving PF-06480605 develop the same adverse laboratory event with Common Terminology Criteria for Adverse Events (CTCAE V4.03)[14] Grade 3 or higher, or if 1 subject develops a laboratory adverse event with a CTCAE Grade 4 or higher, then the study may be terminated.

- If ≥2 subjects experience an ECG (electrocardiogram) abnormality defined as a prolonged QTcF of >500 msec over baseline assessment, then the study may be terminated. If a single subject experiences a prolonged QTcF of >500 msec over baseline assessment, then this subject will be discontinued from the study.

Statistical Method

This study employs Simon's two-stage design, which enables a single arm study with an early assessment for futility. Let *p* be the proportion of subjects achieving endoscopic improvement at Week 14 and the following hypotheses will be tested in this study:

H_0: $p \leq 6\%$ *versus* H_1: $p \geq 41\%$

In the first stage, it is planned to have 12 evaluable subjects with colonoscopy at Week 14. If no more than 2 subjects have achieved endoscopic improvement AND no subject has achieved endoscopic remission, then the study will be stopped for futility; otherwise, the study will continue to enroll until approximately 36 evaluable subjects complete the study with colonoscopy at Week 14. If at least 9 subjects achieve endoscopic improvement at Week 14 at the end of the second stage, the null hypothesis H_0 will be rejected.

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, in order to conduct evaluations or assessments required to protect the well-being of the subject.

	Screening (-42 to -1)	Induction Period							3-Months Follow-Up					Early Withdrawal[a]
		Treatment Period							3-Months Follow-Up				Final Onsite Study Visit	
Study Visit	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	
Study Week	**Week -6 to -1**	**Week 0**	**Week 2**	**Week 4**	**Week 6**	**Week 8**	**Week 10**	**Week 12**	**Week 14**	**Week 16**	**Week 20**	**Week 24**	**Week 26**	
Study Day	**Day -42 to -1**	**Day 1**	**Day 15**	**Day 29**	**Day 43**	**Day 57**	**Day 71**	**Day 85**	**Day 99**	**Day 113**	**Day 141**	**Day 169**	**Day 183**	
Visit Window	**N/A**	**N/A**	**±3 Days based on Day 1 visit**						**±7 Days based on Day 1 visit**					
Enrollment Procedures														
Informed Consent	X													
Inclusion/Exclusion Criteria	X	X												
Demographics & Medical history[b]	X													
Vital Signs														
BP and pulse (after sitting for 5 minutes)	X	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X	X	X	X	X	X
Temperature (oral, tympanic or axiallary) [°C or °F])	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight (lbs or kg)[d]	X	X		X		X		X		X	X		X	X
Height (in or cm)[d]	X													
Medical Procedures														
Complete Physical Exam[e]	X								X				X	X
Targeted Physical Exam[e]		X	X	X	X	X	X	X		X	X	X		
ECG (12-lead)[b]	X	X		X		X		X		X	X		X	X
Chest X-ray[f]	X													
Colonoscopy														
Colonoscopy[f]	X								X					X

	Screening (-42 to -1)	Induction Period							3-Months Follow-Up					Early Withdrawal[a]
		Treatment Period							3-Months Follow-Up				Final Onsite Study Visit	
Study Visit	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	
Study Week	**Week -6 to -1**	**Week 0**	**Week 2**	**Week 4**	**Week 6**	**Week 8**	**Week 10**	**Week 12**	**Week 14**	**Week 16**	**Week 20**	**Week 24**	**Week 26**	
Study Day	**Day -42 to -1**	**Day 1**	**Day 15**	**Day 29**	**Day 43**	**Day 57**	**Day 71**	**Day 85**	**Day 99**	**Day 113**	**Day 141**	**Day 169**	**Day 183**	
Visit Window	**N/A**	**N/A**	**±3 Days based on Day 1 visit**						**±7 Days based on Day 1 visit**					
CCI	X								X					X
Disease Activity Analysis														
CCI		X	X	X		X		X			X		X	
Total Mayo Score	X[h]								X[h]					X
Stool Diary Instructions	X	X	X	X	X	X	X	X	X	X	X	X		
Stool Diary Data (e-diary)[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CCI	X								X					X
Laboratory Assessments														
Stool sample tests for enteric pathogens to include C. diff toxins[j]	X													
Serology: HIV[k] HBsAg, total HBcAb, HCVAb confirmed by HCV RNA[k]	X													
Tuberculosis test: PPD or IGRA per local guidelines (assayed at local lab)[l]	X													
Serum Pregnancy Test or FSH[m]	X													
Urine Pregnancy Test[m]		X	X	X	X	X	X	X	X	X	X	X	X	X
Safety laboratory: Hematology, chemistry, UA, PT/PTT/INR	X[n]	X	X	X	X	X	X	X	X	X	X		X	X
HbA1c	X													
Pharmacodynamics														
Retained Pharmacogenomic Sample (Prep D1)		X												
Biomarker hsCRP		X	X	X	X	X	X	X	X	X	X	X	X	X

	Screening (-42 to -1)	Induction Period							3-Months Follow-Up					Early Withdrawal[a]
		Treatment Period							3-Months Follow-Up				Final Onsite Study Visit	
Study Visit	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	
Study Week	**Week -6 to -1**	**Week 0**	**Week 2**	**Week 4**	**Week 6**	**Week 8**	**Week 10**	**Week 12**	**Week 14**	**Week 16**	**Week 20**	**Week 24**	**Week 26**	
Study Day	**Day -42 to -1**	**Day 1**	**Day 15**	**Day 29**	**Day 43**	**Day 57**	**Day 71**	**Day 85**	**Day 99**	**Day 113**	**Day 141**	**Day 169**	**Day 183**	
Visit Window	**N/A**	**N/A**	**±3 Days based on Day 1 visit**						**±7 Days based on Day 1 visit**					
CCI		X[o]	X[o]			X[o]			X					X
Serum Total Soluble TL1A		X[o]	X[o]	X[o]	X[o]	X[o]	X[o]	X[o]	X	X	X	X	X	X
CCI	X	X[o]	X[o]			X[o]			X					X
Stool sample for fecal calprotectin		X	X			X		X					X	X
CCI	X[q]					X		X					X	X
Pharmacokinetics and Immunogenicity														
Pharmacokinetics		X[o]	X[o]	X[o]	X[o]	X[o]	X[o]	X[o]	X	X	X	X	X[r]	X
ADA and NAb		X	X	X		X		X		X	X	X	X[r]	X
CCI		X						X			X		X	X
CCI		X							X					X
ADA epitope, affinity		X	X	X		X		X		X	X	X	X	X
Trial Treatment Procedures[o]														
Randomization (after all screening procedures complete and eligibility confirmed)		X												
Administration of PF-06480605		X[s]	X[s]	X[s]	X[s]	X[s]	X[s]	X[s]						
Dispense Stool Collection Kit for Stool Specimen	X	X			X		X					X		
Adverse Event Monitoring		X	→	→	→	→	→	→	→	→	→	→	→	X
Prior and Concomitant Medication & Treatments	X	→	→	→	→	→	→	→	→	→	→	→	→	X
Contraception Check	X	→	→	→	→	→	→	→	→	→	→	→	→	X
End of Study CRF														X

Abbreviations: ADA = anti-drug antibodies; BP = blood pressure; CRF= case report form; ECG = electrocardiogram; EOS = end of study; FSH = follicle stimulating hormone; HBA1c = hemoglobin A1c; HBsAg = hepatitis B surface antigen; total HBcAb = hepatitis B core antibody; HCVAb = hepatitis C antibody; HCV RNA = hepatitis C virus ribonucleic acid; HIV = human immunodeficiency virus; hsCRP = high-sensitivity C-reactive protein; PK = pharmacokinetics; PPD = purified protein derivative; PT= Promthrombin time; PTT= Partial thromboplastin time; WONCBP = Women of non-childbearing Potential.

a. Any subject who prematurely withdraws during active treatment (Week 0 through Week 12) should return for an early withdrawal visit and then enter into the follow-up period.
b. To include smoking history.
c. At dosing visits, vital signs and ECGs will be collected approximately 30 minutes prior to dosing and 1 hour post-dose.
d. Height and weight measured without shoes.
e. Complete physical exam includes review of the following body systems: general appearance, skin, HEENT, heart, lungs, breast (optional), abdomen, external genitalia (optional), extremities, neurologic function, back and lymph nodes. Targeted physical exam includes the review of the following body systems: skin, heart, lungs, abdomen and examination of body systems where there are symptom complaints by the subject.
f. Chest x-ray may be performed up to 12 weeks prior to screening. Official reading must be located in the source documentation.
g. Colonoscopy to be completed for a subject within approximately 10 days prior to baseline visit, and preferably within 5 to 7 days prior to baseline to allow stool data collection for Mayo score calculation and to obtain endoscopic subscore report from the Central Reader. The endoscopic subscore from the Central Reader will be used to determine eligibility.
h. Total Mayo score will be based on the centrally-read endoscopic subscore, stool frequency, rectal bleeding and physician's global assessment.
i. The subject stool diary to collect stool frequency and rectal bleeding will be collected daily through an e-Diary.
j. To be performed locally or at the central laboratory. 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 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 PCR for detection of toxin RNA are also acceptable alternatives.
k. Per local regulations. To be assayed locally. Confirmation and documentation of a negative HIV test result within 12 months prior to screening will be accepted. Hepatitis testing and analysis (HBsAg, total HBcAb, HCV Ab confirmed by HCV RNA) will be performed by the central laboratory.
l. To be assayed locally. A documented negative PPD test within 12 weeks before screening is acceptable. IGRA official reading and method or test must be located in the source documentation.
m. Serum pregnancy testing at screening and urine pregnancy testing at other scheduled visits are required only for female subjects of childbearing potential. Follicle stimulating hormone (FSH) test to be performed at screening to confirm postmenopausal status in female subjects who have been amenorrheic for at least 12 consecutive months.
n. The screening labs may be repeated once if necessary to confirm eligibility.
C [redacted]
p. At dosing visits, PK samples will be collected preferably after vital signs data and within approximately 30 minutes prior to dosing and 1 hour post-dose (at end of the infusion); biomarker samples will be collected pre-dose.
C [redacted]
r. Subjects with AEs as a result of positive ADA/NAbs may be requested to return for additional follow-up for up to 3 months after the follow-up/EOS visit and will have PK and ADA/NAb samples drawn for analysis. Other assessments may also be performed during these visits as appropriate depending upon the actual AE that is experienced.
s. Subjects will remain at the study site for observation for a minimum of 2 hours after the end of PF-06480605 infusion.

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 affects the entire gastrointestinal tract from mouth to anus and long-term debilitating sequelae, such as fistulae and intestinal strictures.

The incidence rates of UC in North America have been reported as high as 19.2 per 100,000 persons/year and prevalence as high as 248/100,000.[2] It occurs more frequently in Caucasians and affects females about 35% more often than males.[3] Although UC can occur at any age, the incidence peaks between 15 to 25 years with a second peak between 55 to 65 years.[4] UC is a lifelong condition with a serious effect on the quality of life. Current treatment primarily consists of 5-aminosalicylic acid (5-ASA), corticosteroids, immunosuppressive agents (azathioprine/6-mercaptopurine), or biologic agents (anti-TNF or anti-integrin antibodies). However, despite recent advances, more effective pharmacological treatment is needed to induce and maintain remission.

1.1. Mechanism of Action/Indication

PF-06480605 is a fully human neutralizing antibody against TL1A, a member of the TNF family of cytokines. PF-06480605 contains three mutations in the Fc region to reduce effector function. Its mechanism of action is to neutralize the binding and subsequent signaling of TL1A to its functional receptor DR3.

PF-06480605 is currently being developed for the treatment of IBD.

1.2. Background and Rationale

1.2.1. Drug Development Rationale

Although the exact cause of UC remains unclear, inhibition of pro-inflammatory cytokines and integrins have proven to deliver some therapeutic benefit. The first biologic therapy approved for UC was infliximab, a chimeric IgG1 antibody against TNF-α. In the ACT1 and ACT2 trials, infliximab treatment of refractory moderate to severe UC patients demonstrated up to a 24% placebo-corrected clinical remission rate at Week 8. However, at Week 54, the placebo-corrected sustained clinical remission rate had fallen to 18%.[5]

Patients that are intolerant to or eventually lose response to infliximab can be switched to other anti-TNF-α therapies, such as adalimumab or certolizumab pegol. In the ULTRA 1 and ULTRA 2 trials, adalimumab treatment of refractory moderate to severe UC patients demonstrated up to a 10% placebo-corrected clinical remission rate by Week 8. At Week 52, this rate was reported as 8%.[6]

The anti-integrin antibodies, namely vedolizumab, represent another class of drugs that have been approved for treatment of UC. In the GEMINI 1 trial, vedolizumab treatment of refractory moderate to severe UC patients demonstrated a placebo-corrected clinical

remission rate of 11.5% at Week 6.[7] However, at Week 54, the placebo-corrected clinical remission rate was as high as 29.1%. Taken together, alternative therapies still remain a critical unmet medical need for UC patients.

The TL1A/DR3 pathway has been implicated in the regulation of pathogenic Th1, Th2, Th9 and Th17 T-cells, and of NK and NK-T cell responses, in immune-mediated diseases. The TL1A expression on antigen presenting cells (monocytes, macrophages, dendritic cells) and DR3 expression on effector cells (ILC2, T-cells, NK and NK-T cells) is highly dependent on pro-inflammatory conditions. Moreover, data from nonclinical species and humans implicate TL1A in the pathophysiology of IBD.[1]

1.2.2. Safety Data

1.2.2.1. Non-Clinical Safety

Standalone safety pharmacology studies were not conducted with PF-06480605. Safety pharmacology endpoints were incorporated into the design of the 3-month Good Laboratory Practice (GLP) repeat-dose toxicity studies.

Toxicity studies were conducted in CD-1 mice and cynomolgus monkeys and included exploratory and 3-month (13 weeks) GLP repeat-dose toxicity studies (with a 3 month recovery phase). The intravenous (IV) and subcutaneous (SC) routes of administration were selected for the in vivo toxicity studies as they are the routes of clinical administration. In addition, a series of in vitro immunotoxicity screening studies were conducted on PF-06480605 (Fc and C1q binding, human lymphocyte activation, and human cytokine release assay [CRA]) and preliminary immunohistochemical and GLP tissue cross-reactivity studies were conducted in a panel of CD-1 mouse, cynomolgus monkey, and normal human tissues.

PF-06480605 was administered to mice and cynomolgus monkeys once weekly via the IV and SC routes up to 3 months in duration (up to a total of 14 doses). The no-observed-adverse-effect levels (NOAELs) in the 3-month GLP repeat-dose toxicity studies were the highest doses tested, which were 250 and 300 mg/kg/week for both IV and SC routes in mice and cynomolgus monkeys, respectively.

The findings in the exploratory toxicity studies were generally consistent with those observed in the GLP studies. However, in one exploratory study in mice, four female mice died following PF-06480605 administration at the low and intermediate-dose groups. The deaths of the three animals at 1 mg/kg/week occurred on Days 15, 22, and 29 shortly after test article administration. The single animal at 10 mg/kg/week also died shortly after test article administration on Day 22. Because the deaths did not occur in a dose-responsive manner, no deaths were seen in another 30-day mouse exploratory study, and no test article-related deaths were seen in the 3-month GLP repeat-dose toxicity study at doses up to 250 mg/kg/week, the deaths were considered unrelated to direct toxicity of the test article. Although ADAs were not evaluated in this study, based on timing of the deaths, the inverse dose relationship, the administration of a human antibody to a mouse, and the lack of overt clinical signs of toxicity, the cause of death was consistent with immunogenicity. Immunogenicity in animals is not considered predictive of immunogenicity in humans.[8]

Test article-related, nonadverse higher serum globulin concentrations were observed for both IV and SC routes in the 3-month GLP studies in mice and cynomolgus monkeys and were associated with higher total protein values and/or lower albumin/globulin ratios. The higher serum globulin concentrations, increased total protein values, and lower albumin/globulin ratios were considered most likely to represent the presence of PF-06480605 mAb. In addition, findings consistent with an inflammatory process (eg, increased neutrophil counts, fibrinogen concentrations, or incidence of microscopic inflammatory lesions), which can result in increased globulin concentrations, were not observed. The higher serum globulin concentrations, increased total protein values, and lower albumin/globulin ratios reversed by the end of the recovery phase for mice administered 250 mg/kg/week IV and cynomolgus monkeys administered 300 mg/kg/week, the only groups evaluated for recovery phase. Test article-related, nonadverse higher absolute reticulocyte counts and red blood cell distribution width (RDW) values were also observed in mice at 250 mg/kg/week SC. These changes were considered indicative of increased red blood cell (RBC) turnover, as reticulocytes are younger and larger RBCs and were not considered adverse due to the small magnitude of change. Higher mean absolute reticulocyte counts and higher RDW values were not observed in mice administered PF-06480605 by the IV route (all dose levels), and there were no other test article-related effects on hematological parameters. In addition, no test article-related effects were noted on hematological parameters in the 3-month toxicity study in cynomolgus monkeys.

There were no test article-related effects on the modified Irwin test, locomotor activity, and body temperature in mice and no test article-related effects on electrocardiograms (ECGs), heart rate, respiration rate, and body temperature in cynomolgus monkeys in the 3-month GLP studies.

In the 3-month GLP studies, the NOAELs were the highest doses tested, which were 250 and 300 mg/kg/week for mouse and cynomolgus monkeys, respectively, for both IV and SC routes. The exposure margins (based on the average concentration for the dosing interval [C_{av}]) at these NOAELs in mice were 21x and 15x for IV and SC, respectively, and in cynomolgus monkeys were 54x and 37x, for IV and SC, respectively, relative to the 500 mg IV dosage exposure at steady state to be evaluated in this study. Similarly, for $C_{max,}$ the exposure margins at these NOAELs in mice were 29x and 12x for IV and SC, respectively, and in cynomolgus monkeys were 59x and 30x respectively. In vitro, PF-06480605 caused an increase in cytokine release (1 or more of the 3 cytokines evaluated [IFN-γ, IL-6, and TNF-α]) in the solid phase cytokine release assay (CRA) in most human donors that was greater than that observed for the isotype and negative controls, but was substantially lower than that observed with the positive control antibodies (anti-CD3 mAb and anti-CD28 superagonist mAb), which have been shown to produce cytokine release in vivo in humans. However, PF-06480605 did not elicit test article-related cytokine release in the in vitro soluble phase human CRA. No test article-related effect on serum cytokine levels was observed in the 3-month GLP toxicity studies in mice and cynomolgus monkeys.

In the GLP tissue cross-reactivity study, a large number of tissues had staining in the human, mouse, and cynomolgus monkey tissue panels. The staining observed in the human tissue panel was generally similar to that seen in the mouse and cynomolgus monkey tissue panels. Staining was primarily observed only at the highest test article concentrations (5 μg/mL) and may represent nonspecific binding and/or low affinity binding to unrelated epitopes. The majority of staining observed was cytoplasmic in nature, and it is unlikely that the cytoplasm and cytoplasmic structures would be accessible to the test article in vivo. No adverse findings were observed in the dosing phase of the 3-month GLP repeat-dose toxicity studies conducted in mice and cynomolgus monkeys, which provides further support that the staining observed in the ex vivo tissue cross-reactivity study does not translate in vivo.

The nonclinical safety profile of PF-06480605 has been adequately characterized in vitro and in mice and cynomolgus monkeys in vivo to support clinical trials with dosing up to 3 months in duration. The only finding in the 3- month toxicity studies was in the mouse study. If the exposure limit is determined as $1/10^{th}$ of the exposure at the highest dose tested in 3-month mouse IV study ie, C_{max} = 869 μg/mL, C_{av} = 459 μg/mL, for the proposed regimen of 500 mg Q2W, the corresponding exposure margins for C_{max} and C_{av} at steady state is predicted to be 2.9 and 2.1-fold respectively.

A preliminary embryo, fetal, and developmental toxicity study (pEFD) has been completed. PF-06480605 was intravenously administered by bolus injection to pregnant Crl:CD1(ICR) female mice once daily on gestation day (GD) 6 and 12 at 0, 20, 250, or 450 mg/kg/dose. The maternal and developmental no-observed-adverse-effect level (NOAEL) for PF-06480605 was 450 mg/kg/dose, the highest dose tested. Also, there were no findings in male or female reproductive organs in the 3 month toxicity studies in mice and cynomolgus monkeys. It is not known whether PF-06480605 can affect male fertility or whether PF-06480605 is secreted in human milk. Because of the investigational nature of this product, PF-06480605 should not be administered to pregnant women or women who are nursing an infant. Women of childbearing potential are eligible for the B7541002 study provided that these women utilize two highly effective methods of contraception as outlined in Section 4.3.

1.2.3. Previous Human Experience

1.2.3.1. Subject Disposition

A total of 92 healthy subjects, 60 and 32 subjects in single ascending dose (SAD) and multiple ascending dose (MAD) periods, respectively, were assigned to and received study treatment (PF-06480605 or placebo) in the completed first-in-human (FIH) study B7541001. The doses of PF-06480605 tested were 1 mg, 3 mg, 10 mg, 30 mg, 100 mg, 300 mg, 600 mg, and 800 mg (as single IV doses) and 30 mg, 100 mg, 300 mg (as multiple SC doses), and 500 mg IV (as multiple IV doses). Six (6) subjects discontinued from the study: 3 subjects each from the SAD period and the MAD period, which included 1 placebo subject from each period. There were no study discontinuations attributed to treatment-related AEs. There were 2 subjects who were lost to follow-up; one subject in SAD PF-06480605 100 mg cohort and one subject in SAD PF-06480605 600 mg cohort. Additionally, there were 2 subjects who were no longer willing to participate in the study; one subject in MAD PF-06480605

30 mg cohort and one subject in the placebo group. One subject in the placebo group discontinued due to other reasons (withdrawn at investigator request, non-AE).

1.2.3.2. Pharmacokinetics Results

Following single IV infusion dosing of PF-06480605 under fasted conditions at doses ranging between 1 mg and 800 mg, median time to reach maximum concentration (T_{max}) occurred at 1.5 to 2 hours following the end of a 1-hour infusion. After reaching the maximum observed concentration (C_{max}), the concentration time profile exhibited a multiphasic decline over time, with mean terminal half-life ($t_{1/2}$) values ranging between 6 and 23 days. Mean $t_{1/2}$ values at the lower doses appeared to be shorter than those observed at the higher doses which may be due in part to immunogenicity and/or sensitivity of the assay (more quantifiable serum concentrations above the limit of quantification at later time points for the higher doses).

Geometric mean dose normalized area under the curve (AUC) showed an upward trend with an increase in dose following single IV doses with greater than dose proportional increases across the 1 mg to 800 mg dose range. Dose normalized C_{max} appeared to increase in approximately dose proportional manner across the dose range studied.

Drug clearance (CL) following IV dosing of PF-06480605 appeared to decrease as the doses increased, with mean CL value of 0.018 L/hr at the 1 mg dose and 0.007 L/hr at the 800 mg dose. Volume of distribution at steady state (V_{ss}) for IV dosing was low, with mean Vss values ranging between 3.4 and 5.5 L across all doses indicating that drug is localized mainly to the plasma volume.

Between subject variability in PF-06480605 exposure was low to moderate, based on geometric %CV and ranged between 12% and 33% for the area under the concentration-time curve from time 0 to infinity (AUC_{inf}) and 8% to 26% for C_{max}.

Following repeat SC dose administration of PF-06480605 at 30 mg, 100 mg, and 300 mg doses once every 2 weeks for a total of 3 doses, absorption from the site of injection was variable, with peak serum concentrations achieved within a median T_{max} of 96 to 216 hours post-dose on Day 1, 192 to 335 hours post-dose on Day 15, and 48 hours post-dose on Day 29.

Dose normalized PK exposure (as measured by geometric mean area under the curve over the dosing interval [AUC_{tau}] and C_{max}) on Day 1 increased in a dose proportional manner with an increase in dose, however exposure on Days 15 and 29 trended toward greater than dose proportional increases across the 30 mg to 300 mg SC doses. Estimated bioavailability (F) values based on geometric mean AUC_{tau} for the 30 mg, 100 mg, and 300 mg SC doses on Day 1 were 47%, 44%, and 42%, respectively, relative to the corresponding IV doses (AUC 14 days) from the SAD portion of the study.

Overall, observed serum exposures (mean AUC_{tau} and C_{max}) on Days 15 and 29 were higher than those observed on Day 1 following a single dose. Mean observed accumulation ratios (R_{ac}) based on geometric mean AUC_{tau} on Day 29 ranged between 2.4 and 3.2, and R_{ac} for

C_{max} (R_{ac}, C_{max}) based on geometric mean C_{max} on Day 29 ranged between 2.3 and 4.2, indicating that some drug accumulation does occur following multiple SC dosing every 2 weeks at doses ranging between 30 mg and 300 mg. Apparent CL for SC dosing (CL/F) and apparent volume of distribution for SC dosing (Vz/F) geometric mean values for the 100 mg to 300 mg SC doses (individual values for 30 mg SC dose) on Day 29 were approximately similar across all 3 SC doses, with mean CL/F and Vz/F values ranging between 0.013 and 0.018 L/hr and 4.7 and 8.5 L, respectively. Mean $t_{1/2}$ values for the SC doses on Day 29 ranged between 8.7 and 21 days with the longer $t_{1/2}$ values observed at the 100 mg and 300 mg doses.

Following multiple dose administration of a 500 mg IV dose once every 2 weeks for a total of 3 doses, mean C_{max} values on Day 1, Day 15, and Day 29 were observed slightly later than the end of a 1-hour infusion (median T_{max} ranged between 1.54 and 4.08 hours post-dose). Higher geometric mean AUC_{tau} values were observed on Days 15 and 29 compared to Day 1 with similar C_{max} values observed across all dosing days. Mean R_{ac} based on geometric mean AUC_{tau} on Day 29 was 2.1, and R_{ac}, C_{max} based on geometric mean C_{max} on Day 29 was 1.4, indicating that there is slight drug accumulation following multiple IV dosing every 2 weeks. CL and V_{ss} geometric mean values on Day 29 were 0.008 L/hr and 5.6 L, respectively. Mean $t_{1/2}$ was 20 days.

Between subject variability in PF-06480605 exposure on Day 29 for the SC and IV doses based on geometric %CV ranged between 14% and 49% for AUC and 7% to 74% for C_{max}, with the higher variability observed for the SC dosing compared to the IV dose.

The PK parameters reported above were summarized by cohort, irrespective of immunogenicity status of the subject. Importantly, the impact of immunogenicity on PK at the higher doses was not significant as the CL was similar after single (300, 600, 800 mg IV) or comparable multiple doses (500 mg IV) and each showed CL similar to typical IgG1 monoclonal antibodies.

1.2.3.3. Immunogenicity Results

The incidence of ADA ranged from 50% to 100% for SAD and MAD cohorts. In subjects receiving PF-06480605, 56 subjects out of 68 subjects were considered to be positive for ADA. The overall confirmed treatment induced incidence rate was 82.4%; however, there were 11 subjects for whom PF-06480605 concentrations remained above the assay tolerance level throughout the study. Positive ADA samples were detected as early as 336 hours (14 days) post-dose in the SAD cohorts and on Day 29 in the MAD cohorts.

The incidence of neutralizing antibody (NAb) ranged from 0% for 2 SAD and 2 MAD cohorts to 100% for the 3 mg IV cohort. In subjects receiving PF-06480605, 24 subjects out of 68 subjects were considered positive for NAb. The overall confirmed NAb incidence rate was 35.3%. Positive NAb samples were detected as early as 672 hours (28 days) post-dose in the SAD cohorts and 1680 hours (70 days) post-dose in the MAD cohorts. Where data was available, mean serum PF-06480605 concentrations were lower in subjects identified as ADA positive, compared to subjects identified as ADA not-positive, and were even lower in subjects with NAb log titer ≥0.70.

Differences in mean serum PK parameters, namely exposure, between subjects identified as ADA positive and ADA not-positive as well as between subjects with NAb log titer <0.70 and ≥0.70 were more apparent for subjects in MAD cohorts but no direct conclusions were able to be drawn from the data.

In Study B7541001, there were no immunogenicity associated safety signals including injection site reactions or hypersensitivity. Likewise, there were no significant findings from the Cytokine Release Assay (CRA). Furthermore any impact of immunogenicity on PK and PD was restricted to the lower doses of ≤30 mg. At the higher doses there was no significant impact as the CL after single (300 mg, 600 mg, 800 mg) or repeat doses of the 500 mg IV dose level where CL was similar to typical IgG1 monoclonal antibodies.

1.2.3.4. Safety Results

There were no deaths, SAEs, severe AEs, AEs resulting from ADA/Nabs, or subjects with dose reduced or temporary discontinuations due to AEs during the FIH study with PF-06480605. Additionally, there were no clinically significant laboratory abnormalities (eg, CRA), vital signs, or ECGs.

In the single dose period, there were 45 all causality TEAEs reported by 21 subjects out of the 44 subjects treated with PF-06480605. Of these, 15 events were determined to be treatment-related and were reported by 13 subjects. There were 20 all causality TEAEs reported by 7 subjects out of the 16 subjects treated with placebo, of which 9 events were determined to be treatment-related and were reported by 5 subjects.

In the multiple dose period, there were 44 all causality TEAEs reported by 17 subjects out of the 24 subjects treated with PF-06480605. Of these, 21 events were determined to be treatment-related and were reported by 11 subjects. There were 17 all causality TEAEs reported by all of the 8 subjects treated with placebo, of which 6 events were determined to be treatment-related and were reported by 5 subjects.

Overall, headache was the most commonly reported all causality (7 PF-06480605 subjects and 3 placebo subjects) and treatment-related (5 PF-06480605 subjects) TEAE. The second most commonly reported treatment-related TEAE was abdominal pain which was reported by 3 PF-06480605 subjects and 1 placebo subject.

The incidence of TEAEs between cohorts in the SAD period and between cohorts in the MAD period was similar. Overall, there was a higher incidence of treatment-related TEAEs in MAD cohorts compared with SAD cohorts, although the incidence of TEAEs did not increase with higher doses of PF-06480605. Headache was the most commonly reported all causality and treatment-related TEAE.

The majority of TEAEs were mild in severity. There was a higher incidence of moderate severity TEAEs reported by subjects in MAD cohorts compared with SAD cohorts. The study's only treatment-related moderated severity TEAE, abdominal pain, was reported by a subject from a MAD cohort. There were no severe TEAEs reported. There were no injection site or hypersensitivity reactions reported.

There were no subjects from the SAD period who discontinued from the study due to an AE. In the MAD period, there was 1 subject who discontinued from the study due to a treatment unrelated AE, pyuria, on study Day 14. The event was determined to be mild and the subject recovered in one day.

Complete information for this compound may be found in the Single Reference Safety Document (SRSD), which for this study is the Investigator's Brochure (IB).

1.3. Rationale

1.3.1. Study Rationale

This multicenter, single arm (non-placebo controlled), two-stage study will be the first use of PF-06480605 in subjects with moderate to severe UC. The objectives of this study are to evaluate the safety, tolerability, PK and efficacy (based on Mayo endoscopic subscore) of PF-06480605 at 500 mg IV administered Q2W for a total of 7 doses.

The current non-clinical toxicology package available will support a 12-week treatment period. To mitigate the need for a placebo arm, endoscopic improvement, a more objective endpoint, with lower placebo rates than clinical disease activity scores, was selected as the primary endpoint. All colonoscopies will be read by a Central Reader who will be blinded to study treatment. An induction period of 12 weeks of dosing with primary endpoint at Week 14, which is greater than the traditional 8 weeks, was chosen to increase the likelihood of achieving endoscopic improvement. Following completion of dosing at 12 weeks, the subjects will be followed for an additional 14 weeks to characterize PK and immunogenicity.

During the endoscopic evaluations, intestinal biopsies will be obtained and interrogated to provide evidence for pharmacological modulation of the TL1A pathway and to define parameters that might be used to enable a precision medicine strategy in future clinical trials. Furthermore, the peripheral blood and stool will be profiled to provide correlative peripheral biomarkers that could complement the precision medicine approach in intestinal biopsies.

In Study B7541001, there were no immunogenicity associated safety signals or laboratory abnormalities and any impact on exposure was restricted to the low dose groups (≤30 mg). In Study B7541002, a dose level is being evaluated that did not show any immunogenicity related impact on exposure, and is predicted to achieve >90% neutralization of sTL1A at trough throughout the dosing period. Further in study B7541002, the UC patients may be on immunosuppressive therapy which could further reduce the incidence of immunogenicity.

PK, PD, ADA and NAb will be monitored at various time points to characterize the potential impact of immunogenicity and patients with AEs as a result of positive ADA/NAbs may be requested to return for additional follow-up for up to 3 months after the follow-up/EOS visit.

In addition, historical internal data may be utilized to compare with the safety data from this study in order to place the safety findings in context given this is a single arm study.

1.3.2. Dose Rationale

For Study B7541002, 500 mg administered IV Q2W for a total of 7 doses is being proposed based on the following: this dose level has been administered in humans and the PK of PF-06480605 is typical of IgG1 monoclonal antibodies; at this dose no impact of immunogenicity on PK was evident; based on modeling this dosage is expected to show target modulation that might drive pharmacology; and this dosage would provide a safety margin of 2.9 and 2.1-fold for C_{max} and C_{av} respectively compared to $1/10^{th}$ of the maximum exposure (29 and 21-fold relative to the NOAEL) tested in 3-month mouse toxicity study.

The dosage of 500 mg Q2W has been administered in Study B7541001 and the CL and V_{ss} geometric mean values on Day 29 of 0.008 L/hr and 5.6 L, respectively, and mean $t_{1/2}$ of 20 days for PF-06480605 following administration of 500 mg Q2W are similar to the values for other typical IgG1 therapeutic monoclonal antibodies as well as endogenous IgG1.[10] For dosage administrations >30 mg in Study B7541001, a modified quasi-steady state target mediated drug disposition model accounting for any impact of immunogenicity on exposure, adequately characterized the PF-06480605 and sTL1A serum concentrations.

Additionally, assuming that neutralization of TL1A will translate into efficacy, a site of action model was used to predict the degree of neutralization of sTL1A by PF-06480605 (sTL1A coverage) in serum and gut. The percentage of patients achieving a 90% sTL1A (P_{90}) coverage for different regimens were simulated including administration of 150 and 300 mg SC Q2W and 500 mg IV Q2W for 24 weeks. The P_{90} values following administration of 150 mg SC, 300 mg SC and 500 mg IV Q2W for 24 weeks were 61%, 76.3% and 87.2%, respectively. To maximize the chances of seeing efficacy through neutralization of TL1A, 500 mg of PF-06480605 administered IV Q2W was selected as the dosage regimen in Study B7541002.

Assuming that PF-06480605 PK is similar between healthy volunteers and moderate to severe UC patients, PK simulations suggest that PF-06480605 administered as 500 mg Q2W for a total of 7 doses would provide a median (50^{th} prediction interval) of 299 μg/mL and 216 μg/mL for C_{max} and C_{av} at steady state respectively. When compared to $1/10^{th}$ of the exposures at the highest mouse IV dose in the 3-month GLP toxicity studies, it is anticipated that this dosage of 500 mg Q2W will maintain a 2.9 and 2.1-fold (29 and 21-fold relative to the NOAEL) safety margin for C_{max} and C_{av} respectively.

1.3.3. Summary of Benefits and Risks

IBD is a serious and potentially life-threatening disease. Overall, the safety profile observed during the Phase 1 program for PF-06480605 appears to be acceptable at dosages up to 800 mg administered intravenously as single doses and up to 500 mg administered intravenously as multiple doses.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

2.1.1. Primary Objectives

- To evaluate the safety and tolerability of PF-06480605 in subjects with moderate to severe UC.
- To evaluate the efficacy of PF-06480605 in induction of endoscopic improvement (as assessed by Mayo endoscopic subscore) at Week 14 in subjects with moderate to severe UC.

2.1.2. Secondary Objectives

- To evaluate the efficacy of PF-06480605 in induction of remission at Week 14 (defined as a total Mayo score ≤2 with no individual subscore >1) in subjects with moderate to severe UC.
- To evaluate the efficacy of PF-06480605 in induction of endoscopic remission at Week 14 (defined as a Mayo endoscopic subscore of 0) in subjects with moderate to severe UC.
- To describe the PK of PF-06480605 in subjects with moderate to severe UC.
- To evaluate the immunogenicity of PF-06480605 in subjects with moderate to severe UC.
- To evaluate disease and pathway related biomarkers (ie, hsCRP and fecal calprotectin), and serum total sTL1A.

CCI

[redacted]

2.2. Endpoints

2.2.1. Primary Endpoints

- Safety and tolerability of PF-06480605: TEAEs, withdrawal due to AEs, and SAEs will be reported.
- Endoscopic improvement at Week 14 (defined as a Mayo endoscopic subscore of 0 or 1, and without friability).

2.2.2. Secondary Endpoints

- Remission at Week 14 (defined as a total Mayo score ≤2 with no individual subscore >1).
- Endoscopic remission at Week 14 (defined as a Mayo endoscopic subscore of 0).
- PF-06480605 plasma concentrations.
- Incidence of development of anti-drug antibodies (ADAs) and neutralizing antibodies (NAbs).
- Change from baseline in fecal calprotectin.
- Change from baseline in hsCRP.
- Change from baseline in serum total sTL1A.

CCI

[redacted]

3. STUDY DESIGN

3.1. Study Overview

This is a Phase 2a, single arm, two-stage study in subjects with moderate to severe UC. Subjects will receive 500 mg of PF-06480605 intravenously Q2W for a total of 7 doses. At the end of the first stage (12 evaluable subjects with a Week 14 colonoscopy), an IA will be performed for an early efficacy assessment. Enrollment in the second stage will be stopped if the futility criteria are met and any ongoing subjects in the second stage will be moved to the follow-up period. Otherwise, the study will continue to enroll additional subjects in the second stage for final efficacy assessment. An early PK readout of PF-06480605 serum concentrations will be conducted after at least 6 subjects have completed the Week 4 visit to confirm that the predicted exposures of PF-06480605 in UC patients are consistent with expected values, based on the healthy subject PK data. Following this early PK readout analysis, dose may be modified to match the exposures observed in healthy volunteers receiving 500 mg/kg IV (Study B7541001). The study will include an additional research component involving collection of biological samples and planned analysis for de-identified exploratory biomarker and immunogenicity analysis.

Women of childbearing potential (WOCBP) will be eligible for this study provided these women use two highly effective methods of contraception, as outlined in Section 4.3.

Stopping Rules

Individual stopping rules will be implemented to further evaluate safety and feasibility of study continuation, as described below:

- If ≥2 subjects receiving PF-06480605 develop the same adverse laboratory event with Common Terminology Criteria for Adverse Events (CTCAE V4.03) Grade 3 or higher, or if 1 subject develops a laboratory adverse event with a CTCAE Grade 4 or higher, then the study may be terminated.

- If ≥2 subjects experience an ECG abnormality defined as a prolonged QTcF of >500 msec over baseline assessment, then the study may be terminated. If a single subject experiences a prolonged QTcF of >500 msec over baseline assessment, then this subject will be discontinued from the study.

3.2. Duration of Subject Participation

The duration of participation for eligible subjects will be approximately 8 months, including a screening period of up to 6 weeks, a 12 week treatment period, and a follow-up period ending 14 weeks after the last dose of IP. Subjects with AEs as a result of positive ADA/NAbs may be requested to return for additional follow-up for up to 3 months after the follow-up/ EOS visit. During the treatment period, subjects will visit the site every 2 weeks (±3 days) for IP administration (7 visits), and then will return to the site every 4 weeks (±7 days) through Week 24 and again at Week 26, for follow-up visits (5 visits).

3.3. Approximate Duration of Study

This study is estimated to complete in approximately 32 months, maximum, allowing for an estimated 18-24 months of enrollment and approximately 8 months on study.

3.4. Planned Number of Subjects

This study has two stages. In the first stage, it is planned to have 12 evaluable subjects with an endoscopic score at Week 14 for futility assessment. If futility criteria are not met, recruitment will continue until approximately 36 total evaluable subjects complete the study with a final colonoscopy at Week 14.

4. SUBJECT SELECTION

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.

4.1. Inclusion Criteria

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

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

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

2. Subjects who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

3. Male and/or female subjects between ≥18 and ≤75 years of age at the time of informed consent.

4. Male subjects able to father children and female subjects of childbearing potential and at risk for pregnancy must agree to use two highly effective methods of contraception throughout the study and until the Week 26 visit (or 98 days after the last dose of IP).

   Women of childbearing potential (WOCBP) will be eligible for this study provided these women use two highly effective methods of contraception throughout the study and until the Week 26 visit (or 98 days after the last dose of IP), as outlined in Section 4.3. Female subjects who are not of childbearing potential (ie, meet at least 1 of the following criteria):

   - Have undergone a documented hysterectomy and/or bilateral oophorectomy;
   - Have medically confirmed ovarian failure; or

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

   Note: For subjects in France, WOCBP are NOT eligible for this study.

5. A diagnosis of UC for ≥4 months. A biopsy report must be available to confirm the histological diagnosis in the subject's source documentation. In addition, a report documenting disease duration and extent of disease (eg, proctosigmoiditis, left-sided colitis, and pancolitis) based upon prior endoscopy must also be available in source documentation.

6. Subjects with moderate to severe active UC as defined (via screening colonoscopy) by a total Mayo score of ≥6, with a rectal bleeding subscore of ≥1 and an endoscopic subscore of ≥2 on the Mayo.

7. Active disease beyond the rectum (>15 cm of active disease at the screening colonoscopy).

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

   - Steroids;
   - Immunosuppressants (AZA [azathioprine], 6-MP, or MTX [methotrexate]);
   - Anti-TNF inhibitors (eg, infliximab, adalimumab, or golimumab);
   - Anti-integrin inhibitors (eg, vedolizumab).

   For subjects in The Netherlands: Subjects must have inadequate response to, loss of response to, or intolerance to at least one biological therapy, such as an anti-TNF inhibitor.

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

   Inadequate response to, loss of response to, or intolerance to corticosteroid treatment is 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 of ≥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, LFT [liver function testing] abnormalities, lymphopenia, TPMT [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 is defined as one or more of the following:

- Persistent signs and symptoms of active disease despite at least one 8-week regimen of infliximab (3 intravenous doses ≥5 mg/kg), or 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 vedolizumab (intravenous doses of 300 mg at Weeks 0, 2, and 6).

- Note: There is no specific requirement for a subject to "washout" of a current treatment and no patient should be actively removed from prohibited medications in order to meet study inclusion/exclusion criteria.

9. Subjects currently receiving the following treatment for UC are eligible provided 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 total Mayo score screening procedures.

    - Oral corticosteroids (prednisone equivalent up to 20 mg/day; budesonide up to 9 mg/day) 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 total Mayo score screening procedures. Decreases in steroid use due to AEs are allowed.

    - 6-MP or AZA (≤2.5 mg/kg) stable dose for 8 weeks prior to baseline. Decreases due to AEs are permitted.

4.2. Exclusion Criteria

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

1. Subjects with a diagnosis of indeterminate colitis, ischemic colitis, radiation colitis, diverticular disease associated with colitis, microscopic colitis or CD. Subjects with clinical findings suggestive of CD (eg, fistulae, granulomas on biopsy) are also excluded.

2. Subjects with an imminent need for surgery or with elective surgery scheduled to occur during the study.

3. Subjects with colonic dysplasia or neoplasia.

4. Subjects with toxic megacolon.

5. Subjects with primary sclerosing cholangitis.

6. Subjects with known colonic stricture.

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

8. Subjects with a history of colonic or small bowel obstruction or resection.

9. Abnormal findings on the chest x-ray film performed routinely before initiating a new biologic therapy, 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.

10. Any current evidence of untreated latent or active TB infection, evidence of prior or currently active TB by chest x-ray, 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. 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.

    - 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.

    - An IGRA is preferred for subjects with a prior BCG vaccination (to be tested by a site's local lab where 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 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 consultation with pulmonary or infectious disease specialist that determines low risk of infection (ie, subject would be acceptable for immunosuppressant (eg, anti-TNF) treatment without additional action).

    - Subjects with adequately treated latent tuberculosis infection may be enrolled regardless of Mantoux or IGRA results.

11. Presence of active enteric infections (positive stool culture and sensitivity). The presence of *Clostridium difficile* or pseudomembranous colitis. Known active invasive fungal infections such as histoplasmosis or parasitic infections. Subjects with clinically significant underlying disease that could predispose the subjects to infections. A history of serious infection (requiring parenteral antibiotic and/or hospitalization) within 4 weeks before Day 1. Pyoderma gangrenosum is allowed.

12. 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. (Note: a documented negative HIV test within 1 year of screening is acceptable and does not need to be repeated).

13. Presence of transplanted organ. Skin grafts to treat pyoderma gangrenosum are allowed.

14. Significant concurrent medical condition as judged by the investigator 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.

    - Cancer or history of cancer or lymphoproliferative disease within the previous 5 years (other than resected cutaneous basal cell or squamous cell carcinoma that has been treated with no evidence of recurrence).

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

    - Subjects with current, or a history of QT prolongation would be excluded.

    - Class III or Class IV heart failure.

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

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

    - Positive hepatitis B surface antigen (HBsAg), total hepatitis B core antibody (HBcAb; also referred to as anti-HBc), and/or hepatitis C antibody (HCVAb) with confirmation by hepatitis C virus ribonucleic acid (HCV RNA).

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

    - Total bilirubin level ≥1.5 times the ULN.

- Hemoglobin level ≤80 g/L (8.0 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 ≤3.5 x 10^9/L (3500 cells/ mm^3).
- Absolute neutrophil count (ANC) <2000 cells/mm^3.
- Serum creatinine level ≥177 μmol/L (2 mg/dL).
- Glycosylated hemoglobin (HbA_{1C}) >10%.

Screening laboratory tests if considered by the investigator to be transient and inconsistent with the subject's clinical condition may be repeated once during the screening period for confirmation.

17. Subjects receiving the following therapies within the designated time period or are expected to receive any of these therapies during the study period:
    - >9 mg/day of oral budesonide or >20 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.
    - Biologics including anti-TNF inhibitors 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 12 weeks prior to baseline.

      For subjects in France: Subjects must not have received any biologic treatment for at least 5 half-lives prior to first dose of PF-06480605. (eg, infliximab: 47.5 days, adalimumab: 70 days, golimumab: 70 days, vedolizumab: 125 days).
    - Other investigational procedure(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.
18. Current or history within 2 years of serious psychiatric disease or alcohol or drug abuse.

19. Subjects who are investigational 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 directly involved in the conduct of the study.

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

21. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or IP 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.

22. Pregnant female subjects; 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 two highly effective methods of contraception as outlined in this protocol for the duration of the study and until the Week 26 visit (or 98 days after the last dose of IP) or longer based on the compound's half-life characteristics.

4.3. Lifestyle Guidelines

Women of childbearing potential (WOCBP) will be eligible for the study provided these women use two highly effective methods of contraception throughout the study and until the Week 26 visit (or 98 days after the last dose of IP), as outlined below.

Note: For subjects in France, WOCBP are NOT eligible for this study.

All male subjects who are able to father children and female subjects who are of childbearing potential and are sexually active and at risk for pregnancy must agree to use two methods of highly effective method of contraception consistently and correctly for the duration of the active treatment period and until the Week 26 visit (or 98 days after the last dose of IP). The investigator or his or her designee, in consultation with the subject, will confirm that the subject has selected two appropriate methods of contraception for the individual subject from the permitted list of contraception methods (see below) and instruct the subject in its consistent and correct use. Subjects need to affirm that they meet the criteria for correct use of at least 2 of the selected methods of contraception. The investigator or his/her designee will discuss with the subject the need to use highly effective contraception consistently and correctly according to the Schedule of Activities and document such conversation in the subject's chart. In addition, the investigator or his or her designee will instruct the subject to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the subject or the subject's partner.

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

1. Established use of oral, inserted, injected, implanted or transdermal hormonal methods of contraception is allowed provided the subject plans to remain on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness.

2. Correctly placed copper-containing intrauterine device (IUD).

3. Male condom or female condom used WITH a spermicide (ie, foam, gel, film, cream, or suppository). For countries where spermicide is not available or condom plus spermicide is not accepted as highly effective contraception, this option is not appropriate.

4. Male sterilization with absence of sperm in the post-vasectomy ejaculate.

5. Bilateral tubal ligation/bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label).

6. Female partner who meets the criteria for non-childbearing potential, as described below:

   Female subjects of non-childbearing potential must meet at least one of the following criteria:

   - Have undergone a documented hysterectomy and/or bilateral oophorectomy;
   - Have medically confirmed ovarian failure; or
   - Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; and have a serum FSH level confirming the post-menopausal state.

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

All sexually active male subjects must agree to prevent potential transfer of and exposure to drug through semen to their partners by using a condom consistently and correctly, beginning with the first dose of IP and until the Week 26 visit (or 98 days after the last dose of IP).

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 site Regulatory binder.

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

5. STUDY TREATMENTS

For the purposes of this study, and per International Conference on Harmonization (ICH) guidelines IP is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference 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).

5.1. Allocation to Treatment

Subject enrollment and assignment of treatment will be managed through the use of a centralized Interactive Response Technology (IRT) system or another suitable system.

During the screening period, subjects are to be assigned a Single Subject Identifier (SSID) number via an automated IRT system or another equivalent system managed by Pfizer.

Subjects who meet all of the eligibility criteria (See Section SUBJECT SELECTION) are qualified to participate and receive IP within the study. At the point of study eligibility and enrollment, a subject should be assigned an enrollment or treatment number as allocated via the IRT or equivalent system so as to uniquely track their participation in study conduct.

IP will only be administered to subjects who have signed and dated an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) approved informed consent document (ICD) and who have met all eligibility criteria.

The investigator's knowledge of the treatment should not influence the decision to enroll a particular subject or affect the order in which subjects are enrolled.

5.2. Subject Compliance

All doses of IP will be administered by the appropriately designated study staff at the investigational site.

5.2.1. Infusion Discontinuation

Treatment of patients with monoclonal antibodies may result in inappropriate immune responses and range from mild events with no apparent clinical manifestations to life-threatening or catastrophic reactions. Signs and symptoms of these events may develop during or shortly after infusion. As such, subjects must be closely monitored during administration of PF-06480605, and for a minimum of 2 hours after administration has ended.

Some of the major safety concerns associated with immunogenicity are anaphylaxis, cytokine release syndrome, "infusion reactions", and non-acute reactions such as delayed hypersensitivity; and manifestations may be common among these events.

The information below is provided as guidance to assess anaphylaxis, but the clinical judgment of the investigator should be considered as well.

Anaphylaxis is a serious, acute allergic reaction characterized by certain clinical features. Signs and symptoms of anaphylaxis may include:

- Generalized hives, pruritis/itching, flushing, swollen lips/tongue/uvula;
- Symptoms of respiratory compromise (eg, dyspnea, wheeze/bronchospasm, stridor, reduced peak expiratory flow, hypoxemia);
- Reduced blood pressure (systolic blood pressure of less than 90 mm Hg or greater than 30% decrease from baseline) or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence);
- Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting).

The Sponsor recommends use of the Sampson criteria[13] for further guidance regarding the diagnosis of anaphylaxis reactions.

If a subject experiences anaphylaxis, IP administration should be discontinued immediately and permanently.

If a subject experiences symptoms that may be attributed to hypersensitivity reaction or delayed hypersensitivity (eg, fever, rash, arthralgia, myalgia, hematuria, proteinuria, serositis, central nervous system complications, or hemolytic anemia) IP infusion should be stopped.

In the event that symptoms are mild or minor in severity, at the discretion of the investigator, the infusion may be restarted at a slower rate if symptoms are resolved within 1 hour after the stop of infusion. If symptoms return, IP should be discontinued immediately and permanently.

In the event that there is an infusion interruption, the entire duration of IP infusion, from the initial start of infusion, to the completion of infusion, should not exceed 3 hours. Subjects will receive appropriate treatment at the discretion of the investigator.

5.3. Investigational Product Supplies

5.3.1. Dosage Form(s) and Packaging

IP, PF-06480605 Powder for Solution for Injection, 100 mg/vial, is supplied by Pfizer as a lyophilized white cake in a sterile, single-use, glass vial with aluminum flip off seal for IV administration.

5.3.2. Preparation and Dispensing

See the Dosage and Administration Instructions (DAI) for instructions on how to prepare the IP for administration. IP should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, practitioner, or pharmacist) as allowed by local, state, and institutional guidance.

5.4. Administration

PF-06480605 (500 mg) will be administered intravenously as a 60 minute infusion using a calibrated infusion pump at Day 1, Week 2 (Day 15), Week 4 (Day 29), Week 6 (Day 43), Week 8 (Day 57), Week 10 (Day 71) and Week 12 (Day 85) ±3 days during the study for a total of up to 7 doses. IP administration should occur following most study procedures and must not be administered as an IV push or bolus. The start and stop time of the infusion will be recorded on the case report form (CRF). The infusion stop time should be recorded as the time when the end of the saline flush is complete.

Subjects should remain at the study site for a minimum period of at least 2 hours for observation following end of administration of PF-06480605 infusion.

5.5. Investigational Product Storage

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

IP should be stored in its original container and in accordance with the label. See the DAI for storage conditions of the product once reconstituted.

Storage conditions stated in the IB will be superseded by the storage conditions stated in the labeling.

All IP will be shipped to each study site at +2°C to +8°C. Upon receipt at the study site, the IP should be immediately transferred to a +2°C to +8°C temperature-monitored refrigerator for storage.

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 IP receipt throughout the study. Even for continuous monitoring systems, a log or site procedure that ensures active daily evaluation for excursions should be

available. The operation of the temperature monitoring device and storage unit (eg, refrigerator), as applicable, should be regularly inspected to ensure it is maintained in working order.

Any excursions from the product label storage conditions should be reported upon discovery. The site should actively pursue options for returning the product to the storage conditions as described in the labeling, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to the sponsor. Once an excursion is identified, the IP must be quarantined and not used until the sponsor provides documentation of permission to use the IP. It will not be considered a protocol deviation if the sponsor approves the use of the IP after the temperature excursion. Use of the IP prior to sponsor 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 product(s) are briefly out of the temperature range described in the labeling are not considered excursions.

5.6. Investigational Product Accountability

The investigative site must maintain adequate records documenting the receipt, use, loss, or other disposition of the IP supplies.

5.6.1. Destruction of Investigational Product Supplies

The sponsor or designee will provide guidance on the destruction of unused IP (eg, at the site). If destruction is authorized to take place at the study 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.

5.7. Prior Medications

Any prior history (any time prior to signing the ICD with no limitations of time) of corticosteroids, immunosuppressives (AZA, 6-MP, and MTX), anti-TNFs and anti-integrins will be recorded on the CRF.

Any prior UC medications taken during the 30 days prior to screening and biologic therapies within 90 days prior to screening must be recorded on the CRF.

Medications taken within 42 days before the first dose of IP will be documented as prior medications.

5.8. Concomitant Medication(s) and Treatment(s)

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

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

5.8.1. Oral Corticosteroids Taken During the Study

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 Week 14. If oral 5-ASA treatment has been recently discontinued, it must have been stopped for at least 2 weeks prior to Total Mayo Score screening procedures.
- A stable dose of oral corticosteroids (prednisone equivalent up to 20 mg/day; budesonide up to 9 mg/day) for at least 2 weeks prior to baseline and through Week 14. If oral corticosteroids have been recently discontinued, they must have been stopped at least 2 weeks prior to total Mayo score screening procedures. Rectal steroids are prohibited. Decreases in steroid use due to AEs are allowed.
- A stable dose of immunosuppressants (6-MP or AZA ≤2.5 mg/kg) for 8 weeks prior to baseline and through Week 14. Decreases due to AEs are permitted.

5.8.3. Prohibited Medications

- Any live (attenuated) vaccines from 30 days prior to baseline through Week 14.
- IV, intramuscular (IM) (parenteral) or rectal 5-ASA or corticosteroid enemas/suppositories from 2 weeks prior to baseline through Week 14.
- Prednisone dose >20 mg/day or equivalent oral systemic corticosteroid from 2 weeks prior to baseline through Week 14.
- Any investigational or marketed biologic immunosuppressive treatments within 30 days, or 5 half-lives of IP (whichever is greater), prior to baseline and/or during study participation.
- Oral budesonide >9 mg/day or equivalent from 2 weeks prior to baseline through Week 14.

- Use of immunosuppressants used in transplantation (eg, mycophenolate mofetil, cyclosporine, rapamycin, or tacrolimus) from 30 days prior to baseline through Week 14.

5.9. Rescue Medication

Following the Week 14 visit, subjects will no longer need to abstain from the medications that were prohibited during the screening and induction periods. High-dose steroids and other UC treatments will be permitted after the Week 14 visit. Biologic treatment(s) should not be initiated during the follow-up period without discussion with the sponsor due to the long $t_{1/2}$ of PF-06480605.

Subjects are free to 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. If a subject requires initiation of a new therapy for ulcerative colitis, the subject should be withdrawn from the study and appropriate treatment should be administered at the discretion of the investigator.

6. STUDY PROCEDURES

6.1. Screening

Subjects will be screened within 42 days prior to administration of the IP to confirm that they have met all the subject selection criteria for the study. The investigator (or an appropriate delegate at the investigational site) will obtain informed consent from each subject in accordance with the procedures described in Section 12.3 on Subject Information and Consent. At least two visits to the clinical facility will be necessary to complete all screening procedures, including colonoscopy. The colonoscopy should be performed after all other eligibility criteria have been met and within 10 days of baseline, preferably 5 to 7 days prior to the baseline to allow Mayo score calculation.

Subjects may be re-screened one time at the discretion of the sponsor if they fail their initial screening .

Written informed consent must be obtained prior to performance of any protocol specific procedures.

The following procedures will be completed:

- Informed Consent Document (ICD).
- Demography, complete medical history (including UC and smoking).
- Review of inclusion and exclusion criteria.
- Complete history of steroids, immunosuppressive and/or anti-TNF and anti-integrin treatment with no limitation of time prior to signing the ICD.
- Vital signs measurements including sitting blood pressure (BP) and pulse (after 5 minutes of rest) and temperature (oral, tympanic or axillary).

- Measurement of height (in or cm) and weight (lbs or kg) without shoes.
- Complete physical examination.
- Standard 12-lead ECG (see Section 7.2.8 and Schedule of Activities).
- Chest x-ray unless a radiograph was performed within 12 weeks prior to study entry (screening). Official reading/report must be located in the source documentation (see Section 7.2.9 and Schedule of Activities).
- Contraception check.
- Collect blood, urine and/or stool samples for the following laboratory tests; the screening labs may be repeated once if necessary to confirm eligibility:
  - Safety laboratory tests for blood chemistry, hematology and urinalysis.
  - HbA1c.
  - Serum FSH [women of non-childbearing potential (WONCBP) only].
  - Serum pregnancy test (WOCBP only) (Note: If serum pregnancy test is borderline positive, the central lab will run an FSH test as a reflex test).
  - Serology screens for HBsAg, total HBcAb, HCVAb (confirmed by HCV RNA) and HIV (documentation of a negative HIV test result within 12 months of screening will be accepted and must be available in source documentation.
  - TB screening (Mantoux [PPD] or IGRA test per local guidelines [performed at local lab where feasible]) unless a negative test result was obtained up to 12 weeks prior to screening. Documentation of IGRA official reading and method of test must be located in the source documentation.
  - Stool specimen for enteric pathogens with culture and sensitivity for *Clostridium difficile* (performed locally or at the central laboratory) (see Section 7.2.5 for *Clostridium difficile*).
  - CCI [redacted]
  - CCI [redacted]
- Subjects will be instructed on the use of the e-diary for daily collection of subject stool diary data.
- Dispense labeled stool container and plastic bag (for refrigerated or frozen stool sample at subsequent visit).

[redacted]

- UC Assessment:
  - Colonoscopy should be performed within approximately 10 days of baseline, preferably 5 to 7 days prior to the baseline to allow Mayo score calculation. The endoscopic subscore by the Central Reader must be available at baseline visit. The assessment by the Central Reader will be used to derive the Mayo score for study eligibility. The endoscopic report must be available in the source documents.
  - Total Mayo score based on centrally-read endoscopic subscore, stool frequency and rectal bleeding (from e-diary) and physician's global assessment (See Section 7.3.3 and Schedule of Activities).

CCI [redacted]

CCI [redacted]

6.2. Study Period

For the study period described below, where multiple procedures are scheduled at the same time point(s) relative to dosing, it is recommended that the following chronology of events be followed, where possible:

- ECGs: obtain prior to vital signs and as close as possible to scheduled time, but prior to blood specimen collection.
- Sitting BP and pulse rate: obtain as close as possible to scheduled time, but prior to blood specimen collection.
- PK blood specimens: obtain at scheduled time.
- Other procedures: all procedures should be obtained as close as possible to the scheduled time, but may be obtained before or after blood specimen collection.
- The following order is recommended for post-dosing procedures:
  - Complete infusion and flush; record time of completion on CRF when flush is complete;
  - Complete PK draw at scheduled time;
  - Obtain vital signs;
  - Obtain ECG;

- Complete any other required procedures and 2 hour post-dose observation period.

6.2.1. Baseline Visit – Week 0/Day 1

The baseline visit must occur on the projected visit date within approximately 42 days of the completion of screening procedures. All baseline procedures and tests must be completed prior to administration of the first dose of IP. Results of the baseline laboratory tests are not required for IP administration but must be reviewed as soon as possible thereafter.

Prior to dosing the following procedures will be completed:

- Review eligibility criteria to ensure and confirm subject meets entry criteria.
- Measure vital signs including sitting BP and pulse (after 5 minutes of rest) and temperature (oral, tympanic or axillary). Vital sign measurement should occur approximately 30 minutes prior to dosing.
- Record subject's weight.
- Targeted physical examination.
- Collect blood, urine and/or stool samples for the following laboratory tests:
  - Safety laboratory tests for blood chemistry, hematology and urinalysis.
  - Urine pregnancy test (WOCBP only).
  - Retained pharmacogenomic sample (Prep D1).
  - PD Biomarkers: CCI [redacted], serum total sTL1A, CCI [redacted], hsCRP.
  - Stool sample for fecal calprotectin.
  - Pre-dose PK: PK sample should be collected approximately 30 minutes prior to dosing.
  - Immunogenicity: ADA, NAb, ELISpot, B-cell isolation, ADA epitope/affinity.
- UC Assessment: CCI [redacted] and review subject stool e-diary data (See Section 7.3.5 and Schedule of Activities).
- Review stool e-diary completion instructions.
- Dispense labeled stool container and plastic bag (for refrigerated or frozen stool sample at subsequent visit).

- Review prior and concomitant medications/treatments, including steroids.
- Contraception check.

Dosing may occur after all screening procedures are completed and results reviewed.

- Administer PF-06480605 as described in Section 5.4. For WOCBP, the urine pregnancy test must be negative prior to dosing.
- Measure vital signs including sitting BP and pulse (after 5 minutes of rest) and temperature (oral, tympanic or axillary). Vital sign measurement should occur approximately one hour post dose (end of infusion).
- 12-lead ECG.
- Post dose PK: PK sample should be collected approximately one hour post dose (at end of infusion).
- Monitor subject for AEs and injection site reactions (ISRs). Subjects should be monitored for a minimum of 2 hours following end of administration of PF-06480605 infusion.

6.2.2. Visit 2, Week 2/Day 15 (±3 Days Based on Day 1 Visit)

Prior to dosing the following procedures will be completed:

- Measure vital signs including sitting BP and pulse (after 5 minutes of rest) and temperature (oral, tympanic or axillary). Vital sign measurement should occur approximately 30 minutes prior to dosing.
- Targeted physical examination.
- Collect blood, urine and/or stool samples for the following laboratory tests:
  - Safety laboratory tests for blood chemistry, hematology and urinalysis.
  - Urine pregnancy test (WOCBP only).
  - PD Biomarkers: CCI [redacted], serum total sTL1A, CCI [redacted], hsCRP.
  - Stool sample for fecal calprotectin.
  - Pre-dose PK: PK sample should be collected approximately 30 minutes prior to dosing.
  - Immunogenicity: ADA, NAb, ADA epitope/affinity.

- UC Assessment: CCI [redacted] and review subject stool e-diary data (See Section 7.3.5 and Schedule of Activities).
- Review stool e-diary completion instructions (See Schedule of Activities).
- Review prior and concomitant medications/treatments, including steroids.
- Contraception check.
- **Administer PF-06480605** as described in Section 5.4. For WOCBP, the urine pregnancy test must be negative prior to dosing.
- Measure vital signs including sitting BP and pulse (after 5 minutes of rest) and temperature (oral, tympanic or axillary). Vital sign measurement should occur approximately one hour post dose (end of infusion).
- Post dose PK: PK sample should be collected approximately one hour post dose (at end of infusion).
- Monitor subject for AEs and ISRs. Subjects should be monitored for a minimum of 2 hours following end of administration of PF-06480605 infusion.

6.2.3. Visit 3, Week 4/Day 29 (±3 Days Based on Day 1 Visit)

Prior to dosing the following procedures will be completed:

- Pre-dose ECG: ECG should be administered approximately 30 minutes prior to dosing.
- Measure vital signs including sitting BP and pulse (after 5 minutes of rest) and temperature (oral, tympanic or axillary). Vital sign measurement should occur approximately 30 minutes prior to dosing.
- Record subject's weight.
- Targeted physical examination.
- Collect blood, urine and/or stool samples for the following laboratory tests:
  - Safety laboratory tests for blood chemistry, hematology and urinalysis.
  - Urine pregnancy test (WOCBP only).
  - PD Biomarker: serum total sTL1A, hsCRP.
  - Pre-dose PK: PK sample should be collected approximately 30 minutes prior to dosing.

- Immunogenicity: ADA, NAb, ADA epitope/affinity.

- UC Assessment: CCI [redacted] and review subject stool e-diary data (See Section 7.3.5 and Schedule of Activities).

- Review stool e-diary completion instructions (See Schedule of Activities).

- Review prior and concomitant medications/treatments, including steroids.

- Contraception check.

- **Administer PF-06480605** as described in Section 5.4. For WOCBP, the urine pregnancy test must be negative prior to dosing.

- Post dose ECG: ECG should be administered approximately one hour post dose (end of infusion).

- Measure vital signs including sitting BP and pulse (after 5 minutes of rest) and temperature (oral, tympanic or axillary). Vital sign measurement should occur approximately one hour post dose (end of infusion).

- Post dose PK: PK sample should be collected approximately one hour post dose (at end of infusion).

- Monitor subject for AEs and ISRs. Subjects should be monitored for a minimum of 2 hours following end of administration of PF-06480605 infusion.

6.2.4. Visit 4, Week 6/Day 43 (±3 Days Based on Day 1 Visit)

Prior to dosing the following procedures will be completed:

- Measure vital signs including sitting BP and pulse (after 5 minutes of rest) and temperature (oral, tympanic or axillary). Vital sign measurement should occur approximately 30 minutes prior to dosing.

- Targeted physical examination.

- Collect blood, urine and/or stool samples for the following laboratory tests:

  - Safety laboratory tests for blood chemistry, hematology and urinalysis.

  - Urine pregnancy test (WOCBP only).

  - PD Biomarker: serum total sTL1A, hsCRP.

  - Pre-dose PK: PK sample should be collected approximately 30 minutes prior to dosing.

- Review stool e-diary completion instructions (See Schedule of Activities).
- Dispense labeled stool container and plastic bag (for refrigerated or frozen stool sample at subsequent visit).
- Review prior and concomitant medications/treatments, including steroids.
- Contraception check.
- **Administer PF-06480605** as described in Section 5.4. For WOCBP, the urine pregnancy test must be negative prior to dosing.
- Measure vital signs including sitting BP and pulse (after 5 minutes of rest) and temperature (oral, tympanic or axillary). Vital sign measurement should occur approximately one hour post dose (end of infusion).
- Post dose PK: PK sample should be collected approximately one hour post dose (at end of infusion).
- Monitor subject for AEs and ISRs. Subjects should be monitored for a minimum of 2 hours following end of administration of PF-06480605 infusion.

6.2.5. Visit 5, Week 8/Day 57 (±3 Days Based on Day 1 Visit)

Prior to dosing the following procedures will be completed:

- Pre-dose ECG: ECG should be administered approximately 30 minutes prior to dosing.
- Measure vital signs including sitting BP and pulse (after 5 minutes of rest) and temperature (oral, tympanic or axillary). Vital sign measurement should occur approximately 30 minutes prior to dosing.
- Record subject's weight.
- Targeted physical examination.
- Collect blood, urine and/or stool samples for the following laboratory tests:
  - Safety laboratory tests for blood chemistry, hematology and urinalysis.
  - Urine pregnancy test (WOCBP only).
  - PD Biomarkers: CCI [redacted], serum total sTL1A, CCI [redacted], hsCRP.
  - Stool sample for fecal calprotectin and CCI [redacted]

- Pre-dose PK: PK sample should be collected approximately 30 minutes prior to dosing.
- Immunogenicity: ADA, NAb, ADA epitope/affinity.

- UC Assessment: CCI [redacted] and review subject stool e-diary data (See Section 7.3.5 and Schedule of Activities).
- Review stool e-diary completion instructions (See Schedule of Activities).
- Review prior and concomitant medications/treatments, including steroids.
- Contraception check.
- **Administer PF-06480605** as described in Section 5.4. For WOCBP, the urine pregnancy test must be negative prior to dosing.
- Post dose ECG: ECG should be administered approximately one hour post dose (end of infusion).
- Measure vital signs including sitting BP and pulse (after 5 minutes of rest) and temperature (oral, tympanic or axillary). Vital sign measurement should occur approximately one hour post dose (end of infusion).
- Post dose PK: PK sample should be collected approximately one hour post dose (at end of infusion).
- Monitor subject for AEs and ISRs. Subjects should be monitored for a minimum of 2 hours following end of administration of PF-06480605 infusion.

6.2.6. Visit 6, Week 10/Day 71 (±3 Days Based on Day 1 Visit)

Prior to dosing the following procedures will be completed:

- Measure vital signs including sitting BP and pulse (after 5 minutes of rest) and temperature (oral, tympanic or axillary). Vital sign measurement should occur approximately 30 minutes prior to dosing.
- Targeted physical examination.
- Collect blood, urine and/or stool samples for the following laboratory tests:
  - Safety laboratory tests for blood chemistry, hematology and urinalysis.
  - Urine pregnancy test (WOCBP only).
  - PD Biomarker: Serum total sTL1A, hsCRP.

- Pre-dose PK: PK sample should be collected approximately 30 minutes prior to dosing.

- Review stool e-diary completion instructions (See Schedule of Activities).
- Dispense labeled stool container and plastic bag (for refrigerated or frozen stool sample at subsequent visit).
- Review prior and concomitant medications/treatments, including steroids.
- Contraception check.
- **Administer PF-06480605** as described in Section 5.4. For WOCBP, the urine pregnancy test must be negative prior to dosing.
- Measure vital signs including sitting BP and pulse (after 5 minutes of rest) and temperature (oral, tympanic or axillary). Vital sign measurement should occur approximately one hour post dose (end of infusion).
- Post dose PK: PK sample should be collected approximately one hour post dose (at end of infusion).
- Monitor subject for AEs and ISRs. Subjects should be monitored for a minimum of 2 hours following end of administration of PF-06480605 infusion.

6.2.7. Visit 7, Week 12/Day 85 (±3 Days Based on Day 1 Visit)

Prior to dosing the following procedures will be completed:

- Pre-dose ECG: ECG should be administered approximately 30 minutes prior to dosing.
- Measure vital signs including sitting BP and pulse (after 5 minutes of rest) and temperature (oral, tympanic or axillary). Vital sign measurement should occur approximately 30 minutes prior to dosing.
- Record subject's weight.
- Targeted physical examination.
- Collect blood, urine and/or stool samples for the following laboratory tests:
  - Safety laboratory tests for blood chemistry, hematology and urinalysis.
  - Urine pregnancy test (WOCBP only).
  - PD Biomarker: Serum total sTL1A, hsCRP.

- Stool sample for fecal calprotectin and CCI [redacted]
- Pre-dose PK: PK sample should be collected approximately 30 minutes prior to dosing.
- Immunogenicity: ADA, NAb, ELISpot, ADA epitope/affinity.

- UC Assessment: CCI [redacted] and review subject stool e-diary data (See Section 7.3.5 and Schedule of Activities).
- Review stool e-diary completion instructions (See Schedule of Activities).
- Review prior and concomitant medications/treatments, including steroids.
- Contraception check.
- **Administer PF-06480605** as described in Section 5.4. For WOCBP, the urine pregnancy test must be negative prior to dosing.
- Post dose ECG: ECG should be administered approximately one hour post dose (end of infusion).
- Measure vital signs including sitting BP and pulse (after 5 minutes of rest) and temperature (oral, tympanic or axillary). Vital sign measurement should occur approximately one hour post dose (end of infusion).
- Post dose PK: PK sample should be collected approximately one hour post dose (at end of infusion).
- Monitor subject for AEs and ISRs. Subjects should be monitored for a minimum of 2 hours following end of administration of PF-06480605 infusion.

6.2.8. Visit 8, Week 14/Day 99 (±3 Days Based on Day 1 Visit)

- Vital signs measurements including sitting blood pressure (BP) and pulse (after 5 minutes of rest) and temperature (oral, tympanic or axillary).
- Complete physical examination.
- Collect blood, urine and/or stool samples for the following laboratory tests:
  - Safety laboratory tests for blood chemistry, hematology and urinalysis.
  - Urine pregnancy test (WOCBP only).
  - PD Biomarkers: hsCRP, CCI [redacted], serum total sTL1A, CCI [redacted],

CCI [redacted]

- PK.
- Immunogenicity: B-cell isolation.

- UC Assessment:
  - Colonoscopy: The endoscopic report and pathology report must be available in the source documents.
  - Total Mayo score based on centrally-read endoscopic subscore, stool frequency rectal bleeding and physician's global assessment (See Section 7.3.3 and Schedule of Activities).
  - CCI [redacted]
- Review stool e-diary completion instructions (See Schedule of Activities).
- Review prior and concomitant medications/treatments, including steroids.
- Monitor subject for AEs.
- Contraception check.

6.2.9. Visit 9, Week 16/Day 113 (±7 Days Based on Day 1 Visit)

- Vital signs measurements including sitting blood pressure (BP) and pulse (after 5 minutes of rest) and temperature (oral, tympanic or axillary).
- Record subject's weight.
- Targeted physical examination.
- 12-Lead ECG.
- Collect blood, urine and/or stool samples for the following laboratory tests:
  - Safety laboratory tests for blood chemistry, hematology and urinalysis.
  - Urine pregnancy test (WOCBP only).
  - PD Biomarkers: hsCRP, serum total sTL1A.
  - PK.

- Immunogenicity: ADA, NAb, ADA epitope/affinity.

- Review stool e-diary completion instructions (See Schedule of Activities).
- Review prior and concomitant medications/treatments, including steroids.
- Monitor subject for AEs.
- Contraception check.

6.2.10. Visit 10, Week 20/Day 141 (±7 Days Based on Day 1 Visit)

- Vital signs measurements including sitting blood pressure (BP) and pulse (after 5 minutes of rest) and temperature (oral, tympanic or axillary).
- Record subject's weight.
- Targeted physical examination.
- 12-Lead ECG.
- UC Assessment: CCI [redacted] and review subject stool e-diary data (See Section 7.3.5 and Schedule of Activities).
- Collect blood, urine and/or stool samples for the following laboratory tests:
  - Safety laboratory tests for blood chemistry, hematology and urinalysis.
  - Urine pregnancy test (WOCBP only).
  - PD Biomarkers: hsCRP, serum total sTL1A.
  - PK.
  - Immunogenicity: ADA, NAb, ELISpot, ADA epitope/affinity.
- Review stool e-diary completion instructions (See Schedule of Activities).
- Review prior and concomitant medications/treatments, including steroids.
- Monitor subject for AEs.
- Contraception check.

6.2.11. Visit 11, Week 24/Day 169 (±7 Days Based on Day 1 Visit)

- Vital signs measurements including sitting blood pressure (BP) and pulse (after 5 minutes of rest) and temperature (oral, tympanic or axillary).

- Targeted physical examination.
- Collect blood, urine and/or stool samples for the following laboratory tests:
  - Urine pregnancy test (WOCBP only).
  - PD Biomarkers: hsCRP, serum total sTL1A.
  - PK.
  - Immunogenicity: ADA, NAb, ADA epitope/affinity.
- Dispense labeled stool container and plastic bag (for refrigerated or frozen stool sample at subsequent visit).
- Review stool e-diary completion instructions (See Schedule of Activities).
- Review prior and concomitant medications/treatments, including steroids.
- Monitor subject for AEs.
- Contraception check.

6.2.12. Final On-Site Study Visit: Visit 12, Week 26/Day 183 (±7 Days Based on Day 1 Visit)

- Vital signs measurements including sitting blood pressure (BP) and pulse (after 5 minutes of rest) and temperature (oral, tympanic or axillary).
- Record subject's weight.
- Complete physical examination.
- 12-Lead ECG.
- UC Assessment: CCI [redacted] and review subject stool e-diary data (See Section 7.3.5 and Schedule of Activities).
- Collect blood, urine and/or stool samples for the following laboratory tests:
  - Safety laboratory tests for blood chemistry, hematology and urinalysis.
  - Urine pregnancy test (WOCBP only).
  - PD Biomarkers: hsCRP, serum total sTL1A.
  - Stool sample for fecal calprotectin and CCI [redacted]

[redacted]

- PK.
- Immunogenicity: ADA, NAb, ELISpot, ADA epitope/affinity.

- Review prior and concomitant medications/treatments, including steroids.
- Monitor subject for AEs. Subjects with AEs as a result of positive ADA/NAbs may be requested to return for additional follow-up for up to 3 months after the final on site study visit and will have PK samples collected in addition to ADA/NAb samples. Other assessments may also be performed during these visits as appropriate depending upon the actual AE that is experienced.
- Contraception check.

6.3. Subject Withdrawal

Any subject who prematurely withdraws during active treatment (Week 0 through Week 12) should return for an early withdrawal visit and then enter the follow up period. The following procedures will be performed at the early withdrawal visit:

- Vital signs measurements including sitting blood pressure (BP) and pulse (after 5 minutes of rest) and temperature (oral, tympanic or axillary).
- Record subject's weight.
- Complete physical examination.
- 12-Lead ECG.
- UC Assessment:
  - Colonoscopy: The endoscopic report and pathology report must be available in the source documents.
  - Total Mayo score based on centrally-read endoscopic subscore, stool frequency rectal bleeding and physician's global assessment (See Section 7.3.3 and Schedule of Activities).
  - CCI [redacted]
- CCI [redacted]
- Collect blood, urine and/or stool samples for the following laboratory tests:
  - Safety laboratory tests for blood chemistry, hematology and urinalysis.
  - Urine pregnancy test (WOCBP only).

- PD Biomarkers: hsCRP, CCI [redacted], serum total sTL1A, CCI [redacted].
- Stool sample for fecal calprotectin and CCI [redacted]
- PK.
- Immunogenicity: ADA, NAb, ELISpot, B-cell isolation, ADA epitope/affinity.

- Review prior and concomitant medications/treatments, including steroids.
- Monitor subject for AEs.
- Contraception check.
- End of study CRF.

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 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 for a final visit, if applicable, and follow up with the subject regarding any unresolved AEs.

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

7. ASSESSMENTS

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

7.1. Blood Volume

Total planned blood sampling for an individual subject that completes all currently scheduled assessments through the Week 26 visit is approximately 613 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	BUN/Urea and	pH	HbA1c[e]
Hematocrit	Creatinine	Glucose (qual)	FSH[d,e]
RBC count	Glucose	Protein (qual)	β-hCG[f]
Platelet count	Calcium	Blood (qual)	Hepatitis B, C and HIV[e]
WBC count	Sodium	Ketones	QFT-G or other IGRA[e]
Total neutrophils (Abs)	Potassium	Nitrites	hsCRP
Eosinophils (Abs)	Chloride	Leukocyte esterase	
Monocytes (Abs)	AST, ALT	Microscopy[c]	Stool sample[e] to detect enteric infections and C. difficile toxins A and B
Basophils (Abs)	Total Bilirubin		
Lymphocytes (Abs)	Direct bilirubin[a]		
PT/INR/PTT	Alkaline phosphatase		
	Uric acid		Stool sample for fecal calprotectin
	Albumin		
	Total protein		
	Creatine kinase (CK)		ADAs
	CK fractionation[b]		

a. Only if total bilirubin is elevated.
b. Only if CK is elevated.
c. Only if urine dipstick is positive for blood, protein, nitrites or leukocyte esterase.
d. In females who are amenorrheic for at least 12 consecutive months.
e. Complete at screening.
f. If serum pregnancy test is borderline positive, the central lab will run a FSH test to confirm menopause.

7.2.2. Pregnancy Testing

For female subjects of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed at screening, before IP administration at the baseline visit, and at the end of treatment visit. A negative pregnancy result is required before the subject may receive the IP. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected), and repeated at all visits and at the end of the study to confirm the subject has not become pregnant during the study. Pregnancy tests may also be repeated as per request of IRBs/IECs or if required by local regulations.

In the case of a positive confirmed pregnancy, the subject will be withdrawn from administration of IP but may remain in the study in follow up.

7.2.3. Purified Protein Derivative (PPD) Tuberculin Test

Subjects may be screened for TB using the PPD Tuberculin Test per local guidelines. The test consists of 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 to determine if the test is positive or negative. The test is positive if the induration diameter is ≥25 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. 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.

7.2.4. 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. 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.

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

7.2.5. Screening for Clostridium Difficile

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.

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

Single sitting 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.

Sitting blood pressure will be measured with the subject's arm supported at the level of the heart, and recorded to the nearest mm Hg. 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 are acceptable, although, when done manually, pulse rate will be measured in the brachial/radial artery for at least 30 seconds. When the timing of these measurements coincides with a blood collection, 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.

7.2.7. Medical History, Physical Examination, Height and Weight

Medical history (including UC and smoking history) will be collected at the Screening visit.

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.

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).

7.2.8. Electrocardiogram (ECG)

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

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 measurements 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. However, all ECGs will be interpreted by a central reader. Pfizer and the central ECG vendor will provide sites with the instructions and supplies for processing.

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.

7.2.9. Chest Radiograph

Chest X-ray (posterior-anterior and lateral views are recommended however local guidelines should be followed) with no evidence of current, active TB or previous inactive TB, general infections, heart failure or malignancy taken at screening or within the 12 weeks prior to screening and read by a qualified radiologist. Documentation of the official reading must be located and available in the source documentation.

7.3. Diagnostic and Efficacy Assessments

7.3.1. Colonoscopy

Colonoscopy should be performed 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 baseline visit. The assessment by the Central Reader will be used to derive the total Mayo score for study eligibility. The endoscopic report and pathology report must be available in the source documents.

A colonoscopy is also performed at Visit 8 (Week 14) or at the early withdrawal visit where applicable. Bowel preparation should be conducted as per local routine. The position of the endoscope at the Visit 8 or early withdrawal visit 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 colonoscopy. The colonoscopy report and any photographs and/or video recordings taken during the procedure per local custom should be filed in the subject's chart. The findings of the colonoscopy component should be completed at the end of the procedure to document the endoscopic subscore.

7.3.2. Biopsy Collection from Colonic Mucosa

Biopsies will be collected at Screening and Week 14 and early withdrawal visit. The largest standard forceps should be used to obtain biopsies during each colonoscopy procedure. Biopsies should be taken one at a time, and each should be immediately placed into a separate sample collection tube, as specified in the central vendor procedure manual. During each colonoscopy procedure, 12-15 biopsies should be taken from abnormally inflamed colonic mucosa, and 3 biopsies should be taken from normal appearing mucosa, resulting in a total of 15-18 biopsies from each subject, if possible. Frankly ulcerated areas should be

avoided. If 15-18 biopsies cannot be collected during colonoscopy, then samples from inflamed tissues should be prioritized. Pfizer and the central laboratory vendor will provide sites with instructions for the collection, processing, and shipment of biopsy samples.

All pre-treatment biopsies should be obtained in a targeted manner from the most affected area 15-30 cm from the anal verge. During post-treatment colonoscopy, samples should be obtained from approximately the same anatomic location as the baseline assessment. For all biopsies collected, record the colonic segment and approximate distance from the anal verge for each sample in the source documents.

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

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 2).

- 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 e-diary data recorded over the 3 consecutive days prior to the endoscopy bowel preparation procedure. Investigator sites will be trained on the electronic diary usage and will train subjects on use of the e-Diary. Electronic diary data entered by the subject will be reviewed by the site at each visit.

For baseline endoscopy and post-baseline endoscopy, if there are missing e-diary data, the average will be taken from the 3 most recently available days reported within 5 days prior to the endoscopy preparation.

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

If there are less than 3 available days reported within the 5 days prior to the study visit, 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.

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 (ie, physical findings) and subject's performance status when making the PGA assessment. It is preferred that the same physician performs all such assessments for a given subject throughout the study.

The Mayo Score at the screening visit must be ≥6 and ≤12 with an endoscopic subscore of at least 2 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.

7.3.4. Subject Stool Diary

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

- 'Normal' number of stools per day (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).

Diary data will be assessed at the clinic, at each study visit from baseline (Day 1) until the end of follow up period (Week 26). The information extracted will be used for calculation of Mayo score taking into account the data recorded over the last 3 days prior to each study visit. Three (3) day patient e-diary data must be completed and assessed prior to any bowel preparations. If there are missing e-diary data, the average will be taken from the 3 most recently available days reported within 5 days prior to the endoscopy preparation. If there are less than 3 available days reported within the 5 days prior to the study visit, the average will be taken from the limited available data unless there is no e-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 e-diary data or no e-diary data recorded prior to the baseline endoscopy preparation, then the patient cannot be randomized into the study.

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

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7.4. Pharmacodynamics

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7.4.2. Serum Soluble TL1A

Blood samples (6 mL) to provide approximately 3 mL serum will be collected into appropriately labeled glass collection tubes (no additives). Serum samples will be collected and aliquoted for the analysis of total serum sTL1A at times specified in the Schedule of Activities.

Detailed collection, processing, storage, and shipment instructions are provided in the lab manual.

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

A blood specimen for determination of hsCRP will be obtained at the times specified in the Schedule of Activities. Blood samples for determination of hsCRP will be analyzed at the same laboratory performing the safety laboratory analyses.

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.

Instructions and supplies for the collection, processing and shipment of samples will be supplied under separate cover by Pfizer, the designated laboratory vendor, and the vendor laboratory manual.

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7.5. Pharmacokinetics

7.5.1. Serum for Analysis of PF-06480605

Blood samples (3 mL) to provide approximately 1.2 mL serum for PK analysis will be collected into appropriately labeled tubes at times specified in the Schedule of Activities.

The actual times may change but the number of samples will remain the same. All efforts will be made to obtain the PK samples at the exact nominal time relative to dosing. However, samples obtained within 10 % of the nominal time from dosing will not be captured as a protocol deviation, as long as the exact time of the sample collection is noted on the source document and data collection tool (eg, CRF).

Details regarding the collection, processing, storage and shipping of the blood samples will be provided in the lab manual. The samples must be processed and shipped as indicated to maintain sample integrity. Any deviations from the processing steps (eg, sample collection and processing steps, interim storage or shipping conditions), 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. Any deviation from the specified sample handling procedure resulting in compromised sample integrity, will be considered a protocol deviation.

Samples will be analyzed using a validated analytical method in compliance with Pfizer standard operating procedures (SOPs).

As part of understanding the PK of the IP, samples may be used for further characterization and/or evaluation of the bioanalytical method. CCI [redacted] Samples collected for this purpose will be retained in accordance with local regulations and, if not used within this timeframe, will be destroyed.

7.5.2. Shipment of Serum Samples for Analysis of PF-06480605

The shipment address and contact information for the lab will be provided to the Investigator site prior to initiation of the trial.

7.6. Immunogenicity

7.6.1. Serum for Analysis of Anti-Drug Antibodies (ADA) and Neutralizing Antibodies

Blood samples (3 mL) to provide approximately 1.2 mL serum for ADA and NAb analyses will be collected into appropriately labeled tubes with no preservative (no anticoagulant and no serum separator gel may be used) at times specified in the Schedule of Activities.

A tiered ADA testing strategy will be used: all samples that are positive at baseline will be confirmed for antibody specificity. Confirmed positive samples will be further characterized for titer and tested in the NAb assay, if bioanalytically feasible.

Details regarding the collection, processing, storage and shipping of the blood samples will be provided in the lab manual. The samples must be processed and shipped as indicated to maintain sample integrity. Any deviations from the processing steps (eg, sample collection and processing steps, interim storage or shipping conditions), 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. Any deviation from the specified sample handling procedure resulting in compromised sample integrity will be considered a protocol deviation.

Samples will be analyzed using validated analytical methods in compliance with Pfizer SOPs.

As part of understanding the immunogenicity of PF-06480605, samples may be used for additional characterization of an observed immunogenicity response and/or evaluation of the bioanalytical method. CCI [redacted] Samples collected for this purpose will be retained in accordance to local regulations and if not used within this timeframe will be destroyed.

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8. ADVERSE EVENT REPORTING

8.1. Adverse Events

All observed or volunteered AEs regardless of treatment group or suspected causal relationship to the IP will be reported as described in the following sections.

For all AEs, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as a SAE requiring immediate notification to Pfizer or its designated representative. For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE. The investigator is required to assess causality. 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.

As part of ongoing safety reviews conducted by the sponsor, any nonserious 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.

8.2. Reporting Period

For SAEs, the active reporting period to Pfizer or its designated representative begins from the time that the subject provides informed consent, which is obtained prior to the subject's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving IP, through and including 28 calendar days after the last administration of the IP. SAEs occurring to a subject after the active reporting period has ended should be reported to the sponsor 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 IP are to be reported to the sponsor.

AEs (serious and non-serious) should be recorded on the CRF from the time the subject has taken at least 1 dose of IP through the subject's last visit.

8.3. Definition of an Adverse Event

An AE is any untoward medical occurrence in a clinical investigation 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 symptoms and signs;

- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease;
- Drug abuse;
- Drug dependency.

Additionally, they may include the signs or symptoms resulting from:

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

8.4. Medication Errors

Medication errors may result, in this study, from the administration or consumption of the wrong product, by the wrong subject, at the wrong time, or at the wrong dosage strength. Such medication errors occurring to a study participant are to be captured on the medication error CRF, which is a specific version of the AE page, and on the SAE form when appropriate. In the event of medication dosing error, the sponsor should be notified immediately.

Medication errors are reportable irrespective of the presence of an associated AE/SAE, including:

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

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

8.5. Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- 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 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 reporting as an AE.

8.6. 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.

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.

8.6.1. Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported by the investigator as described in previous sections, and will be handled as SAEs in the safety database (see the section on Serious Adverse Event Reporting Requirements).

8.6.2. Potential Cases of Drug-Induced Liver Injury

Abnormal values in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) levels concurrent with abnormal elevations in total bilirubin level that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy's law cases) and should always be considered important medical events.

The threshold of laboratory abnormalities for a potential case of drug-induced liver injury depends on the subject's individual baseline values and underlying conditions. Subjects who present with the following laboratory abnormalities should be evaluated further to definitively determine the etiology of the abnormal laboratory values:

- Subjects with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT values ≥3 times the upper limit of normal (× ULN) concurrent with a total bilirubin value ≥2 × ULN with no evidence of hemolysis and an alkaline phosphatase value ≤2 × ULN or not available;

- For subjects with preexisting ALT **OR** AST **OR** total bilirubin values above the ULN, the following threshold values should be used in the definition mentioned above:

    - For subjects with 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).

    Concurrent with

    - For subjects with preexisting values of total bilirubin above the normal range: Total bilirubin level increased from baseline by an amount of at least 1 × ULN **or** if the value reaches ≥3 × ULN (whichever is smaller).

The subject should return to the investigational 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, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/international normalized ratio (INR), and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug, and supplement consumption, family history, occupational

exposure, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (eg, biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for liver function test (LFT) abnormalities identified at the time, should be considered potential Hy's law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's law cases should be reported as SAEs.

8.7. 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 TB unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit should be 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 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 AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE, and the resulting appendectomy should be recorded as treatment of the AE.

8.8. Severity Assessment

If required on the AE CRFs, 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.

8.9. 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 in the CRF, as appropriate, 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 IP 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 IP caused the event, then the event will be handled as "related to IP" for reporting purposes, as defined by the sponsor (see the section on Reporting Requirements). If the investigator's causality assessment is "unknown but not related to IP," 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, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

8.10. Exposure During Pregnancy

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

1. 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 IP; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the IP.

   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).

2. A male has been exposed (eg, because of treatment or environmental exposure) to the IP prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a study subject or study subject's partner becomes or is found to be pregnant during the study subject's treatment with the IP, the investigator must submit this information to the Pfizer drug safety unit on an 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) 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 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 preprocedure 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 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 IP.

Additional information regarding the EDP may be requested by the investigator. 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 study 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.

8.11. 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 the drug safety unit within 24 hours of the investigator's awareness, using the SAE report form, regardless of whether there is an associated AE/SAE. Since the information does not pertain to a subject enrolled in the study, the information is not reported on a CRF; however, a copy of the completed SAE report form is maintained in the investigator site file.

8.12. Withdrawal Due to Adverse Events (See Also the Section on Subject Withdrawal)

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

When a subject withdraws because of an SAE, the SAE must be reported in accordance with the reporting requirements defined below.

8.13. Eliciting Adverse Event Information

The investigator is to report all directly observed AEs and all AEs spontaneously reported by the study subject /legally acceptable representative. In addition, each study subject /legally acceptable representative will be questioned about AEs.

8.14. Reporting Requirements

Each AE is to be assessed to determine if it meets the criteria for SAEs. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

8.14.1. Serious Adverse Event Reporting Requirements

If an SAE occurs, Pfizer is to be notified within 24 hours of investigator awareness of the event.

In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available AE information. This time frame also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of EDP, exposure via breastfeeding, and occupational exposure cases.

In the rare event that the investigator does not become aware of the occurrence of an SAE immediately (eg, if an outpatient study subject initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the AE.

For all SAEs, the investigator is obligated to pursue and provide information to Pfizer in accordance with the time frames for reporting specified above. In addition, an investigator may be requested by Pfizer to obtain specific additional follow-up information in an expedited fashion. This information collected for SAEs is more detailed than that captured on the AE CRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications, vaccines, and/or 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 or its designated representative.

8.14.2. Nonserious Adverse Event Reporting Requirements

All AEs will be reported on the AE page(s) of the CRF. It should be noted that the form for collection of SAE information is not the same as the AE CRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used on both forms. AEs should be reported using concise medical terminology on the CRFs as well as on the form for collection of SAE information.

8.14.3. 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.

9. DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a statistical analysis plan (SAP), which will be maintained by the sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

9.1. Statistical Methods

This study employs Simon's two-stage design. Let p be the proportion of subjects achieving endoscopic improvement at Week 14 and the following hypotheses will be tested in this study:

H_0: $p \leq 6\%$ *versus* H_1: $p \geq 41\%$,

where 6% was the observed placebo endoscopic improvement rate in anti-TNF experienced subjects from two tofacitinib Phase 3 induction studies (A3921094 and A3921095) in subjects with UC. In the first stage, it is planned to have 12 evaluable subjects with colonoscopy at Week 14. If no more than 2 subjects have achieved endoscopic improvement AND no subject has achieved endoscopic remission, then the study will be stopped for futility; otherwise, the study will continue to enroll until 36 evaluable subjects complete the study with colonoscopy at Week 14. If at least 9 subjects achieve endoscopic improvement at Week 14 at the end of the second stage, the null hypothesis H_0 will be rejected.

9.2. Sample Size Determination

The sample size was determined based on the primary endpoint of endoscopic improvement at Week 14 using Simon's two-stage design. The operating characteristics of the design described in Section 9.1 were assessed through Monte Carlo simulations. With 12 evaluable subjects in the first stage and a maximum total of 36 evaluable subjects and the H_0 rejection criterion described in Section 9.1, the Simon's two-stage design has at least 90% power under the alternative hypothesis H_1 while the type-I error is less than 0.001. On the other hand, the probability of stopping early for futility in the first stage is at least 86% under the null hypothesis H_0 and an endoscopic remission rate of 1%.

9.3. Efficacy Analysis

9.3.1. Analysis of the Primary Endpoint

The primary efficacy endpoint, endoscopic improvement at Week 14, will be used to assess the efficacy of PF-06480605 under Simon's two-stage design decision criteria. The primary analysis population will be Per Protocol population, which consists of all subjects who are not major protocol violators with all planned doses received and a final colonoscopy at Week 14. The point estimate of the endoscopic improvement rate, 2-sided 95% confidence interval and p-value will be calculated using the method described by Koyama and Chen (2008)[11] according to the actual sample size in the primary analysis population. Details of the methodology will be documented in the SAP.

The endoscopic improvement rate at Week 14 for All Treated population will also be computed with appropriate confidence interval as a sensitivity analysis. Subjects who drop out early from the study without a Week 14 colonoscopy will be considered as failures in the sensitivity analysis.

9.3.2. Analysis of Secondary Endpoint

The binary secondary efficacy endpoints, including remission and endoscopic remission at Week 14, as defined in Section 2.2.2, will be summarized by point estimates and appropriate confidence intervals. These endpoints will be analyzed separately for All Treated population and Per Protocol population. Subjects who drop out early from the study without a Week 14 colonoscopy will be considered as failures in the All Treated population analysis.

9.4. Analysis of Other Endpoints

9.4.1. Pharmacokinetic Analysis

The PK concentration population is defined as all enrolled subjects who received at least one dose of PF-06480605 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 and safety) during 12 weeks of treatment in subjects with moderate to severe active UC may be explored using either observed or modeled exposures. Any population analyses conducted will not be part of the clinical study report (CSR) and may be reported separately.

An early PK readout of PF-06480605 serum concentrations will be conducted after at least 6 subjects have completed the Week 4 visit to confirm that the predicted exposures of PF-06480605 in UC patients are consistent with expected values, based on the healthy subject PK data. Following this early PK readout analysis, dose may be modified to match the exposures observed in healthy volunteers receiving 500 mg/kg IV (Study B7541001).

9.4.2. Immunogenicity Analysis

The immunogenicity assessment population is defined as all enrolled subjects who received at least one dose of PF-06480605 with at least one post-treatment anti-drug (PF-06480605) antibody determination.

Overall incidence of development of ADA and of NAb will be reported along with relationships of incidence with respect to time. Both continuous endpoints and categorical endpoints (ie, positive and negative) will be reported for the ADA and NAb assays by time points samples were collected. Data permitting, the impact of ADA and NAb on PK, PD, safety and efficacy profiles may be explored.

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9.4.4. Pharmacodynamic Analysis

The pharmacodynamic analysis population is defined as all treated subjects who have at least one PD assessment. The PD endpoints will be summarized by time and presented in a tabular or graphical form. Data permitting, the endpoints may be analyzed longitudinally to study the effect over time. Further details will be documented in the SAP.

9.5. Safety Analysis

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 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.

9.5.1. Electrocardiogram Analysis

Descriptive statistics for RR, QRS, QTcF, and HR, and change from baseline in those parameters will be summarized by timepoint. Baseline will be defined as the ECG measurements at the screening visit. The number (%) of subjects with maximum post dose QTcF values and maximum increases from baseline in the following categories will be tabulated:

Safety QTcF

	Borderline (msec)	Prolonged (msec)
Absolute Value	≥450 - <480	≥480
Absolute Change	30-<60	≥60

In addition, the number of subjects with corrected and uncorrected QT values ≥500 msec will be summarized.

9.6. Interim Analysis

A formal IA is planned at the end of the first stage for futility assessment. The IA will be performed by the study team. The results and decision of the IA will be reviewed and endorsed by sponsor senior management. The sponsor may conduct ongoing reviews of the data during the course of the study for the purpose of safety assessment, facilitating PK/PD modeling, and/or to support clinical development.

9.7. Data Monitoring Committee

This study will not use a data monitoring committee.

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 study site may be subject to review by the institutional review board (IRB)/ethics committee (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 study site for the inspection and will allow Pfizer or its agent, whenever feasible, to be present during the inspection. The investigator will promptly provide copies of the inspection findings to Pfizer or its agent. Before response submission to the regulatory authorities, the investigator will provide Pfizer or its agents with an opportunity to review and comment on responses to any such findings.

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

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

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

A CRF is required and should be completed for each included subject. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

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

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

In some cases, the CRF, or part of the CRF, may also serve as source documents. In these cases, a document should be available at the investigative site as well as at Pfizer and clearly identify those data that will be recorded in the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

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

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or an independent third party arranged by Pfizer. Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

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

12. ETHICS

12.1. Institutional Review Board/Ethics Committee

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

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

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical

Sciences 2002), Guidelines for GCP (ICH 1996), and the Declaration of Helsinki (World Medical Association (1996 & 2008).

In addition, the study will be conducted in accordance with the protocol, the ICH guideline on GCP, and applicable local regulatory requirements and laws.

12.3. Subject Information and Consent

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

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

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

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

The investigator must ensure that each study subject or his or her legally acceptable representative, is fully informed about the nature and objectives of the study and possible risks associated with participation.

Whenever consent is obtained from a subject's legally acceptable representative, the subject's assent (affirmative agreement) must subsequently be obtained when the subject has the capacity to provide assent, as determined by the IRB/EC. If the investigator determines that a subject's decisional capacity is so limited he/she cannot reasonably be consulted, then, as permitted by the IRB/EC and consistent with local regulatory and legal requirements, the subject's assent may be waived with source documentation of the reason assent was not obtained. If the study subject does not provide his or her own consent, the source documents must record why the subject did not provide consent (eg, minor, decisionally impaired adult), how the investigator determined that the person signing the consent was the subject's legally acceptable representative, the consent signer's relationship to the study subject (eg, parent, spouse), and that the subject's assent was obtained, or waived. If assent is obtained verbally it must be documented in the source documents.

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

12.4. Subject Recruitment

Advertisements approved by IRBs/ECs and investigator databases may be used as recruitment procedures.

Pfizer will have an opportunity to review and approve the content of any study recruitment materials directed to potential study subjects before such materials are used.

12.5. 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 competent 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 IP, 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 IP safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of PF-06480605 at any time.

If a study is prematurely terminated or discontinued, 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 for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

Primary completion date 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 primary completion date for studies in adult populations or within 6 months of the primary completion date 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 principal investigator of the results of the study based on information collected or generated by principal investigator, 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 they are 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 study sites, and that any subsequent publications by the principal investigator 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.

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Appendix 1. Abbreviations

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

Abbreviation	Term
ADA	Anti-drug antibody
AE	adverse event
ALT	alanine aminotransferase
ANC	Absolute neutrophil count
5-ASA	5-aminosalicylic acid
AST	aspartate aminotransferase
AUC	Area under the curve
AUC_{inf}	Area under the concentration-time curve from time 0 to infinity
AUC_{ss}	Area under the curve at steady state
AUC_{τ}	Area under the curve over the dosing interval
AZA	azathioprine
BCG	Bacillus Calmette-Guerin
BP	Blood pressure
C_{av}	Average concentration for the dosing interval
CD	Crohn's disease
C_{max}	Maximum observed concentration
CL	clearance
CL/F	Apparent clearance
CRA	Cytokine release assay
CRF	case report form
CSA	clinical study agreement
CTA	clinical trial application
CTCAE	Common Terminology Criteria for Adverse Events
DAI	dosage and administration instructions
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DR3	Death receptor 3
DcR3	Decoy Receptor 3
EC	ethics committee
ECG	electrocardiogram
EDP	exposure during pregnancy
EDTA	edetic acid (ethylenediaminetetraacetic acid)
EOS	End of study
EudraCT	European Clinical Trials Database
F	bioavailability
FIH	First-in-human
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GDH	Glutamate dehydrogenase

Abbreviation	Term
GLP	Good laboratory practice
HCV	Hepatitis C virus
HEENT	Head eyes ears nose throat
HIV	human immunodeficiency virus
hsCRP	High sensitivity c-reactive protein
IA	Interim analysis
IB	investigator's brochure
IBD	Inflammatory bowel disease
ICH	International Conference on Harmonisation
ID	identification
IGRA	Interferon gamma release assay
CCI	[redacted]
IM	intramuscular
IND	investigational new drug application
INR	international normalized ratio
IP	Investigational product
IRB	institutional review board
IRT	Interactive response technology
ISR	Injection site reaction
IUD	intrauterine device
IV	intravenous
LFT	liver function test
LSLV	last subject last visit
MAD	Multiple ascending dose
msec	milliseconds
MTX	methotrexate
N/A	not applicable
NAb	Neutralizing antibody
NOAEL	No observed adverse effect level
P_{90}	percentage of simulations that resulted in 90% coverage
PBMC	Peripheral blood mononuclear cells
PD	pharmacodynamic
pEFD	Preliminary embryofetal and developmental
PGA	Physician's global assessment
PK	pharmacokinetic
PPD	Purified protein derivative
PT	prothrombin time
R_{ac}	Observed accumulation ratio
RBC	Red blood cell
RDW	Red blood cell distribution width
RHI	Robarts Histopathology Index
RNA	ribonucleic acid
SAD	Single ascending dose

Abbreviation	Term
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SCL	Supply Chain Lead
SoA	Site of action
SOP	standard operating procedure
SRSD	single reference safety document
SSID	Single subject identifier
TB	tuberculosis
sTL1A	Soluble TL1A
$T_{1/2}$	Terminal half-life
TEAE	Treatment emergent adverse event
TL1A	Tumor necrosis factor-like ligand 1A
T_{max}	Time to reach maximum concentration
TMDD	Targeted mediated drug disposition
TNF	Tumor necrosis factor
TPMT	Thiopurine methytransferase
UC	Ulcerative colitis
CCI	[redacted]
ULN	upper limit of normal
US	United States
V_{ss}	Volume of distribution at steady state
VZ/F	Apparent volume of distribution
WBC	White blood cells
WOCBP	Women of childbearing potential
WONCBP	Women of non child bearing potential

Appendix 2. 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 stool less than half the time
2 = Obvious blood with stool most of the time
3 = Blood alone passes
Subscore, 0 to 3

Findings on endoscopy:

0 = Normal or inactive disease
1 = Mild disease (erythema, decreased vascular pattern, 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 3. France appendix

This appendix applies to study sites located in France.

1. GCP Training

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

2. Investigational Product

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

3. Inspections

The study site and investigator will promptly resolve any discrepancies that are identified between the study data and the subject's medical records.

4. Studies Involving Human Cell, Tissue, and/or Organ Transplants

The investigator agrees to abide by the ethical principles set forth in the World Health Organization's Guiding Principles for Human Cell, Tissue and Organ Transplantation (WHA63.22), http://www.who.int/transplantation/en/ with regard to the study.