A PHASE 2A, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY, SAFETY, TOLERABILITY AND PHARMACOKINETICS OF PF-06687234 AS ADD-ON THERAPY TO INFLIXIMAB IN ACTIVE ULCERATIVE COLITIS SUBJECTS WHO ARE NOT IN REMISSION (BUILD UC)

Investigational Product Number:	PF-06687234
Investigational Product Name:	Not Applicable (N/A)
United States (US) Investigational New Drug Application (IND) Number:	CCI [redacted]
European Clinical Trials Database (EudraCT) Number:	2017-002108-28
Protocol Number:	B7581002
Phase:	2A

Document History

Document	Version Date	Summary of Changes and Rationale
Amendment 4 (US only)	10 April 2020	• Section 9.1 and 9.5: Modified the interim analysis for futility to be performed with approximately 20% and 40% randomized subjects for 12-week treatment. Rationale: The early interim analysis for futility with approximately 20% randomized subjects was added to enable early internal decision making.
Amendment 3	30 August 2018	• Schedule of Activities, Section 2, 7.5.1, 7.5.2 and 7.5.3: Changed to reflect serum PK sampling for PF-06687234. Rationale: Serum sample rather than plasma will be used for PF-06687234 PK assay. • Schedule of Activities footnote v, Section 3.2, and 6.4: Added text for subject discontinuation in the presence of detectable NAb against IL-10 portion of PF-06687432. Rationale: Clarified immunogenicity monitoring process for early withdrawal of subjects due to detectable NAb against IL-10 portion of PF-06687432. • Section 4.3: Changed to state "Subjects will have up to 4 weeks after the first screening visit to complete all screening procedures prior to randomization." Rationale: Clarified randomization criteria to be consistent with Section 6.1. • Section 6.2.1: Widened the interval from approximately 1 hour to 'approximately 1 hour but not exceed 3 hours' between infliximab infusion completion and IP dosing. Rationale: Allowing more time for a subject to travel from an infusion center (if applicable) to a

		study site. • Section 7.6.1: Clarified to state "The positive samples will be further characterized in the NAb assays, if bioanalytically feasible". Rationale: To clarify that positive ADA samples will be further tested for NAb. • Schedule of Activities footnote h: Added text "The total Mayo score at Week 0 will be calculated based stool frequency, rectal bleeding and endoscopy performed during screening period and PGA obtained at baseline." Rationale: To clarify the procedure for calculation of total Mayo score. • Section 1.3.1 Study Rationale: Inserted a paragraph to recognize the changes to standard of care that use alternative dosing intervals of infliximab to manage UC subjects in clinical practice. Rationale: To provide rationale, references, and practice guidance to allow infliximab dosing every 6 weeks in the protocol. • Schedule of Activities, footnote y, Section 4, inclusion criterion 7, and exclusion criterion 6, Section 6.2.8, 6.2.15, and 6.2.17: Changed to allow subjects on infliximab dosing interval of every 6 weeks into the study and clarified the time requirement for study eligibility after change of infliximab regimen (dosage and dosing interval). Rationale: Optimizing infliximab dosing (adjusting either dosage or dosing intervals other than every 8 weeks in maintenance) is an evidence-based recommendation for managing patients to achieve treatment target. Clinical data support dose escalation and adjusting administration intervals to improve treatment efficacy. Based on new UC treatment guidelines, infliximab maintenance dosing

		intervals more frequent than every 8 weeks are commonly prescribed in clinical practice as part of standard of care. As infliximab is a background treatment in this study, allowing subjects on an infliximab dosing interval of every 6 weeks (in addition to subjects on an infliximab dosing interval of every 8 weeks) into the study will better align subject eligibility to current standard of care. • Section 4.1, inclusion criterion 7: deleted "a maximum two years" limitation for background infliximab therapy for an eligible subject. Rationale: There is no evidence to support the exclusion of subjects on background infliximab therapy for more than 2 years if they meet other eligibility criteria for study entry. • Section 3.1, and 9.1: Changed estimated sample size from 98 to 76 with estimated evaluable size of 32 in each group (64 in total) with 15% dropout rate. Rationale: The sample size has been revised based on likely dropout rate of 15% and one-sided alpha=0.05 type 1 error rate using organizational experience from recent clinical trials in ulcerative colitis (UC). • Schedule of Activities, Section 6.2.1: Added collection of infliximab ADA samples at baseline visit and at other study visits when administration of infliximab occurs. Added collection of infliximab trough samples at study visits when administration of infliximab occurs. Rationale: To establish baseline infliximab ADA status and infliximab trough level for potential inclusion in efficacy analyses. • Section 4.1, inclusion criterion 5: Modified the criterion to state "Subjects who have partial response to anti-TNF (infliximab) and active UC as defined by (via screening endoscopy) a total Mayo Score ≥4 but ≤9 and an endoscopic

		subscore ≥2. Rational: To widen the entry total Mayo score inclusion criterion allowing the inclusion of a wider, more representative sample of subjects with active UC. • Section 4.1, inclusion criterion 6: Changed to state: "UC extending at least 15 cm proximal to the anal verge at the time of the screening endoscopy." Rationale: Modification will allow the inclusion of subjects with disease severity consistent with other inclusion criteria whilst still excluding subjects with isolated proctitis. • Section 4.2, exclusion criterion 4: Clarified the exclusion criterion to state: "Subjects with extensive colitis for at least 8 years who have not had a colonoscopy with surveillance biopsies within 2 years of the baseline visit." Rationale: To clarify that a colonoscopy is required for subjects with extensive colitis and without surveillance colonoscopy within 2 years and that this surveillance can be performed during the screening colonoscopy if necessary. • Section 4.2, exclusion criterion 5: Clarified the exclusion criterion that subjects with prior history of adenomatous polyps will be eligible if the polyps have been completely removed and pathology is negative. Rationale: To clarify subject eligibility. • Section 4.2, exclusion criterion 24: Changed the exclusion criterion eGFR to <60 mL/min/1.73 mm^2 based on age appropriate calculation. Rationale: No renal risk has been identified for PF-06687234 (or for rhIL-10 from the literature). Significant numbers of subjects with UC could have renal function that would place them in

		Chronic Kidney Disease (CKD) stage II. The amended eGFR exclusion criterion will potentially allow the inclusion of a more representative population of UC without introducing a safety risk. • Section 4.2 exclusion criterion 13: Changed exclusion criterion to state: "Current evidence of active TB or latent TB infection or inadequately treated TB infection demonstrated by chest x-ray, a positive Mantoux (purified protein derivative [PPD]) tuberculin skin test or a positive Interferon Gamma Release Assay (IGRA to be tested at the site's local lab) during screening or within 12 weeks prior to randomization. " Rationale: As a standard of care, all UC patients need to receive a TB test for latent TB infection and have adequate antimycobacterial treatment prior to initiation of infliximab therapy. The revised exclusion criterion is to exclude subjects with evidence of active TB or latent TB patients without adequate treatment into the study. • Section 1.2.1.1 Non-Clinical Safety and Section 1.3.2 Dosing Rationale: Updated the section with study results from 6-month toxicity study in mice and revised the safety margin to 3.2x compared with a clinical dose of 0.5 mg/kg/week on a body surface area basis in mice and 5.8x compared with a clinical dose of 0.5 mg/kg/week on a body surface area basis in cynomolgus monkeys. Rationale: Updated with newly available 6 months toxicity data in mice and revised the safety margin based on clinical dose of 0.5 mg/kg/week. • Several additional minor changes and sentence revisions were made throughout the document. Rationale: Revisions were made for the purpose of clarification and to correct any minor

		grammatical or spelling errors.
Amendment 2	06 March 2018	• Section 1.2.2.1 Subject Disposition: Updated ongoing Philogen Dekavil study in RA subjects. Rationale: Updated enrollment and safety information in Philogen Dekavil RA study. • Section 4.1 Inclusion Criteria: Deleted "or legally acceptable representative" in Criterion #1 and in Sections 8.1.2 and 12.3. Rationale: Global change to comply with regulatory feedback received not allowing inclusion of subjects who are unable to give the consent. • Section 4.1 Inclusion Criteria: Modified the inclusion criterion #3 to add "weight >40 kg" as part of inclusion criterion. Rationale: To exclude subjects with weight ≤40 kg to avoid IP exposure >600 μg/kg/week. • Section 4.2 Exclusion Criteria: Added exclusion criterion #30: "Known history of hypersensitivity, intolerance, or allergic reaction to PF-06687234 or any constituent of the IP". Rationale: To exclude subjects who had known history of hypersensitivity, intolerance or allergic reaction to PF-6687234 or any constituent of the IP. • Section 4.2 Exclusion Criteria: Updated the exclusion criterion #18 to "Exposure to a live (attenuated) vaccine within 30 days prior to screening or anticipated need for any live (attenuated) vaccine during the study." Rationale: To protect safety of the study participants and comply with regulatory request. • Section 4.4.1 Contraception: Removed 'using male or female condom plus spermicide as a highly effective method of contraception' and modified the contraception requirement to '2

		methods of contraception (at least one of which is considered to be highly effective)'. Rationale: To comply with Clinical Trial Facilitation Group (CTFG) guidance of the Heads of Medicines Agency (HMA) which does not allow condom plus spermicide as a highly effective method. • Section 4.4.1 Contraception: Added "Male subjects must refrain from sperm donation for the duration of the active treatment period and until Week 16 or 28 days after the last dose of the investigational product." Rationale: For safety reasons and to comply with regulatory request. • Added a new subsection 5.11 Rescue Medication with the following text: **"**Rescue therapy should be provided by the investigator as deemed clinically appropriate. Subjects requiring rescue medication prior to the end of the study will be discontinued from IP (PF-06687234 or placebo) and will enter the follow-up period. Subjects requiring rescue medication after Week 11 (after last IP administration) should also complete the follow-up period." Rationale: To provide clarification that rescue therapy should be provided by investigators as deemed clinically appropriate and that subjects requiring rescue medication will be discontinued from the study. • Section 5.2 Breaking the Blind: To clarify that if the immediate unblinding is necessary, the discussion between investigator and the member of study team member is not required in advance of unblinding. Rationale: To protect the subject's safety. • Section 5.4.3 Preparing and Dispensing, Section 5.5 Administration: To clarify that IP and placebo are prepared by qualified unblinded site

		staff and administration of prepared IP or placebo to subjects is performed by qualified blinded site staff. Rationale: To clarify the process that preparation of IP and placebo are performed by unblinded site staff and administration of IP or placebo is performed by blinded site staff. • Section 6.4 Guidance for Monitoring and Discontinuation: Added a discontinuation criterion that a subject with detected neutralizing antibody against IL-10 domain will be discontinued from the treatment and the study. Rationale: To protect the safety of the study participants. • References: Replace the reference #22 with "Chan ISF., Zhang Z. Test-based exact confidence intervals for the difference of two binomial proportions. Biometrics, 1999; 55: 1201–1209." Rationale: To provide the correct reference as the reference noted in earlier versions of the protocol was incorrect. • Several additional minor changes were made in the document. Rationale: Revisions were made for the purpose of correcting any minor errors.
Amendment 1	06 September 2017	• Throughout the protocol modified language to allow the use of specific infliximab biosimilars. Rationale: To allow more flexibility for subjects who are currently treated with an infliximab biosimilar and minimize need to switch off of pre-study biosimilar to Remicade® during the study. • Added Appendix 5 Protocol Specific Infliximab Biosimilars. Rationale: To clarify in the protocol the

		infliximab biosimilars that subjects will be allowed to be treated with during the study. Only listed biosimilars (in addition to Remicade®) will be used, in order to allow for validated infliximab trough levels and anti-drug antibodies to be completed in timely fashion during the study. • Schedule of Activities and Sections 6.2.9 and 6.2.10: Changed the collection of the serum infliximab concentration and ADA against infliximab from Visit 8 Week 7 to Visit 9 Week 8. Rationale: To more accurately capture the trough levels of infliximab and concurrent ADA immediately before dosing. • Section 4.1 Inclusion criteria: Modified inclusion criterion #7 "Must be on a stable dose 5-10 mg/kg of Remicade®, Inflectra™ or Remsima® for a minimum of 14 weeks (4 doses) and a maximum of two years prior to study entry with no anticipation of need for change in infliximab treatment regimen throughout the study (no switches from pre-study infliximab version to a different infliximab version will be permitted)." Rationale: To provide further clarification regarding the infliximab treatment regimen that is required at study entry and throughout the study. • Section 4.2 Exclusion criteria: Exclusion criteria #24 modified hemoglobin level from ≤95 g/L (9.5 g/dL) to ≤100 g/L (10.0 g/dL). Rationale: The minimum hemoglobin exclusion criterion was raised so as to not conflict with inclusion criteria #11. • Section 5.10.3 Prohibited Medications: Modified from stating "Any iTNF treatment or biologic therapy other than Remicade® 12 weeks prior to screening and through Week 16" to stating "Any

		non-infliximab iTNF treatment or biologic therapy within 24 weeks of screening visit." Rationale: To further clarify and cover the timeframe that iTNF treatment or biologic therapy other than infliximab iTNF treatment that would be prohibited during the study. • Section 5.10.3 Prohibited Medications: Modified from stating "Any investigational procedures(s) or product(s), such as immunomodulators used in transplantation (eg, mycophenolate mofetil, cyclosporine, rapamycin, or tacrolimus) or live (attenuated) vaccine within 30 days prior to baseline and through Week 16" to stating "Any investigational procedures(s) or product(s), such as immunomodulators used in transplantation (eg, mycophenolate mofetil, cyclosporine, rapamycin, or tacrolimus)". Rationale: This is to correct a typographical error and duplicative language since live (attenuated) vaccine within 30 days prior to baseline and through Week 16 is already listed as a prohibited medication. • Section 6.2.15 Week 12/Early Withdrawal Visit: Modified from stating "PK: Plasma PF-06687234 concentration sample should be collected approximately 30 minutes prior to dosing" to stating "PK: Plasma PF-06687234 concentration sample should be collected". Rationale: This is to correct a typographical error and to be consistent with the Schedule of Activities for the Week 12/Early Withdrawal visit during which there is no dosing of PF-06687234. • Section 6.4 Guidelines for Monitoring and Discontinuations: Removed the mandatory retesting of hemoglobin. Rationale: Removed automatic hemoglobin retesting criteria to limit the number of blood draws and leave it up to discretion of

		investigator regarding retesting necessity and timing. • Section 6.4 Guidelines for Monitoring and Discontinuations: Added individual subject discontinuation criteria for specific AST or ALT result when co-occurring with specific symptoms. Rationale: To provide additional guidance to regulators and investigators on individual subject discontinuation criteria for specific AST or ALT results when co-occurring with specific symptoms. • Section 6.4 Guideline for Monitoring and Discontinuations: Added the following specific language: In the event that ≥2 subjects on IP develop the same AE MEDRA Preferred Term graded as severe intensity as defined in Section 8.3 or if 1 patient develops an SAE as defined in Section 8.2.3, and the event(s) are assessed as potentially causally related to the IP and not clearly related to the underlying disease process or other causes, an ad-hoc IRC meeting will be convened. At this time the IRC will make recommendations to the study team. These recommendations will be to stop the study, continue with modifications or continue with the study unchanged. In addition, the sponsor will notify relevant regulatory authorities that such an ad-hoc IRC meeting has been convened and will provide case details to relevant regulatory authorities within 15 days of making the determination to convene the IRC meeting. Rationale: To further protect patient safety and to establish requirement for prompt ad-hoc IRC review meetings in setting where a severe AE or an SAE is assessed as potentially causally related to the investigational product have been met and the required notification to relevant regulatory authorities regarding the ad-hoc IRC

		meeting and relevant case details. • Appendix 2: Added Reference: Schroeder KW, Tremaine WJ and Listrup DM. NEJM 1987;24;317(26) 1625-1629. Rationale: To correct administrative error from original protocol.
Original protocol	22 May 2017	N/A

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

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

APPENDICES

PROTOCOL SUMMARY

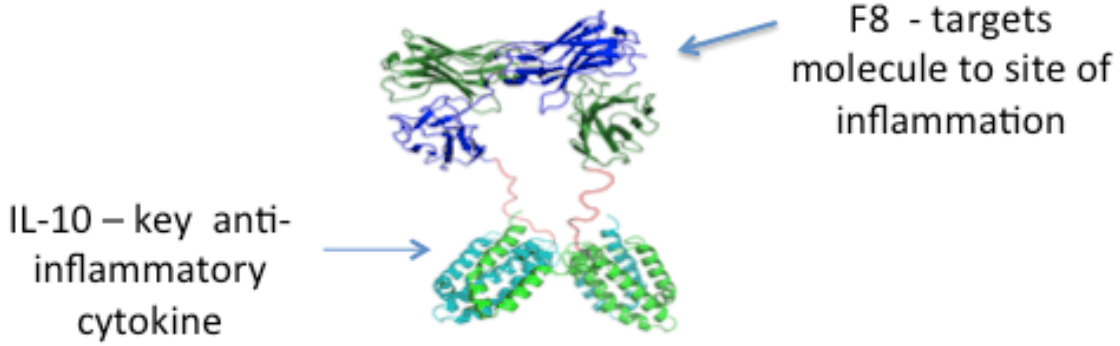
Background and Rationale:

Pfizer has exclusively in-licensed F8IL10 (Dekavil) from Philogen S.pA., Siena, Italy, for development in inflammatory disorders. In nonclinical or clinical studies sponsored by Philogen or conducted using Philogen manufactured material, the product is identified as F8IL10. In nonclinical and clinical studies conducted by or for Pfizer using Pfizer manufactured material, the investigational product is identified as PF-06687234. PF-06687234 is comparable to F8IL10.

Interleukin-10 (IL-10) is a pleiotropic cytokine with wide-ranging effects on the anti and pro-inflammatory functions of both the innate and adaptive arms of the immune system. IL-10 can enhance T regulatory cell function, block dendritic cell maturation, and induce down-regulation of Th1 cytokines and major histocompatibility complex (MHC) class II antigens, and increase B cell survival, proliferation, and antibody production. At the molecular level, IL-10 can modulate the NF-κB and janus kinase signal transducers and activators of transcription (JAK-STAT) signaling pathways. A critical role for IL-10 in inflammatory bowel disease (IBD) pathophysiology is strongly supported by human genetics, as complete loss of IL10, IL10RA and IL10RB results in severe early onset IBD.[4] Taken together, IL-10-based therapies could have significant utility in treatment of IBD.

PF-06687234 is a fully human single chain variable fragment (scFv)-cytokine fusion protein consisting of the scFv F8 (specific to the Extra-Domain A of fibronectin, selectively expressed in newly formed blood vessels during inflammatory responses) fused to the anti-inflammatory cytokine IL-10. PF-06687234 is designed to enrich IL-10 delivery to inflamed tissues, potentially leading to higher local concentrations, greater clinical efficacy, and decreased systemic toxicity and is currently being investigated in subjects with ulcerative colitis (UC).

Figure 1. Structural Diagram of PF-06687234



Objectives and Endpoints:

Primary Efficacy Objective(s):	Primary Efficacy Endpoint(s):
• To evaluate the efficacy of PF-06687234 in induction of clinical remission in subjects with UC and a partial response to anti-TNF-α.	• Proportion of subjects in clinical remission at Week 12 (as defined by a modified total Mayo Score with a traditional endoscopic subscore ≤1, stool frequency subscore ≤1 and rectal bleeding subscore = 0).[a]
Primary Safety Objective(s):	**Primary Safety Endpoint(s):**
• To evaluate the safety and tolerability of PF-06687234 in subjects with UC and a partial response to anti-TNF-α.	• Incidence and severity of adverse events, serious adverse events and withdrawals due to adverse events, ECGs, vital signs and safety laboratory tests.
Secondary Objective(s):	**Secondary Endpoint(s):**
• To evaluate the efficacy of PF-06687234 in induction of endoscopic improvement in subjects with UC and partial response to anti-TNF-α. • To evaluate histological improvement in subjects with UC and partial response to anti-TNF-α. • To evaluate the efficacy of PF-06687234 in induction of clinical response in subjects with UC and a partial response to anti-TNF-α. • To describe the PK of PF-06687234 in subjects with UC. • To evaluate the immunogenicity of PF-06687234 in subjects with UC.	• Proportion of subjects with endoscopic improvement at Week 12 (defined as decrease of ≥1 point in a modified endoscopic subscore or an absolute endoscopy score of ≤1).[b] • Mean change from baseline at Week 12 in Geboes histology score. • Proportion of subjects with a clinical response at Week 12 defined with a decrease from baseline of at least 3 points in total Mayo score with at least 30% change, accompanied by at least one point decrease or absolute score of 0 or 1 in rectal bleeding subscore. • Proportion of subjects with change from baseline in partial Mayo Score of ≤2 with no individual subscore >1 at Weeks 2, 4, 6, 8, 12. • Serum concentrations of PF-06687234. • Incidence of the development of HAFAs and Nabs against PF-06687234.
Exploratory Objective(s):	**Exploratory Endpoint(s):**
• To collect banked biospecimens and additional non-banked samples (eg, intestinal biopsies, stool for microbiome analysis, serum and plasma for analysis of proteins, whole blood for RNA analysis and epigenetics and/or cytometry) for exploratory research, unless prohibited by local regulations or ethics committee decision. • To evaluate disease pathway and related biomarkers (ie, hsCRP and fecal calprotectin). • To describe the full PK profile in a subgroup of subjects. • To evaluate tissue concentrations of PF-06687234 in biopsy samples.	• Collection of banked biospecimens and additional non-banked samples (eg, intestinal biopsies, stool for microbiome analysis, serum and plasma for analysis of proteins, whole blood for RNA analysis and epigenetics and/or cytometry) unless prohibited by local regulations or ethics committee decision. Additional information on collection and potential use is provided in the Banked Biospecimens section. • Change from baseline in fecal calprotectin at Weeks 4, 8, 11. • Change from baseline in hsCRP at Weeks 4,8,11. • $AUC_{(0\text{-}Tau)}$, C_{max}, T_{max}, $t_{1/2}$, CL/F, Vz/F. • PF-06687234 tissue concentration in inflamed and non-inflamed biopsies.

a. The assessment of clinical remission will utilize the current definition of the traditional Mayo endoscopic subscore, which allows for assessment of mild friability in the subscore of 1.

b. The Central Readers for endoscopy Mayo subscores will also employ an assessment as to the presence or absence of any friability (including mild). In this assessment the presence of any friability (including mild) will be scored as 2 (modified endoscopic subscore).

Apparent clearance (CL/F), Apparent volume of distribution (Vz/F), Area under the concentration-time curve to the end of the dosing period ($AUC_{(0\text{-}Tau)}$), Anti-tumor necrosis factor-α (anti-TNF-α), maximum observed concentration (C_{max}) electrocardiogram (ECG), human anti-fusion antibody (HAFA), neutralizing antibodies (NAbs), pharmacokinectic (PK), ribonucleic acid (RNA), time to reach maximum concentration (T_{max}), terminal half-life ($t_{1/2}$).

Study Design and Treatments:

This is a Phase 2A, randomized, double-blind, placebo-controlled, parallel group, multicenter study in subjects with active UC and a non-remission response to infliximab. Each subject will be randomly assigned to 1 of 2 treatment arms (1 active; 1 placebo) with approximately 76 subjects in total (38 subjects per arm) enrolled for the study to achieve a total of 64 evaluable subjects.

Using the Mayo scoring definitions in Appendix 2 and Appendix 3, clinical remission in this protocol is defined as those subjects with a traditional endoscopic subscore of 0 or 1, stool frequency subscore of 0 or 1 and rectal bleeding subscore of 0.

Eligible subjects for enrollment will meet criteria for partial response to infliximab but in non-remission during screening, despite at least 14 weeks after initiation of infliximab therapy for active ulcerative colitis prior to study entry.

The duration of participation for eligible subjects will be approximately 26 weeks. This will include a 4-week screening period, a 12-week investigational product treatment period, a 4-week follow-up period and a telephone contact conducted 6-weeks after the follow-up visit. During the treatment period subjects will visit the clinic every week (±2 days) for subcutaneous (SC) administration of 20 mg of the investigator product (IP) for a total of 12 visits. In addition, all subjects enrolled in the study will be continuing treatment with their infliximab therapy as a background therapy during the study. Subjects will be administered their infliximab therapy by intravenous (IV) administration at the clinic on Day 1, and subsequent doses appropriately at study visits based on the subject's background dosing interval for infliximab.

Subjects will be required to return to the clinic for one visit 4 weeks after the last visit during the treatment period to evaluate for safety which will constitute an onsite follow-up visit. Subjects on infliximab every 8 weeks will also be administered infliximab therapy at this visit. Subjects on infliximab every 6 weeks will require an additional site visit for administration of infliximab at Week 18.

There will be a telephone contact at Week 22 to confirm any serious adverse events (SAEs) have been reported to the sponsor and to provide results of Week 16 immunogenicity testing.

Subjects with no detectable HAFA or NAb against IL-10 portion of PF-06687234 by the Week 16 visit will not require further follow-up beyond the Week 22 telephone contact. However, subjects with detectable HAFA or NAb against the IL-10 portion of PF-06687234 at Week 16 will be informed of their immunogenicity status at the Week 22 telephone contact. These subjects will be required to return for an onsite visit at Week 28 for repeat immunogenicity testing. If these subjects have detectable HAFA or NAb against the IL-10 portion of PF-06687234 from the immunogenicity sample collection at Week 28, they will require one additional follow-up collection 3 months after Week 28 at approximately Week 40.

Statistical Methods:

This study employs a randomized parallel design with one treatment arm and one placebo arm. The primary endpoint is clinical remission defined by the modified total Mayo score with subscores of stool frequency ≤1, endoscopy scores ≤1 and rectal bleeding score of=0. The placebo and the treatment arm are assumed to have the remission rates as 22% and 52%. With one-sided alpha=0.05, to detect a treatment difference 30% in clinical remission 64 (32*2) samples are needed to have 80% power. Assuming 15% dropout rate, total 76 subjects will be recruited in the trial. Based on the recruitment rates, an interim analysis for futility based on conditional power less than 10% may be performed.

The primary endpoint will be analyzed using exact Chan and Zhang method[22] and all other endpoint data will be analyzed using either the linear mixed model or the generalized linear mixed model.

SCHEDULE OF ACTIVITIES

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

The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities table, in order to conduct evaluations or assessments required to protect the well-being of the subject.

	Screening (-28 to -1)	Treatment Period													Follow-up		
Study Visit[a]	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**[y] **(if applicable)**	**Telephone Contact**
Study Week	**Week -1 to -4**		**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Week 5**	**Week 6**	**Week 7**	**Week 8**	**Week 9**	**Week 10**	**Week 11**	**Week 12/EW**[b]	**Week 16**	**Week 18**	**Week 22**
Study Day	**-28 to -1**	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**57**	**64**	**71**	**78**	**85**	**113**	**127**	**155**
Visit Window	**N/A**	**N/A**				**±2 days based on Day 1**[x]											
	Enrollment Procedures																
Informed consent	X																
Inclusion/Exclusion Criteria	X	X															
Demographics & Medical history[c]	X																
	Vital Signs																
Weight (lbs or kgs)[d]	X	X				X				X				X	X		
Height (in or cm)[d]	X																
BP and Pulse (after sitting for approximately 5 minutes)[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Temperature (°C or °F)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
	Medical Procedures																
Complete Physical Exam[f]	X													X	X		
Targeted Physical Exam[f]		X		X		X		X		X		X					
ECG (12-lead)	X							X						X	X		
Chest X-ray	X																

	Screening (-28 to -1)	Treatment Period													Follow-up		
Study Visit[a]	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**[y] **(if applicable)**	**Telephone Contact**
Study Week	**Week -1 to -4**		**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Week 5**	**Week 6**	**Week 7**	**Week 8**	**Week 9**	**Week 10**	**Week 11**	**Week 12/EW**[b]	**Week 16**	**Week 18**	**Week 22**
Study Day	**-28 to -1**	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**57**	**64**	**71**	**78**	**85**	**113**	**127**	**155**
Visit Window	**N/A**	**N/A**				**±2 days based on Day 1**[x]											
Video Flexible Sigmoidoscopy or Colonoscopy[g]	X													X			
Endoscopic tissue biopsies for exploratory mRNA, tissue protein, tissue concentration (PF-06687234), epigenetics and/or cytometry/microbiom and tissue histology (central reader)[r]	X													X			
	Disease Activity Assessments																
Total Mayo Score[h]		X												X			
Partial Mayo Score[h]		X		X		X		X		X		X					
Bowel Movement eDiary Instructions and/or Reminder	X	X	X	X	X	X	X	X	X	X	X	X	X				
Bowel Movement Diary Data (eDiary)[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Geboes score	X													X			
UCEIS	X													X			
	Laboratory Assessments																
Safety laboratory: Hematology, chemistry, UA	X	X	X	X		X		X		X		X		X	X		
PT, PTT/INR	X									X					X		
Serum pregnancy test or FSH[j]	X																
Urine pregnancy test[j]		X	X	X	X	X	X	X	X	X	X	X	X	X	X		

	Screening (-28 to -1)	Treatment Period													Follow-up		
Study Visit[a]	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**[y] **(if applicable)**	**Telephone Contact**
Study Week	**Week -1 to -4**		**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Week 5**	**Week 6**	**Week 7**	**Week 8**	**Week 9**	**Week 10**	**Week 11**	**Week 12/EW**[b]	**Week 16**	**Week 18**	**Week 22**
Study Day	**-28 to -1**	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**57**	**64**	**71**	**78**	**85**	**113**	**127**	**155**
Visit Window	**N/A**	**N/A**				**±2 days based on Day 1**[x]											
Stool specimen for enteric pathogens to include C-Diff toxins[k]	X													X			
Serology: HIV, HBsAg, total HBcAb, HCVAb confirmed by HCV RNA[l]	X																
Tuberculosis: PPD or IGRA per local guidelines (assayed at local lab if feasible)[m]	X																
HbA1c	X																
	Pharmacodynamic (PD)																
Serum for exploratory protein biomarkers		X				X								X			
Blood for epigenetic testing of immune cells		X				X								X			
Stool sample for fecal calprotectin[q]	X					X				X			X				
Blood for gene expression profiling	X	X				X								X			
Stool sample for exploratory biomarkers (microbiome)[q]	X									X			X				
hsCRP		X				X				X			X				

	Screening (-28 to -1)	Treatment Period													Follow-up		
Study Visit[a]	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**[y] **(if applicable)**	**Telephone Contact**
Study Week	**Week -1 to -4**		**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Week 5**	**Week 6**	**Week 7**	**Week 8**	**Week 9**	**Week 10**	**Week 11**	**Week 12/EW**[b]	**Week 16**	**Week 18**	**Week 22**
Study Day	**-28 to -1**	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**57**	**64**	**71**	**78**	**85**	**113**	**127**	**155**
Visit Window	**N/A**	**N/A**				**±2 days based on Day 1**[x]											
Genomic banked biospecimens Prep D1[n]		X															
Other exploratory/banked biospecimens (Prep B1.5, Prep B2.5, Prep R1)[n]		X		X		X				X				X			
	Pharmacokinetics (PK) and Immunogenicity																
Serum PF-06687234 concentration[o]		X	X		X				X				X	X	X		
Serum infliximab concentration for subjects on infliximab every 8 weeks[t]	X[s]									X[t]							
Serum infliximab concentration for subjects on infliximab every 6 weeks[t]	X[s]							X[t]						X[t]			
HAFA and Nab against PF-06687234[p]	X	X			X				X				X	X	X[v]		
ADA against infliximab for subjects on infliximab every 8 weeks[u]		X								X							

	Screening (-28 to -1)	Treatment Period													Follow-up		
Study Visit[a]	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**[y] **(if applicable)**	**Telephone Contact**
Study Week	**Week -1 to -4**		**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Week 5**	**Week 6**	**Week 7**	**Week 8**	**Week 9**	**Week 10**	**Week 11**	**Week 12/EW**[b]	**Week 16**	**Week 18**	**Week 22**
Study Day	**-28 to -1**	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**57**	**64**	**71**	**78**	**85**	**113**	**127**	**155**
Visit Window	**N/A**	**N/A**				**±2 days based on Day 1**[x]											
ADA against Infliximab for subjects on infliximab every 6 weeks[u]		X						X						X			
	Treatment Procedures																
Contraception check	X	→	→	→	→	→	→	→	→	→	→	→	→	→	X		
Randomization (after all screening procedures complete and eligibility confirmed)		X															
Administration of PF-06687234 or Placebo[y]		X	X	X	X	X	X	X	X	X	X	X	X				
Administration of Remicade® or protocol specific infliximab biosimiliar if on an every 8 week dosing interval for infliximab (See Appendix 5) Intravenous Infusion[y]		X								X					X		

	Screening (-28 to -1)	Treatment Period													Follow-up		
Study Visit[a]	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15[y] (if applicable)**	**Telephone Contact**
Study Week	**Week -1 to -4**		**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Week 5**	**Week 6**	**Week 7**	**Week 8**	**Week 9**	**Week 10**	**Week 11**	**Week 12/EW[b]**	**Week 16**	**Week 18**	**Week 22**
Study Day	**-28 to -1**	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**57**	**64**	**71**	**78**	**85**	**113**	**127**	**155**
Visit Window	**N/A**	**N/A**				**±2 days based on Day 1[x]**											
Adminstration of Remicade® or protocol specific infliximab biosimilar if on an every 6 week dosing interval for infliximab (See Appendix 5) Intravenous Infusion[y]		X						X						X		X	
Dispense Stool Collection Kit for Stool Specimen	X				X				X			X	X				
Prior and Concomitant Medication(s) & Treatment(s)	X	X	→	→	→	→	→	→	→	→	→	→	→	→	→		
Serious and non-serious adverse event monitoring	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X[w]
Disposition (Subject Status)																	X

Abbreviations: ADA = anti-drug antibodies; BP = blood pressure; CRF = case report form; ECG = electrocardiogram; EW = Early Withdrawal; FSH = follicle stimulating hormone; IHC = immunohistochemistry; HAFA = Human Anti Fusion Antibody; 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; HEENT = head, eyes, ears, nose, throat; HIV = human immunodeficiency virus; hsCRP = high-sensitivity C-reactive protein; IGRA = interferon gamma release assay; INR = international normalized ratio; ISRs = Injection site reactions; PD = Pharmacodynamic; PK = Pharmacokinetics; PPD = purified protein derivative; PT = promthrombin time; PPT = partial thromboplastin time; SAE = serious adverse event; UA = urinalysis; UC = ulcerative colitis; WOCBP = woman of childbearing potential.

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

b. 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.

c. To include UC and smoking history.

d. Height and weight measured without shoes.

e. At Day 1 and Week 1 BP and pulse will be collected approximately 30 minutes prior to dosing, approximately 30 minutes post dosing and approximately 1 hour post dosing. If subject experiences no safety issues (eg, severe injection site reactions, severe elevations BP and/or pulse) at Weeks 2-12 BP and pulse will be collected approximately 30 minutes prior to dosing and approximately 30 minutes post dosing.

f. 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.

g. Flexible sigmoidoscopy or colonoscopy to be completed for a subject within approximately 14 days (preferably 5 to 7 days) prior to baseline visit 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. The Partial Mayo score will be based on stool frequency, rectal bleeding and physician's global assessment (refer to Appendix 2 and Appendix 3). The total Mayo score at Week 0 will be calculated based on stool frequency, rectal bleeding and endoscopy performed during screening period and PGA obtained at baseline.

i. The subject bowel movement diary to collect stool frequency and rectal bleeding should be collected daily using an electronic diary (e-Diary).

j. Serum pregnancy testing at screening and urine pregnancy testing at other scheduled visits are required only for WOCBP. FSH test to be performed at screening to confirm postmenopausal status in female subjects who have been amenorrheic for at least 12 consecutive months. *Note: If serum pregnancy test (for WOCBP) is borderline positive, the central lab will run an FSH test as a reflex test.*

k. To be performed locally if feasible 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 alternative. ***During the treatment period only testing for C. difficile will be conducted at Week 12 visit***.

l. As per local regulations and 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.

m. To be assayed locally (IGRA assayed locally if feasible). A documented negative PPD test within 12 weeks before screening is acceptable. IGRA official reading and method of test must be located in the source documentation.

n. If not collected on the designated collection day, collect at the next available time point when biospecimens are being collected in conjunction with a subject visit.

o. Samples for serum PF-06687234 concentration should be collected approximately 30 minutes prior to dosing. See Section 6.2.11 for further details.

p. Samples for HAFA and Nab against PF-06687234 will be collected prior to dosing for all the selected time points.

q. Collection of stool for microbiome and fecal calprotectin analyses **must be** prior to administration of any bowel prep for endoscopy.

r. At each biopsy collection time point, the 14 biopsies should be taken for the analyses described: 11 from abnormally inflamed colonic mucosa and 3 from normal appearing colonic mucosa in a targeted manner from the most affected area 15-30 cm from the anal verge in the colon. See Section 7.3.2 for additional details.

s. A sample will be collected for infliximab serum concentration at any time during the first screening visit.

t. Samples for trough serum infliximab concentration should be collected approximately 30 minutes prior to infliximab dosing. See Sections 6.2.8, 6.2.10, 6.2.15 for additional details.

u. Samples for ADA against infliximab will be collected prior to infliximab dosing.

v. Subjects with no detectable HAFA or NAb against the IL-10 portion of PF-06687234 by Week 16 will not require further follow up beyond Week 22 telephone contact. Subjects with detectable HAFA or NAb against the IL-10 portion of PF-06687234 from the sample collection at Week 16 will be informed of their immunogenicity status at the Week 22 telephone contact and will be required to return for an onsite visit at Week 28 for repeat immunogenicity sample collection. If these subjects have detectable HAFA or NAb against the IL-10 portion of PF-06687234 from Week 28 sample collection, they will require one additional follow up collection 3 months after Week 28 sample collection at approximately Week 40. For early withdrawal subjects with detectable NAb against IL-10 of PF-06687432 and HAFA during the treatment period, their immunogenicity tests will be repeated at the Follow-up visit and approximately every three months for a maximum of 6 months from the follow-up visit until the level of NAb against the IL-10 portion of PF-06687432 and HAFA return to baseline level, or for 6 months, or stabilize at a level acceptable to the investigator and sponsor. At the discretion of the sponsor, the subjects with positive NAb against IL-10 may be tested for immunogenicity at shorter intervals (<3 months) or followed for longer than 6 months duration.

w. Only SAEs will be collected on the CRF at the Week 22 telephone contact.

x. At no point during the study can consecutive IP administration be given less than 4 consecutive days apart. During the course of the study consecutive IP administrations within the same calendar week are not permitted on more than 3 occasions.

y. Monitor for AEs and injection site reaction (ISRs). Subjects should be monitored during and post Remicade® or protocol specific infliximab biosimilar (See Appendix 5) administration as per local standard of care and for a minimum of 1 hour following administration of PF-06687234 or placebo. Subjects on an every 6 week infliximab dosing schedule will be administrated infliximab at Baseline, Week 6, Week 12 and Week 18. Administration of infliximab at Week 12 must be performed after all study safety and efficacy assessments are completed. Subjects on an every 8 week infliximab dosing schedule will be administered infliximab at Baseline, Week 8, and Week 16. If applicable, Visit 15 (Week 18) is only for subjects on an every 6 week infliximab dosing schedule and not required for subjects on an every 8 week infliximab dosing schedule. Subjects may use infusion centers outside of study sites for administration of infliximab; however, they should report any AE or ISR related to infliximab infusion to the designated study site personnel.

SCHEDULE OF ACTIVITIES Additional Pharmacokinetic Sub-study

	Screening	Treatment Period																			Follow-up	
Study Visit	**Screening**	**1**				**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**				**13**	**14**	**Telephone Contact**
Study Week	**Week -1 to -4**					**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Week 5**	**Week 6**	**Week 7**	**Week 8**	**Week 9**	**Week 10**	**Week 11**				**Week 12/EW[b]**	**Week 16**	**Week 22**
Study Day	**-28 to -0**	**1**	**1**	**2**	**4**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**57**	**64**	**71**	**78**	**78**	**79**	**81**	**85**	**113**	**155**
Hours Post Last Dose		**0**	**6 (±15 min)**	**24 (±3 hr)**	**72 (±7 hr)**											**0**	**6 (±15 min)**	**24 (±3 hr)**	**72 (±7 hr)**	**168**		
Visit Window																						
Pharmacokinetics (PK) and Immunogenicity																						
Serum PF-06687234 concentration		X[a]	X	X	X	X[a]		X[a]				X[a]				X[a]	X	X	X	X	X	

a. Samples to be taken predose.

b. 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.

1. INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic inflammatory condition of the gastrointestinal tract that affects five million people worldwide with considerable variability in incidence and prevalence by region. The prevalence of IBD is highest in the second and third decade of life with another peak between 60 to 70 years of age.[1] Ulcerative colitis (UC), one of two major phenotypes; the other is Crohn's disease (CD), is characterized by continuous superficial mucosal inflammation that is localized to the colon and rectum. UC involves a relapsing and remitting clinical course characterized by bloody diarrhea (with or without mucus), urgency, tenesmus, abdominal pain and weight loss, but can also present with variable extra intestinal manifestations in the eye, skin, and joint compartments.[2] There is also an increased risk of colorectal cancer in UC patients compared to the general population. Given the chronic nature of the condition, patients experience poor health-related quality of life, and the direct and indirect costs of clinical management represent a significant economic burden to society.

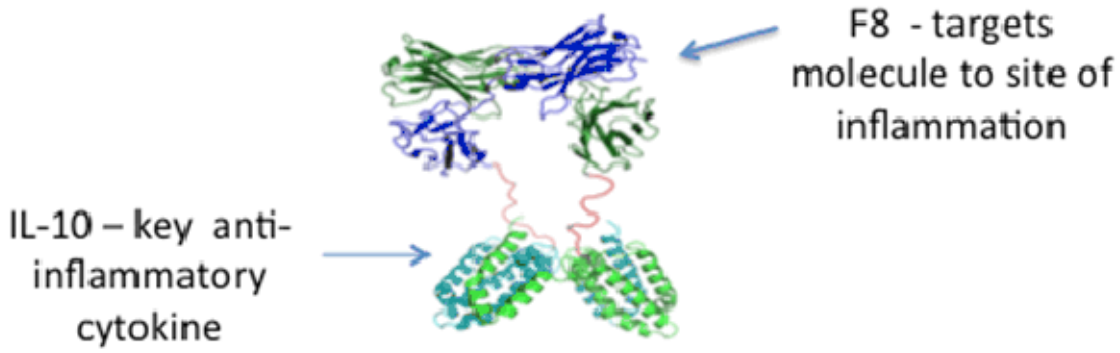
The goal of current treatments is to achieve resolution of signs and symptoms of active disease (clinical remission) in the short term and to decrease the frequency of subsequent disease flares in the long term. In the setting of moderate to severe UC, the treatment algorithm includes 5-aminosalicylates, corticosteroids, immunomodulators (primarily azathioprine and 6-mercaptopurine), and monoclonal antibodies against tumor necrosis factor (TNF)-α or α4β7 integrin. Anti-TNF-α therapies (infliximab, adalimumab, and golimumab) are the most commonly used biologic agents to treat UC. However, some patients do not achieve clinical remission with anti-TNF-α therapy, and up to 50% will develop loss of response over time.[3] In these patients, a dose escalation strategy with therapeutic drug monitoring (TDM) may be used to ensure adequate serum drug levels needed to achieve efficacy. Another strategy is to explore the potential for additive benefit with the addition of another immunosuppressant as seen with the combination of infliximab with azathioprine in UC.[15] However, such combinations targeting immune suppression are not without increased risk of serious infections and malignancies. Consequently, safer and more efficacious approaches that combine other mechanisms of immune modulation are needed to improve therapeutic outcomes of existing therapies, offer additional options, and delay the need for surgical intervention, particularly in those with moderate to severe disease inadequately managed or refractory to standard treatments.

1.1. Mechanism of Action/Indication

Pfizer has exclusively in-licensed F8IL10 (Dekavil) from Philogen S.pA., Siena, Italy, for development in inflammatory disorders. In nonclinical or clinical studies sponsored by Philogen or conducted using Philogen manufactured material, the product is identified as F8IL10. In nonclinical and clinical studies conducted by or for Pfizer using Pfizer manufactured material, the investigational product is identified as PF-06687234. PF-06687234 is comparable to F8IL10.

PF-06687234 is a fully human single chain variable fragment (scFv)-cytokine fusion protein comprised of the antibody fragment F8 and the anti-inflammatory cytokine interleukin-10 (IL-10). F8 is the scFv antibody fragment, which selectively binds to the splice variant of fibronectin Extra-Domain A (EDA), which is primarily expressed in newly formed blood vessels during inflammation. The bioactive component of PF-06687234, IL-10, is a pleiotropic cytokine with wide-ranging effects on the anti - and pro-inflammatory functions of both the innate and adaptive immune system. IL-10 can enhance T regulatory cell function, block dendritic cell maturation, and induce down-regulation of Th1 cytokines and MHC class II antigens, and increase B cell survival, proliferation, and antibody production. At the molecular level, IL-10 can modulate the critical NF-κB and JAK-STAT signaling pathways. A critical role for IL-10 in IBD pathophysiology is strongly supported by human genetics, as complete loss of IL10, IL10RA and IL10RB results in severe early onset IBD.[4] Taken together, IL-10-based therapies could have significant utility in treatment of IBD.

Figure 2. Structural Diagram of PF-06687234



In fact, recombinant human (rh) IL-10 (Tenovil) has been examined in multiple autoimmune disorders, including CD.[5] In the CD trial, Tenovil demonstrated clinical response, but not clinical remission, which could be attributed to the short half-life of Tenovil (~1.5 hours), insufficient tissue penetration, and/or short treatment duration. Furthermore, dose-related anemia and thrombocytopenia may have prevented exploration of potentially higher efficacious doses.

Unlike Tenovil however, PF-06687234 is designed (not yet proven clinically) to enrich IL-10 delivery to inflamed tissues (eg, areas of active colitis), potentially leading to higher local concentrations and prolonged pharmacology, greater clinical efficacy, and decreased systemic toxicity. The targeted IL-10 mechanism, intended to drive or restore anti-inflammatory pathways, presents a novel approach suitable for addition to existing treatments such as anti-TNF-α agents that inhibit pro-inflammatory pathways but with limited benefit.

1.2. Background and Rationale

1.2.1. Drug Development Rationale

The etiology of UC remains complex and multifactorial, involving immune dysregulation, genetics, environmental factors, and microbiota. Unlike conventional treatments such as corticosteroids and thiopurines that target broad immune suppression, current available biologic therapies target specific pro-inflammatory mediators - cytokines and integrins, to provide therapeutic benefit in some UC patients.

Studies have shown that a large proportion of UC patients will not achieve remission or loss of remission to anti-TNF-α therapy[6,7,8] over time (secondary nonresponse). In secondary nonresponders, dose adjustment through dose escalation or more frequent administration[32-36] and combination with other agents have been considered to optimize response to treatment. Indeed, increased efficacy of infliximab has been shown in the UC SUCCESS study when used concurrently with azathioprine, in part likely due to the effect of an immunomodulator on anti-drug antibodies and therapeutic drug concentrations.[9]

Even with advances in biologic therapies for UC, a substantial proportion of moderate to severe UC patients do not achieve sustained clinical remission on these therapies, because of intolerance, lack of efficacy, and/or loss of efficacy. There still remains a critical medical need for alternative treatments, approaches, and regimens to increase the proportion of patients with moderate to severe UC who can achieve long-term clinical remission, including complete mucosal healing.

The targeted pharmaco-delivery of cytokines by means of antibody cytokine fusion proteins (ie, antibody-cytokine fusion proteins) has the potential to enhance therapeutic activity at the site of disease while sparing healthy tissues. This approach has been extensively studied for various indications including different types of cancer but also chronic inflammatory conditions.

The bioactive component of PF-06687234, IL-10, is a cytokine mainly produced by activated monocytes and T cells, which is deeply involved in the regulation of inflammatory responses and immune reactions. IL-10 has been considered an attractive candidate for therapeutic use in patients suffering from IBD. In fact, IL-10 seems to play a key role in these diseases, since IL-10 knock-out mice develop chronic enterocolitis. Large multicenter trials in CD, testing multiple rhIL-10 (ilodecakin, Tenovil) dosages have been reported in subjects with mild/moderate or therapy-refractory CD,[10,11] as well as in patients undergoing surgery to prevent postoperative recurrence.[12] rhIL-10 treatment did not result in significantly higher remission rates or clinical improvement compared with placebo treatment[13] and the development of rhIL-10 as a therapeutic drug for IBD was discontinued. The authors concluded that the therapeutic action of systemically administered rhIL-10 is limited by pro-inflammatory effects of the cytokine and that this problem may be overcome by approaches that result in effective mucosal delivery without causing an increase in systemic IL-10 concentrations.[14]

Consequently, the conjugation of IL-10 to the antibody fragment F8 potentially allows for the selective delivery of the cytokine to sites of inflammation. In a mouse model of IBD, a significantly higher colon accumulation of ^{125}I-F8IL10 was observed as compared with normal mice 24 hours after systemic administration demonstrating clear selective localization at sites of inflammation.

Unlike anti-TNF-α biologic therapies, which rely on direct inhibition of pro-inflammatory cytokines, PF-06687234 is likely to exert beneficial clinical effects based on direct agonist effect through binding to IL-10 receptors by modulation of the innate and adaptive immune system towards restoring immune homeostasis. In preclinical animal models, an additive and/or synergistic effect has been shown after concomitant administration of anti-TNF-α and F8IL10, viral IL10 or rhIL-10.[15,17,24] Therefore, additive or synergistic beneficial clinical effects may be possible with "add on" therapy of PF-06687234 to existing anti-TNF-α therapies.

1.2.1.1. Non-Clinical Safety

The nonclinical toxicity studies were conducted with F8IL10 (Philogen sponsored) and PF-06687234 (Pfizer sponsored) in accordance with ICH S6(R1). All pivotal studies in accordance with Good Laboratory Practice (GLP) were conducted in an Organization for Economic Co-operation and Development (OECD) mutual acceptance of data (MAD) compliant member state. As described in the current Investigator's Brochure (IB), mice and cynomolgus monkeys were chosen as the nonclinical species based on their comparable pharmacological properties to human.

Nonclinical toxicity studies conducted with F8IL10 (Philogen sponsored) and PF-06687234 (Pfizer sponsored) included repeat-dose studies with once or twice/weekly subcutaneous (SC) injection administration up to 8 weeks in duration in cynomolgus monkeys and up to 6 months duration in mice with a 5 week recovery period. PF-06687234 and its associated vehicle were tolerated when administered to rabbits as a single intravenous (IV) or peripheral venous (PV) dose (at 20.6 and 1 mg, respectively) followed by a 3-day observation period. There were no local irritation, macroscopic, or microscopic findings. As is standard for therapeutic proteins, no genetic toxicity studies were conducted. Safety pharmacology endpoints evaluated in mouse and cynomolgus monkey toxicity studies did not identify effects on the cardiovascular, central nervous or respiratory systems.

To investigate safety effects related to serious infections, PF-06687234 (Dekavil) and PF-06410293, an anti-TNF-α monoclonal antibody (adalimumab), were tested in panel of in vitro human immune function assays. No additive or synergistic effect was observed in any assay when PF-06687234 and PF-06410293 were used in combination, relative to each investigational product alone.

Preliminary embryo fetal development studies up to 100 mg/kg/dose (200 mg/kg/week) of F8IL10 in pregnant mice and rabbits demonstrated no evidence of teratogenicity.

Target organs were similar in mice and monkeys. The predominant direct adverse effects (attributed to IL-10 pharmacology) were decreases in red blood cells (RBC) parameters (RBC count, hemoglobin, and hematocrit) and platelet counts. Similar effects were observed previously with rhuIL-10 in monkeys. At higher doses these hematological effects were associated with secondary effects related to systemic hypoxia and hemorrhage. In monkeys, these hematologic findings increased in severity when the same total weekly dose was administered with a twice weekly dosing regimen versus once weekly dosing. The hematological values returned to the normal range in both mice and monkeys at the end of the recovery phase. Findings in the toxicity studies also comprised several investigational product-related effects attributed to an immunogenic response to a foreign protein. These included a high incidence of anti-drug antibodies (ADAs) in mice (82-100%) and monkeys (60-100%), associated with adverse clinical signs and mortality in mice consistent with anaphylaxis, injection site reactions, and microscopic findings in mice and monkeys consistent with immune complex deposition (ICD). The latter included glomerulopathy and inflammatory cell infiltrates in multiple tissues characteristic of ICD including liver, epididymis, synovium, choroid plexus, and various other tissues. ADA titers were still measurable after the recovery period and there was a range of full to partial recovery of effects attributed to ICD.

The no-observed-adverse-effect level (NOAEL) in mice in the 3 month study was 20 mg/kg/week (twice weekly). Excluding AEs secondary to immunogenicity, the 20 mg/kg/week was the highest dose in the 6-month mouse study without adverse findings attributed directly to PF-06687234 and was associated with a safety margin of 3.2x compared to a clinical dose of 0.5 mg/kg/week on a body surface area basis. The NOAEL in cynomolgus monkeys in the 8-week study was 9 mg/kg/week (weekly) and was associated with a safety margin of 5.8x compared to a clinical dose of 0.5 mg/kg/week on a body surface area basis.

In the toxicology studies, PF-06687234 serum concentrations were measurable on Day 1 but due to immunogenicity, limited serum PF-06687234 concentrations were detected after repeat administration. Therefore, exposure obtained on Day 1 at the NOAEL doses in the above toxicity studies were considered as the NOAEL exposures. In mice and cynomolgus monkeys the NOAEL exposures were associated with C_{max} values of 5.51 μg/mL and 14.0 μg/mL respectively. The corresponding NOAEL C_{av} values were 0.913 μg/mL and 9.67 μg/mL, respectively.

The nonclinical safety program performed for this investigational product supports chronic dosing in clinical trials with inclusion of women of childbearing potential.

Please refer to the IB for more details on non-clinical safety information with PF-06687234.

1.2.2. Previous Human Experience

Table 1. Overview of F8IL10 and PF-06687234 Clinical Program (June 2018)

Study Protocol	Description	Study Duration	Dose/Regimen
Phase 0			
11/203 (Investigator-initiated research study by VUMC, Amsterdam)	Positron emission tomography (PET) study	Single dose	^{124}I-F8IL10: 0.4 mg IV
Phase 1			
PH-F8IL10-02/08 (Philogen-sponsored study)	Open label, uncontrolled, dose escalation, safety and pharmacokinetic study in RA subjects on background of MTX	8 weeks (4 weeks of mandatory and 4 weeks of optional dosing)	F8IL10: Weekly SC doses of 6, 15, 30, 60, 110, 160, 210, 300,450 and 600 µg/kg (ie, 0.4 to 40 mg)
B7581001 (Pfizer-sponsored study)	Placebo-controlled, dose escalation, safety, tolerability, pharmacokinetic, and immunogenicity study in healthy adult subjects	Single dose	PF-06687234: 2 or 20 mg[a] (ie, 30 or 300 µg/kg)
B7581003 (Ongoing Pfizer-sponsored study)	Open-label, single IV dose of [^{124}I]IB-PF-06687234 and concurrent non-radiolabeled PF-06687234, PET-CT assessment in moderate to severe UC subjects	Single dose	PF-06687234: 7.4 mg [^{124}I]IB-PF-06687234: 1mg
Phase 2			
PH-F8IL10-03/13 (Ongoing Philogen-sponsored study)	Placebo-controlled , double blind, efficacy and safety study in RA subjects on background of MTX	8 weeks	F8IL10: Weekly SC dose of30 or 160 µg/kg

MTX = Methotrexate; RA = Rheumatoid arthritis; SC = Subcutaneous.
a. Doses >20 mg were not explored in healthy subjects in agreement with US FDA (as noted in Section 1.2.2.1).

1.2.2.1. Subject Disposition

As of June 2018, 48 subjects (including 8 healthy subjects, 38 rheumatoid arthritis (RA) and 2 IBD subjects) have received at least one dose of either F8IL10 or PF-06687234 up to a maximum dose of 600 µg/kg. Of these 48 subjects, 3 RA and 2 IBD subjects received a single tracer dose of ^{125}I-F8IL10.

Weekly doses of F8IL10 have been tested in RA subjects for up to 8 weeks (PF-F8IL10-02/08). The formulation utilized in current Philogen studies is comparable to the formulation utilized in the Pfizer Phase 1 study. This includes 5 subjects (3 RA and 2 IBD) who received a single tracer dose of ^{125}I-F8IL110 in a PET study conducted at VU University Medical Center in Amsterdam (11/203).

In the Philogen Phase 1 study (PH-F8IL10-02/08), RA subjects on background of methotrexate (MTX) were administered F8IL10 doses of 6, 15, 30, 60, 110, 160, 210, 300,450 and 600 μg/kg (ie, 0.4 to 40 mg) as a SC injection. Thirty-five (35) RA subjects received at least one dose and 33 of 35 completed the mandatory 4 weekly cycles of treatment. One subject from the 450 μg/kg cohort was discontinued from treatment due to purpura of lower limbs. Twenty-four (24) out of 35 treated subjects completed the mandatory 4 weeks cycles and the 4 weeks of optional cycles, for a total of 8 weeks of exposure to the study drug.

In the ongoing Philogen Phase 2 double-blind study in RA subjects on a background of MTX (PH-F8IL10-03/13) as of June 2018, 26 subjects have been enrolled and randomized to once-weekly 30 or 160 μg/kg dose of F8IL10 or placebo. The treatment duration for the study is 8 weeks. Based on preliminary data, as provided by Philogen as of June 2018, neither suspected unexpected serious adverse reactions (SUSARs) nor serious adverse events (SAEs) have been reported to date in this study. Immunogenicity assessment has been completed for the first 20 study subjects and did not reveal an antibody response specific to F8IL10.

In the Pfizer Phase 1 study in healthy subjects (B7581001), 10 subjects received a single dose of either placebo (2 subjects), 2 mg (4 subjects) or 20 mg (4 subjects) of PF-06687234. All subjects completed the 28 day trial. In this study, the US Food and Drug Administration (FDA) only permitted dosing of healthy subjects up to a single SC dose of 20 mg of PF-06687234 due to the potential for neutralizing antibodies against endogenous IL-10, which places healthy subjects at risk to developing chronic enterocolitis. Following determination that the risk-benefit did not support further dosing in healthy subjects, the Pfizer Phase 1 study (B7581001) was prematurely terminated per agreement with FDA and subsequent dosing planned in Phase 2 studies in UC subjects. It should be noted that no neutralizing antibodies against IL-10 have been observed with PF-06687234 to date.

1.2.2.2. Pharmacokinetic Results

PK profiles following F8IL10 and PF-06687234 have been characterized in RA (PH-F8IL10-02/08 Protocol) subjects and healthy subjects (B7581001).

Following SC administration, the PK profiles of F8IL10 in RA subjects (n=3 per cohort) were atypical with a high degree of variability especially between 6 and 300 μg/kg/week (PH-F8IL10-02/08). The PK exposures could not be characterized due to limited sampling time points, however Week 4 plasma trough samples were quantifiable for F8IL10 suggesting a half-life ($t_{½}$) longer than recombinant IL-10.

Additional PK samples were taken for the 450 (n=6) and 600 (n=3) µg/kg/week cohorts Geometric mean of the maximum concentration (C_{max}) and C_{av} (calculated as the area under the concentration curve from zero to 168 hours AUC_{0-168}/168) on Week 1 for 450 µg/kg/week were 0.026 and 0.006 µg/mL and for Week 4 were 0.014 and 0.0005 µg/mL, respectively. Similarly for the 600 µg/kg/week dose level the C_{max} and C_{av} for Week 1 were 0.062 and 0.01 µg/mL respectively and for Week 4 were 0.023 and 0.001 µg/mL respectively.

The free IL-10 plasma profiles following PF-06687234 in healthy subjects (n=5, 4 active, 1 placebo) were different from a typical SC route of administration for a non-targeted molecule but also showed a high degree of variability especially at the 2 mg dose. Only one subject in the 2 mg dose cohort showed the typical profile expected from a SC administration with a half-life of approximately 48 hours. The exposures following 20 mg PF-06687234 were generally less variable compared to 2 mg. The exposures showed a less than dose proportional increase between 2 and 20 mg. The mean $t_{½}$ for the 20 mg dose cohort was 49.4 hours. The observed C_{max} and C_{av} (calculated as AUC_{last}/168) for the 20 mg dose were 0.0056 µg/mL and 0.0027 µg/mL, respectively, and well below the PK stopping limits of C_{max} of 5.51 µg/mL and C_{av} of 0.913 µg/mL (NOAEL exposures for mice after single dose). Pharmacokinetic data should be interpreted with caution given limitations of the corresponding bioanalytical assay, as is described in the current Investigator's Brochure (IB).

1.2.2.3. Immunogenicity Results

In RA subjects on the background of MTX (PH-F8IL10-02/08), using two different assays the total incidence rate for Human Anti Fusion Antibody (HAFA) was 17.6% (6 out of 34 subjects). No further testing was conducted for domain specificity and neutralizing antibodies.

In healthy subjects (B7581001), the HAFA incidence rate was 12.5% (1 out of 8 subjects). In this subject, HAFA developed at Day 28 post injection. Another subject showed HAFA at pre-dose but did not show any treatment boosting following PF-06687234 administration. The HAFA for both subjects were non-neutralizing and were against the F8 portion of the molecule and not against IL-10.

In the B7581001 study, there were no neutralizing antibody safety signals or dose-related laboratory abnormalities.

1.2.2.4. Safety Results in Clinical Trials

IL-10, the bioactive moiety contained in the F8IL10 fusion protein, has been investigated extensively in clinical trials in healthy volunteers at single doses up to 100 µg/kg administered IV[27] and subjects suffering from several chronic inflammatory disorders, including psoriasis and CD.[24,28]

Please refer to the IB for more details on clinical safety information with PF-06687234.

1.2.2.4.1. Safety Summary Philogen Phase 1 Study (PH-F8IL10-02/08)

In this study, there were no SAEs assessed as related to study drug, no SUSARs and no deaths reported, and no pattern of clinically significant vital sign changes.

Mild local injection site reactions (60%, 21 subjects) and anemia (5.7%, 2 subjects) were the most common adverse events (AEs) reported. All of the injection site reactions were considered mild and disappeared (spontaneously or after a minor local treatment) within a few weeks after the end of treatment. One non-study drug related SAE (hospitalization for moderate dyspnea) was reported in an RA subject dosed with 2 weekly doses of F8IL10 at 450 μg/kg concurrently with weekly 10 mg MTX subcutaneous injections. In addition, this subject developed purpura on both legs (moderate severity and assessed as study drug related) which was classified as a dose limiting toxicity, per protocol, this same also developed thrombocytopenia with platelet count of 120,000/microliter (from 313,000 at baseline, assessed as study drug related) and increased alanine aminotransferase (ALT) (from 21 IU/L at baseline to 112 IU/L at Week 3, assessed as study drug related). This subject was hospitalized for 2 days and study treatment discontinued. During the hospitalization, the investigator started treatment with methylprednisolone 20 mg twice daily and the subject was discharged from the hospital in good, general clinical condition with purpuric lesions considerably regressed and clear reduction of the subjective dyspnea. Purpura, dyspnea, increased ALT and thrombocytopenia all resolved within 1 week after hospital discharge.

Three (3) patients (1 each in the 110 μg/kg, 160 μg/kg, and 450 μg/kg cohorts) discontinued treatment due to persistence of injection site reaction; Grade 3 anemia and Grade 2 anemia respectively. In addition, one patient was withdrawn from the study after Grade 2 dyspnea requiring hospitalization, which was assessed by the investigator as not related to the treatment and purpura which was assessed as possibly related to study treatment.

Anemia was reported as an AE in two subjects treated at the dosage of 160 μg/kg and 450 μg/kg. One (1) case of anemia was severe (decrease from baseline HGB of 2.1-2.9 g/dl or HGB <8, >7 g/dl) and the other moderate (decrease from baseline of 1.5-2.0 g/dl). In both of the anemia cases designated as an AE the events spontaneously resolved within 3-4 weeks after the interruption of study drug.

In 24/35 (68%) of the subjects a non-dose dependent HGB drop of at least 1 g/dl from baseline was observed. In 9/35 (25.7%) of the subjects a moderate hemoglobin decrease from baseline was observed (1.5-2.0 g/dl) and in 7/35 (20%) of the subjects a severe decrease (2.1-2.9 g/dl from baseline or HGB <8, >7 g/dl) was observed.

1.2.2.4.2. Safety Summary Pfizer Phase 1 Study (B7581001)

PF-06687234 has been investigated in a double blind, placebo controlled, third party open (subject blind, investigator blind, sponsor open) Phase 1 study in healthy subjects (Protocol B7581001). This study was designed to provide safety, tolerability, PK, and immunogenicity data by evaluating single SC dose, multiple SC dose and a single IV dose regimen of PF-06687234 in healthy subjects. In the 2 completed single dose regimen cohorts (2 mg and 20 mg) with 4 active and 1 placebo treated subjects in each cohort, no SAEs were

reported. Two subjects had mild headache (one in 2 mg cohort, one in placebo) and two subjects had mild injection site reactions (one treated with 2 mg, one with 20 mg). No clinically significant trends in lab results were observed. None of the subjects withdrew from study for treatment related AEs.

1.3. Rationale

1.3.1. Study Rationale

This multicenter, two arm, Phase 2A study will be the first to assess PF-06487234 as add-on therapy to existing anti-TNF-α (infliximab, IV) regimen in subjects with active UC. The objectives of this study are to evaluate the efficacy (based on a modified Mayo score), safety, PK, immunogenicity, and tolerability of PF-06687234 at 20 mg SC administered once weekly for a total of 12 doses in subjects already being treated with infliximab infusions.

As previously noted (Section 1.2.1), optimizing infliximab dosing (adjusting either dosage and/or frequency) is an evidence-based recommendation for managing UC patients[32-35] to achieve treatment targets. Reducing the dosing interval to every 6 weeks has been shown to be safe and efficacious and is recommended[36] to restore clinical response in UC patients in whom clinical benefit is attenuated after an initial response to infliximab. Routine clinical practice often employs a more frequent infliximab regimen than the every 8 weeks contained in the labeling for infliximab to keep UC patients in clinical response prior to switching to an alternative biologic if needed. To align with current standard clinical practice, this study will allow subjects to continue on their stable existing infliximab regimen of either every 6 weeks or every 8 weeks as background infliximab treatment for UC. The use of the every 6 week regimen, consistent with current medical practice in the target population, does not alter the risk:benefit in the study because:

- Eligible participants continue on their stable background therapy, and
- No PK interaction affecting exposures is expected, and
- Close surveillance of the study participant for the duration of the study is part of the ongoing monitoring for an enrolled subject, and
- Safe use of an every 6 week regimen has precedent in the label of infliximab for other inflammatory conditions, such as ankylosing spondylitis.

The primary endpoint chosen is clinical remission based on a modified total Mayo score, consistent with regulatory expectations for assessment of signs and symptoms using a patient-reported outcome and endoscopy.[25,26] However, in this initial efficacy study, assessment of clinical remission will utilize the current definition of the Mayo endoscopic subscore, which allows for assessment of mild friability in subscore of 1.

Preclinical studies in mice have indicated a potential additive or synergistic effect when an IL-10 fusion protein was combined with soluble TNF receptor[15] (compared with either agent alone) in a murine model of arthritis.[17,24] The combination of TNF-α blocking agent and IL-10 has not been studied in a murine model of IBD. In earlier studies, recombinant mouse IL-10 or adenovirus encoding viral IL-10 and TNF-α blocking agents were studied alone and in combination. IL-10 in combination with an anti-TNF-α antibody produced an additive therapeutic effect which demonstrated a greater duration of efficacy in a murine model of arthritis.[24] Significant synergism was observed with the combination of vIL-10 and soluble tumor necrosis factor receptor immunoglobulin (sTNFR-Ig) in the collagen induced arthritis murine model utilized in this study.[17] Collectively, these data suggest the potential for an additive or synergistic beneficial therapeutic effect on inflammation for IL-10 as add on therapy in humans under anti-TNF-α. A benefit-risk assessment is provided in Section 1.3.3.

The current non-clinical toxicology package will support up to a 12-week treatment period for the B7581002 study. All sigmoidoscopy/colonoscopy videos will be read remotely by central readers who will be blinded to study treatment. A treatment period of 12 weeks of PF-06687234 or placebo dosing in addition to ongoing anti-TNF-α regimen was chosen to allow for sufficient time for mucosal healing and symptom remission in the study population. Following completion of dosing at 12 weeks, the subjects will be followed for an additional 4 weeks for further evaluation of safety.

During endoscopic evaluations, colon biopsies will be obtained and interrogated to provide evidence for pharmacologic modulation of the IL-10 pathway and to define parameters that might 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 the colon biopsies.

1.3.2. Dose Rationale

The proposed dosage for Study B7581002 is weekly SC administration of 20 mg (~300 μg/kg) PF-06687234 for 12 weeks. This dose level has been previously administered in the first in human (RA) study.

F8IL10 or PF-06687234 has not been previously administered to UC subjects and currently no placebo-controlled efficacy data are available in RA. Therefore, the dosage for Study B7581002 was selected on the basis of Tenovil (rhIL-10) data in CD with certain assumptions. In CD subjects, a non-monotonic dose response was observed for Tenovil where in a lower dose level showed clinical signals unlike the highest dose.[10,11] Specifically, Tenovil administration at 5 μg/kg/day[10] for 28 days demonstrated clinical and endoscopic remission. In another study in CD subjects, Tenovil administration at 8 μg/kg/day[11] for 28 days showed clinical improvement. In both studies the highest dose of 20 μg/kg/day did not show the efficacy signals. Tenovil administration in CD subjects led to dose related decreases in hematocrit and hemoglobin.[5] The greatest decrease was observed at the 20 μg/kg/day dose.

Based on PK data from CD patients[10] the estimated C_{av} in terms of free IL-10 concentrations following Tenovil administration at 5 μg/kg/day and 10 μg/kg/day were approximately 0.5 and 2.0 ng/mL respectively. Assuming that these concentrations associated with an efficacy response in CD subjects translate to UC subjects, the efficacious concentration range in UC was predicted as 0.5 to 2.0 ng/mL. Assuming linearity in exposure for Tenovil between 10 and 20 μg/kg/day doses, the corresponding IL-10 C_{av} for the 20 μg/kg/day dose would be approximately 4.0 ng/mL. The dosage for study B7581002 was therefore selected to achieve the target free IL-10 plasma concentrations between 0.5 and 2.0 ng/mL and avoid sustained concentrations above 4.0 ng/mL. Observed plasma concentration data with F81L10 (PH-F8IL10-02/08 Protocol) and simulations using plasma data from the healthy subjects (Study B7581001) suggests that 20 mg SC (~300 μg/kg to ~500 μg/kg) administered weekly to UC subjects with weight >40 kg may achieve the targeted free IL-10 concentrations.

In summary, a weekly 20 mg (~300 μg/kg to ~500 μg/kg) PF-06687234 SC dose in subjects with weight >40 kg is: (a) expected to achieve concentrations equivalent to those observed to be efficacious with Tenovil, (b) anticipated to not be associated with significant decreases in hematocrit and hemoglobin levels, (c) has already been tested in humans (single dose healthy subjects and multiple dose in RA subjects) and is less than the highest dose level deemed safe and tolerated as monotherapy, albeit in a limited number of RA subjects, (d) has a 3.2-fold and 5.8-fold safety margin compared to the NOAEL doses from two mice studies (3 and 6-month studies) and an 8-week cynomolgus monkey study compared with a clinical dose of 0.5 mg/kg/week on a body surface area basis, and (e) is a reasonable target based on evidence of a non-monotonic dose response with Tenovil, which suggests a higher dose may not be necessarily beneficial.

It is not expected that infliximab and PF-06687234 would have any significant pharmacokinetic drug-drug interaction requiring dosing adjustments. Also in vivo, IL-10 did not have any significant effect on cytochrome activity and therefore PF-06687234 is not expected to have a drug-drug interaction with the concomitant medications[31] expected in this study.

1.3.3. Summary of Benefit and Risks

IBD is a chronic inflammatory disease of the gastrointestinal tract. The need for safer and more efficacious approaches that combine other mechanisms of immune modulation are needed to improve therapeutic outcomes of existing therapies and offer additional options, particularly in those who do not achieve clinical remission despite treatment. IL-10 is a pleiotropic cytokine with wide-ranging effects on the anti- and pro-inflammatory functions of both the innate and adaptive arms of the immune system. The rationale for IL-10 to treat IBD is supported by genetic evidence that complete loss of IL-10R1 and IL-10R2 causes severe colitis.[20] In addition, genetic variation in other pathway members supports the IL-10 agonist hypothesis as 17% of CD subjects have two (NOD2) mutations[18,19] that can lead to reduced IL-10 production.

In vitro, PF-06687234 demonstrates potent IL-10 agonist activity in whole blood STAT1/3 phosphorylation assays and shows potent inhibition of pro-inflammatory cytokine production. In vivo, F8IL10 protected from weight loss and increases stool scores in a T-cell transfer mouse model of IBD and decreased disease related gene expression in the colon and pro-inflammatory cytokine levels in the serum. Therapeutic treatment of F8IL10 in a mouse collagen induced arthritis model was able to stabilize clinical features of arthritis. Furthermore, in line with previous reports[17,24] the combination of F8IL10 with a tumor necrosis factor (TNF) blocking agent (muTNFR-Fc) provided an additive and/or synergistic therapeutic effect on disease progression,[15] providing a rationale for the use of PF-06687234 as an add-on anti-TNF-α biologics. The in vitro and in vivo nonclinical profiling supports the rationale that PF-06687234 is able to modulate disease activity and markers of inflammation and will represent a novel anti-inflammatory approach for the treatment of IBD.

Additional information for PF-06687234 may be found in the single reference safety document (SRSD), which for this study is the current Investigator's Brochure.

F8IL10 has been tested in a Phase 1 study (PH-F8IL10-02/08) at a maximum dose of 600 μg/kg/wk in RA subjects. The active dose (approximately 300 μg/kg or flat dose of 20 mg SC) in this study is two-fold lower than the highest dose studied in RA Phase 1 high dose cohorts. This selected dose is expected to yield plasma concentrations between 0.5 and 2.0 ng/ml. Due to the "leakiness" in the gut the plasma exposure of PF-06687234 in UC is not expected to be greater than that in RA. Further IL-10 has been also administered as recombinant IL-10 (Tenovil) in CD and as pegylated IL-10 in cancer patients where mean serum IL-10 concentrations as of 6 ng/mL and 50 ng/mL have been reported respectively. Based on this data and clinical studies conducted to date, the dose of 300 to 500 μg/kg/wk is expected to be well-tolerated. Further, no pharmacokinetic interaction is expected between infliximab and PF-06687234 that could lead to an increase in the exposure of either agent. Based on the evidence provided above for additive and/or synergistic therapeutic effect on disease progression, for the combined use of PF-06687234 with anti-TNF-α biologics, the pharmacodynamics interaction between infliximab and PF-06687234 is hypothesized to be favorable.

While efficacy of PF-06687234 has yet to be investigated in clinical trials with UC subjects (alone or as add on therapy to anti-TNF-α standard treatment), recombinant human IL-10 (Tenovil) as monotherapy demonstrated efficacy on secondary endpoints in trials with CD subjects.[10,11] In addition, preclinical and genetic evidence provide a theoretical rationale that there is the potential for benefit in the UC patient population.

This study is investigating the administration of PF-06687234 concurrent to treatment with infliximab. Combinations of biologics in a prior study with another anti-TNF-α therapy, etanercept[21] for treatment of RA resulted in higher rates of serious infections than in either individual biologic regimen. In view of these data, the combination of infliximab with other biological therapeutics used to treat the same conditions as infliximab is not recommended in the labeling for infliximab. However, it should be noted that unlike the previous intent to test combination of two immunosuppressive agents,[21] in this study, the potential benefit of

PF-06687234 that is expected to modulate the innate and adaptive immune system towards restoring immune homeostasis (based on direct agonist effect through binding to IL-10 receptors) will be explored in those who have not achieved clinical remission despite targeted immunosuppressive therapy with infliximab. Although in vitro human immune function assays (viral T cell responses, monocyte/granulocyte phagocytosis and natural killer (NK) cell assays) did not show any additive or synergistic effects with addition of PF-06687234 to adalimumab (another anti-TNF-α agent) relative to each agent alone, the potential for additive or synergistic infection or other unexpected risks in the clinic cannot be completely excluded.

It should be noted that in RA clinical trials to date conducted by Philogen, combination of weekly MTX, a broad immunosuppressant and weekly F8IL10 injections has not resulted in serious safety signal with dosing up to 8 weeks in duration.

Further, in this study (B7581002), subjects will be required to come for weekly visits during the entire 12 week study active dosing period. These frequent visits will allow for close monitoring including, weekly hematological parameters, targeted exams and vital sign assessments. The protocol also includes immediate stopping rules for predefined criteria (Section 6.4). Randomized subjects with serious infections will be immediately discontinued from the study. An internal review committee (Section 9.6), independent of the study team will also review the accumulating safety data and propose protocol changes to ensure subject safety.

Banked biospecimens will be collected for the purpose of conducting research; specific uses are described in the Banked Biospecimens section. Comparing the deoxyribonucleic acid (DNA), ribonucleic acid (RNA), protein, and metabolite variation patterns of subjects who respond well and those who respond poorly to treatment may help to better define the most appropriate group of subjects in which to target a given treatment. Collecting biospecimens for exploratory pharmacogenomic/genomic/biomarker analyses and retaining them in the Biospecimen Banking System (BBS) make it possible to better understand the investigational product's mechanism of action and to seek explanations for differences in, for example, exposure, tolerability, safety, and/or efficacy not anticipated prior to the beginning of the study.

Banked biospecimens retained in the BBS also can be used in research on IBD and other inflammatory diseases.

Providing these biospecimens is a required study activity for study sites and subjects, unless prohibited by local regulations or ethics committee (EC) decision.

In summary, PF-06687234 has been generally safe and well tolerated in clinical studies to date. While the therapeutic benefit has not been investigated, there is preclinical evidence that suggests subjects with UC may benefit from treatment with an IL-10 agonist added on to preexisting anti-TNF-α therapy. Potential risks of PF-06687234 include injection site reactions, anemia and thrombocytopenia. Risks specific to combining PF-06687234 with infliximab at this time are not fully understood and may include increased risk of serious

infections. Appropriate monitoring and stopping rules are proposed to manage and mitigate potential risks to subjects. None of these effects preclude the continued exploration of safety, tolerability, PK, pharmacodynamics (PD) and efficacy in the intended patient population.

2. STUDY OBJECTIVES AND ENDPOINTS

Primary Efficacy Objective(s):	**Primary Efficacy Endpoint(s):**
• To evaluate the efficacy of PF-06687234 in induction of clinical remission in subjects with UC and a partial response to anti-TNF-α.	• Proportion of subjects in clinical remission at Week 12 (as defined by a modified total Mayo Score with a traditional endoscopic subscore ≤1, stool frequency subscore ≤1 and rectal bleeding subscore = 0).[a]
Primary Safety Objective(s):	**Primary Safety Endpoint(s):**
• To evaluate the safety and tolerability of PF-06687234 in subjects with UC and a partial response to anti-TNF-α.	• Incidence and severity of adverse events, serious adverse events and withdrawals due to adverse events, ECGs, vital signs and safety laboratory tests.
Secondary Objective(s):	**Secondary Endpoint(s):**
• To evaluate the efficacy of PF-06687234 in induction of endoscopic improvement in subjects with UC and partial response to anti-TNF-α. • To evaluate histological improvement in subjects with UC and partial response to anti-TNF-α. • To evaluate the efficacy of PF-06687234 in induction of clinical response in subjects with UC and a partial response to anti-TNF-α. • To describe the PK of PF-06687234 in subjects with UC. • To evaluate the immunogenicity of PF-06687234 in subjects with UC.	• Proportion of subjects with endoscopic improvement at Week 12 (defined as decrease of ≥1 point in a modified endoscopic subscore or an absolute endoscopy score of ≤1).[b] • Mean change from baseline at Week 12 in Geboes histology score. • Proportion of subjects with a clinical response at Week 12 defined with a decrease from baseline of at least 3 points in total Mayo score with at least 30% change, accompanied by at least one point decrease or absolute score of 0 or 1 in rectal bleeding subscore. • Proportion of subjects with change from baseline in partial Mayo Score of ≤2 with no individual subscore >1 at Weeks 2, 4, 6, 8, 12. • Serum concentrations of PF-06687234. • Incidence of the development of HAFAs and Nabs against PF-06687234.
Exploratory Objective(s):	**Exploratory Endpoint(s):**
• To collect banked biospecimens and additional non-banked samples (eg, intestinal biopsies, stool for microbiome analysis, serum and plasma for analysis of proteins, whole blood for RNA analysis and epigenetics and/or cytometry) for exploratory research, unless prohibited by local regulations or ethics committee decision. • To evaluate disease pathway and related biomarkers (ie, hsCRP and fecal calprotectin). • To describe the full PK profile in a subgroup of subjects. • To evaluate tissue concentrations of PF-06687234 in	• Collection of banked biospecimens and additional non-banked samples (eg, intestinal biopsies, stool for microbiome analysis, serum and plasma for analysis of proteins, whole blood for RNA analysis and epigenetics and/or cytometry) unless prohibited by local regulations or ethics committee decision. Additional information on collection and potential use is provided in the Banked Biospecimens section. • Change from baseline in fecal calprotectin at Weeks 4, 8, 11.

biopsy samples.	• Change from baseline in hsCRP at Weeks 4,8,11. • $AUC_{(0\text{-}Tau)}$, C_{max}, T_{max}, $t_{1/2}$, CL/F, Vz/F. • PF-06687234 tissue concentration in inflamed and non-inflamed biopsies.

a. The assessment of clinical remission will utilize the current definition of the traditional Mayo endoscopic subscore, which allows for assessment of mild friability in the subscore of 1.

b. The Central Readers for endoscopy Mayo subscores will also employ an assessment as to the presence or absence of any friability (including mild). In this assessment the presence of any friability (including mild) will be scored as 2 (modified endoscopic subscore).

Apparent clearance (CL/F), Apparent volume of distribution (Vz/F), Area under the concentration-time curve to the end of the dosing period ($AUC_{(0\text{-}Tau)}$), Anti-tumor necrosis factor-α (anti-TNF-α), maximum observed concentration (C_{max}) electrocardiogram (ECG), human anti-fusion antibody (HAFA), neutralizing antibodies (Nabs), pharmacokinectic (PK), ribonucleic acid (RNA), time to reach maximum concentration (T_{max}), terminal half-life ($t_{1/2}$).

3. STUDY DESIGN

3.1. Study Overview

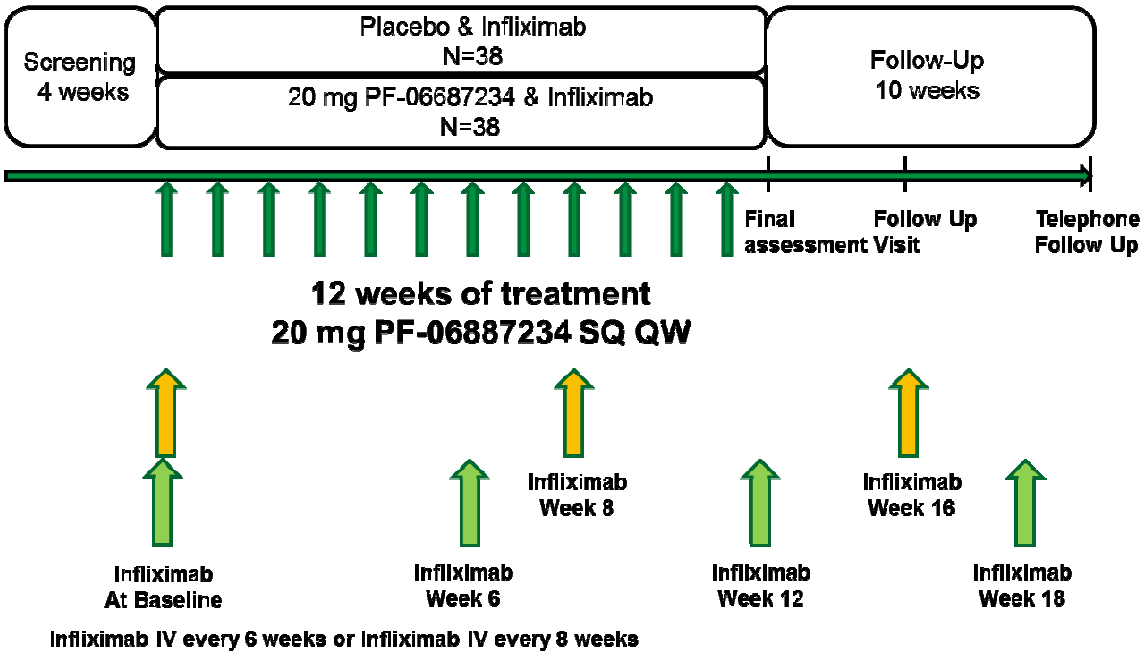
This is a Phase 2A, randomized, double-blind, placebo-controlled, parallel group, multicenter study in subjects with active UC and a non-remission (partial) response to anti-TNF-α therapy. Each subject will be randomly assigned to 1 of 2 treatment arms (1 active; 1 placebo) with approximately 76 subjects in total (38 subjects per arm) enrolled for the study to achieve a total of 64 evaluable subjects.

Using the Mayo scoring definitions in Appendix 2 and Appendix 3, clinical remission in this protocol is defined as those subjects with a traditional endoscopic subscore of 0 or 1, stool frequency subscore of 0 or 1 and rectal bleeding subscore of 0.

Eligible subjects for enrollment will meet criteria for partial response to infliximab but in non-remission during screening, despite at least 14 weeks after initiation of infliximab therapy for active UC prior to study entry.

Women of childbearing potential (WOCBP) will be eligible for this study provided these women use two methods of contraception, as outlined in Section 4.4.1.

Figure 3. Study Design Schematic



3.1.1. Additional Pharmacokinetic Sampling

For most subjects participating in Study B7581002 a sparse PK sampling scheme will be followed. As the PK of PF-06687234 in UC subjects has not been characterized, to better understand the PK of PF-06687234, a more extensive PK sampling scheme may be used in a subgroup of approximately 12 subjects who provide consent from any investigational site. For specific details refer to Section 7.5.2 regarding the additional PK sampling.

3.2. Duration of Subject Participation

The duration of participation for eligible subjects will be approximately 26 weeks. This will include a 4-week screening period, a 12-week treatment period, a 10-week follow-up period which will include a telephone contact conducted 6-weeks after the onsite follow-up visit. During the treatment period subjects will visit the clinic every week (±2 days) for SC administration of 20 mg of the investigator product (IP) or placebo for a total of 12 visits. In addition, all subjects enrolled in the study will be continuing treatment with their infliximab therapy as a background therapy during the study. Subjects will be administered their infliximab at the baseline visit on study Day 1 and subsequent doses given at appropriate study visits based on subject's background dosing interval for infliximab.

Subjects will be required to return to the clinic for one visit 4 weeks after the last visit during the treatment period to evaluate for safety which will constitute an onsite follow-up visit. Subjects on infliximab every 8 weeks will also be administered their infliximab therapy at this visit. Subjects on infliximab every 6 weeks will require an additional site visit for administration of their infliximab at Week 18. There will be a telephone contact conducted at Week 22 to confirm any SAEs have been reported to the Sponsor and to provide results of Week 16 immunogenicity testing.

Subjects with no detectable HAFA or NAb against IL-10 portion of PF-06687234 by the Week 16 visit will not require further follow-up beyond the Week 22 telephone contact. However, subjects with detectable HAFA or NAb against the IL-10 portion of PF-06687234 at Week 16 will be informed of their immunogenicity status at the Week 22 telephone contact. These subjects will be required to return for an onsite visit at Week 28 for repeat immunogenicity testing. If these subjects have detectable HAFA or NAb against the IL-10 portion of PF-06687234 from the immunogenicity sample collection at Week 28, they will require one additional follow-up collection 3 months after Week 28 at approximately Week 40. For early withdrawal subjects with detectable NAb against IL-10 of PF-06687432 and HAFA during the treatment period, their immunogenicity tests will be repeated at the Follow-up visit, and approximately every three months for a maximum of 6 months from the follow-up visit until the level of NAb against the IL-10 portion of PF-06687432 and HAFA return to baseline level, or for 6 months, or stabilize at a level acceptable to the investigator and sponsor. At the discretion of the sponsor, the subjects with positive NAb against IL-10 may be tested for immunogenicity at shorter intervals (<3 months) or followed for longer than a 6 month duration.

3.3. Approximate Duration of Study

Study enrollment is estimated to be completed in approximately 19 months. The completion of the study is estimated to occur in approximately 26 months.

4. SUBJECT ELIGIBILITY CRITERIA

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

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

4.1. Inclusion Criteria

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

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

3. Male and/or female subjects ≥18 years to ≤75 years of age and weight >40 kg at the time of informed consent. For subjects in South Korea: male and/or female ≥19 years to <70 years of age and weight >40 kg at the time of informed consent.

4. A diagnosis of active UC (histologic) for ≥4 months. A biopsy report supporting the diagnosis prior to the baseline visit must be available in the source documents. In addition, a report documenting disease duration and extent of disease (eg, proctosigmoiditis, left-sided colitis, or pancolitis) based upon prior endoscopy must also be available in the source documentation.

5. Subjects who have partial response to anti-TNF (infliximab) and active UC as defined by (via screening endoscopy) a total Mayo Score ≥4 but ≤9 and an endoscopic subscore ≥2. Endoscopy (flexible sigmoidoscopy or colonoscopy), should be performed within 14 days of baseline (Day 1). The endoscopic Mayo subscore assessed by the Central Reader must be available at the baseline visit. The assessment by the Central Reader will be used to derive the total Mayo score to determine study eligibility. Primary non-responder to anti-TNF therapy should be excluded.

6. UC extending at least 15 cm proximal to the anal verge at the time of the screening endoscopy.

7. Must be on a stable dose 5 to 10 mg/kg of Remicade®, or protocol specified infliximab biosimilars (see Appendix 5) for a minimum of 14 weeks prior to study entry with no anticipation of need for change in infliximab treatment regimen throughout the study (no switches from infliximab version at baseline to a different infliximab version will be permitted through Week 12). For a subject who has recently switched dose or dosing intervals of infliximab during maintenance therapy, the subject must be on the same dose and dosing interval for at least two treatment cycles (minimum 12 weeks) before study entry. Subject must maintain the same infliximab regimen of every 6 weeks or every 8 weeks throughout the study.

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

   - Oral 5-aminosalicylic acid derivative (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 date of total Mayo Score assessment.

   - 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 date of total Mayo Score assessment. Decreases in steroid use due to AEs are allowed.

   - 6-MP, azathioprine (AZA) (≤2.5 mg/kg), or MTX stable dose for 8 weeks prior to baseline.

9. Male subjects able to father children and female subjects of childbearing potential and at risk for pregnancy must agree to use two methods of contraception throughout the study and until the Week 16 visit (or 28 days after the last dose of IP).

    - Women of childbearing potential (WOCBP) will be eligible provided these women use two methods of contraception throughout the study and until the Week 16 visit (or 28 days after the last dose of IP), as outlined in Section 4.4.

    - Female subjects of nonchildbearing potential must meet at least 1 of the following criteria:

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

        - Have undergone a documented hysterectomy and/or bilateral oophorectomy;

        - Have medically confirmed ovarian failure.

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

4.2. Exclusion Criteria

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

1. Pregnant female subjects; breastfeeding female subjects; fertile male subjects and female subjects of childbearing potential who are unwilling or unable to use 2 methods of contraception as outlined in this protocol for the duration of the study (Week 16 visit) or for at least 28 days after the last dose of investigational product.

2. Subjects with a diagnosis or documented history of total colectomy and/or pouchitis, indeterminate colitis, microscopic colitis, ischemic colitis, infectious colitis, radiation colitis, and diverticular disease associated with colitis, or clinical findings suggestive of Crohn's disease (eg, fistulae, granulomas on biopsy).

3. Subjects considered in imminent need for surgery or with major elective surgery (requiring general anesthesia) scheduled to occur during the study.

4. Subjects with extensive colitis for at least 8 years who have not had a colonoscopy with surveillance biopsies within 2 years of the baseline visit.

5. Subjects with history of or at screening endoscopy, biopsy documented colonic dysplasia or neoplasia. Subjects with prior history of adenomatous polyps will be eligible if the polyps have been completely removed and pathology is negative.

6. Subjects who require infliximab dosing interval other than every 6 weeks or every 8 weeks during this study.

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

8. Subjects with primary sclerosing cholangitis.

9. Subjects with known colonic stricture, or history of colonic or small bowel obstruction or resection.

10. Subjects with history of or current colonic or small bowel stoma.

11. History of known cyclic neutropenia, thrombocytopenia, lymphopenia, leukopenia or any history of chronic anemia (HGB <10 g/dL) which is judged by the investigator to have an unclear specific etiology or is non self-limiting.

12. 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.

13. Current evidence of active TB or latent TB infection or inadequately treated TB infection demonstrated by chest x-ray, a positive Mantoux (purified protein derivative [PPD]) tuberculin skin test or a positive Interferon Gamma Release Assay (IGRA to be tested at the site's local lab) 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 should be used 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 the results of the IGRA are indeterminate, the test may be repeated, and if a negative result is obtained, enrollment may proceed. A positive test on repeat is exclusionary.

- Subjects with repeat indeterminate IGRA results may be enrolled after 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).

14. Presence of active enteric infections (positive stool culture and sensitivity). The presence of *Clostridium difficile* infection (reference C. diff section) or pseudomembranous colitis or history of recurrent Clostridium difficile infection. Known active invasive fungal infections such as histoplasmosis or parasitic infections.

15. 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 and as per local regulations.

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

17. Previous severe hypersensitivity reaction to infliximab (Remicade® or infliximab biosimilar) or known hypersensitivity to inactive components of infliximab (eg, Remicade® or infliximab biosimilar) or to any murine protein.

18. Exposure to a live (attenuated) vaccine within 30 days prior to screening or anticipated need for any live (attenuated) vaccine during the study.

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

    - Any major illness/condition or evidence of an unstable clinical condition (eg, cardiovascular, renal, hepatic, hematologic, gastrointestinal, endocrine, pulmonary, immunologic [eg, Felty's syndrome], neurologic 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.

    - Clinically significant infections within 6 months of baseline (eg, those requiring hospitalization or parenteral antimicrobial therapy, or opportunistic infections), history of any infection requiring antimicrobial therapy within 2 weeks of baseline, or a history of any infection otherwise judged by the investigator to have the potential for exacerbation by participation 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 (>450 msec in males and >470 msec in females).
- Class III or Class IV heart failure.

20. 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.
    - Anti-integrin inhibitors (eg, vedolizumab) within 14 weeks prior to baseline.
    - Any prior use of natalizumab.
    - Interferon therapy within 8 weeks prior to baseline.
    - Subjects with prior treatment with lymphocyte-depleting agents/therapies (eg, CamPath® [alemtuzumab], alkylating agents [eg, cyclophosphamide or chlorambucil], total lymphoid irradiation, etc).
    - Subjects who have received rituximab or other selective B lymphocyte-depleting agents within 1 year prior to baseline.
    - Subjects previously receiving leukocyte apheresis, including selective lymphocyte, monocyte, or granulocyte apheresis, or plasma exchange within 6 months of baseline.
    - JAK inhibitors within 3 months prior to baseline.
    - Other investigational procedures(s) or product(s), such as immunomodulators used in transplantation (eg, mycophenolate mofetil, cyclosporine, rapamycin, or tacrolimus) or live (attenuated) vaccine within 30 days prior to baseline.
21. Subjects with significant trauma or major surgery within 4 weeks of screening.
22. Prior evidence of liver injury or toxicity due to methotrexate.
23. History of sensitivity to heparin or heparin-induced thrombocytopenia.
24. 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) are excluded. Subjects with false positive anti-HBc may be enrolled based upon consultation with hepatologist confirming no infection with hepatitis B.

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

- HGB level ≤100 g/L (10.0 g/dL).

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

- White blood cell (WBC) count ≤3.0 x 10^9/L (3000 cells/mm^3) or absolute neutrophil count (ANC) <1200 cells/mm^3 or absolute lymphocyte count of <0.5 x 10^9/L (<500 cells/mm^3).

- Estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m^2 based on the age appropriate calculation.

- Glycosylated hemoglobin (HbA_{1C}) >10%

- Subjects with HbA_{1C} > ULN without a diagnosis of diabetes mellitus should be evaluated prior to randomization for confirmation of diagnosis.

- ***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.***

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

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

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

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

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

30. Known history of hypersensitivity, intolerance, or allergic reaction to PF-06687234 or any constituent of the IP.

4.3. Randomization Criteria

Subjects will be randomized into the study provided they have satisfied all subject eligibility criteria. Subjects will have up to 4 weeks after the first screening visit to complete all screening procedures prior to randomization.

A computer-generated randomization schedule will be used to assign subjects to the treatment groups.

4.4. Lifestyle Requirements

4.4.1. Contraception

All fertile male subjects and female subjects who are of childbearing potential as applicable to the study who are, in the opinion of the investigator, sexually active and at risk for pregnancy with their partner(s) must agree to use 2 methods of contraception (at least one of which is considered to be highly effective) consistently and correctly for the duration of the active treatment period and until Week 16 or 28 days after the last dose of investigational product. The investigator or his or her designee, in consultation with the subject, will confirm that the subject has selected 2 appropriate methods of contraception for the individual subject and his or her partner from the permitted list of contraception methods and will confirm that the subject has been instructed in their consistent and correct use. At time points indicated in the Schedule of Activities, the investigator or designee will inform the subject of the need to use 2 methods of contraception consistently and correctly and document the conversation and the subject's affirmation in the subject's chart (subjects needs to affirm their consistent and correct use of at least 2 of the selected methods of contraception). In addition, the investigator or designee will instruct the subject to call immediately if 1 or both of the selected contraception methods is discontinued or if pregnancy is known or suspected in the subject or the 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 hormonal methods of contraception associated with inhibition of ovulation (eg, oral, inserted, injected, implanted, transdermal) provided the subject or male subject's female partner 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) or intrauterine system (IUS).

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

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

NOTE: Sexual abstinence, defined as completely and persistently refraining from all heterosexual intercourse (including during the entire period of risk associated with the study treatments) may obviate the need for contraception ONLY if this is the preferred and usual lifestyle of the subject.

All sexually active male subjects must agree to prevent potential transfer to and exposure of partner(s) to drug through ejaculate by using a condom consistently and correctly, beginning with the first dose of investigational product and continuing for the duration of the active treatment period and until Week 16 or 28 days after the last dose of PF-06687234.

Male subjects must refrain from sperm donation for the duration of the active treatment period and until Week 16 or 28 days after the last dose of the investigational product.

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

5. STUDY TREATMENTS

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

For this study, the investigational product is PF-06687234.

5.1. Allocation to Treatment

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

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

5.2. Subject Compliance

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

5.3. Breaking the Blind

The study will be subject, investigator and sponsor blinded.

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

5.4. Investigational Product Supplies

5.4.1. Dosage Form(s) and Packaging

PF-06687234 will be supplied by Pfizer as a sterile lyophilized powder for solution for injection. Lyophilized investigational product vials contain a white uniform cake. PF-06687234 investigational product will be provided in dosage strength of 20 mg/vial in single-use, sterile vials. Placebo for PF-06687234 will also be provided by Pfizer as a sterile liquid solution in single-use, sterile vials.

PF-06687234 and placebo are supplied in a 6 mL glass vial with a stopper and aluminum overseal. PF-06687234 investigational product is designed to be reconstituted with 1.3 mL of sterile Water for Injection resulting in approximately 1 mL of extractable solution at 20 mg/mL. The reconstituted solution for PF-06687234 has a nominal volume of 1.0 mL. PF-06687234 and placebo sterile vials will be supplied as individual vials for subsequent unit dosing preparation. Both the IP and placebo vials will be provided to the site with open label packaging.

Infliximab allowed in this study is the innovator product REMICADE® or protocol specific infliximab biosimilar approved for treatment of UC in the relevant geographic region (See Appendix 5). Infliximab (REMICADE® or protocol specific infliximab biosimilar) may be supplied by Pfizer (from commercial source) or by the clinical site conducting the study. All ancillary supplies, including sterile water for injection, used to prepare and administer doses will be provided by the clinical site conducting the study.

5.4.2. Remicade® or Protocol Specific Infliximab Biosimilar Label Instructions

All instructions, warnings and precautions, and adverse reactions associated with using infliximab can be found in the relevant geographic region Remicade® Package Insert or protocol specific infliximab biosimilar Package Insert (See Appendix 5).

5.4.3. Preparation and Dispensing

PF-06687234 lyophilized powder will be reconstituted using sterile water for injection. The PF-06687234 and placebo investigational products will be prepared at the investigational site by two operators, both of whom are fully trained and experienced in aseptic technique and preparation and administration of solutions for subcutaneous use. Dose preparation must be performed with locally accepted aseptic handling technique.

See the Investigation Product (IP) Manual for instructions on how to prepare the investigational products for administration.

PF-06687234 and placebo will be prepared by qualified unblinded site personnel according to the IP manual.

The investigational product will be administered in blinded fashion to the subject by the blinded site personnel.

5.5. Administration

IP dose may be temporarily withheld for a maximum of 14 consecutive days once during the treatment period at the discretion of the investigator. However, at no point during the study can consecutive IP administration be given less than 4 consecutive days apart. During the course of the study consecutive IP administrations within the same calendar week are not permitted on more than 3 occasions.

During the study, Remicade® or protocol specific infliximab biosimilar (See Appendix 5) approved for treatment of UC will be administered as an IV infusion using a calibrated infusion pump by investigator site personnel on Day 1, Week 8 and Week 16 for a total of three doses for subjects on infliximab every 8 weeks, and Day 1, Week 6, Week 12 and Week 18 for subjects on infliximab every 6 weeks. Remicade® or protocol specific infliximab biosimilar administration should occur following most study procedures (except PF-06687234 administration) and must not be administered as an IV push or bolus. The start and stop time of the infusion will be recorded on the CRF. No dose adjustment during the study will be permitted.

PF-06687234 will be administered as a 20 mg SC injection by the blinded investigator site personnel on Day 1, Week 1 (Day 8), Week 2 (Day 15), Week 3 (Day 22), Week 4 (Day 29), Week 5 (Day 36), Week 6 (Day 43), Week 7 (Day 50), Week 8 (Day 57), Week 9 (Day 64), Week 10 (Day 71) and Week 11 (Day 78) for a total 12 doses. IP administration should occur following most study procedures as outlined in Schedule of Activities (SOA).

The preferred body location for the SC injection is the abdomen: the 5 cm area around the navel should be avoided. If abdominal injections are not possible, arm or thigh locations may also be used. If an arm is used for the SC injection, the opposite arm should be used for the PK blood sample collections.

Subjects should remain at the study site for a minimum of 1 hour for observation following PF-06687234 administration. For subjects in the additional PK substudy, on Study Day 1 and Study Day 78, the subject will remain at the site for a minimum of 1 hour for observation following PF-06687234 administration. After the 1 hour observation period, the subject may leave the study site as long as the subject agrees to return 5 hours later for collection of the 6 hour post investigational product PK sample.

5.6. Injection/Infusion Discontinuation

Treatment of subjects with biologics 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 Remicade® or protocol specific infliximab biosimilar (See Appendix 5) as per standard of care and PF-06687234, for a minimum 1 hour after administration.

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 for further guidance regarding the diagnosis of anaphylaxis reactions (See Appendix 4).

If a subject experiences anaphylaxis, Remicade® or protocol specific infliximab biosimilar (See Appendix 5) and/or PF-06687234 administration (when possible) should be discontinued immediately and permanently (See Section 6.4).

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/injection should be stopped.

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

In the event that there is an infusion interruption, the entire duration of Remicade® or protocol specific infliximab biosimilar 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.

5.7. Investigational Product Storage

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

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

See the IP manual for storage conditions of the product both prior to and following reconstitution.

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

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

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

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

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

5.8. Investigational Product Accountability

The investigator site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies, as the co-medication (Remicade® or protocol specific infliximab biosimilar). All investigational products will be accounted for using a drug accountability form/record.

5.8.1. Destruction of Investigational Product Supplies

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

5.9. Prior Medication(s)

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

Any prior UC medications taken within 90 days prior to screening must be recorded on the CRF.

All other medications taken within 4 weeks before the first dose of IP will be documented as prior medication(s).

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

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

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

5.10.1. Oral Corticosteroids Taken During the Study

Any oral corticosteroid(s) taken during the screening and treatment periods of the study will be captured on the appropriate CRF.

5.10.2. 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 total Mayo score assessment and through Week 16. 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 assessment. Decreases in dose are allowed if due to AEs.

- A stable dose of oral corticosteroid treatment (prednisone/equivalent up to 20 mg/day; budesonide up to 9 mg/day) for at least 2 weeks prior to total Mayo score screening assessment and through Week 16. If oral corticosteroids have been recently discontinued, they must have been stopped at least 2 weeks prior to total Mayo score screening assessment. Decreases in steroid use due to AEs are allowed.

- A stable dose of immunomodulators (6-MP, MTX or AZA ≤2.5 mg/kg) from baseline and through Week 16. Decreases due to AEs are permitted.

5.10.3. Prohibited Medications

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

- Any non-infliximab iTNF treatment or biologic therapy within 24 weeks of screening visit.

- Oral budesonide (>9 mg/day) or prednisone (>20 mg/day) or equivalent oral systemic corticosteroid 2 weeks prior to baseline and through Week 12.

- Any live (attenuated) vaccines from 30 days prior to screening or anytime throughout the study.

- IV, IM (parenteral), or topical (rectal) treatment of 5-ASA or corticosteroid enemas/suppositories within 2 weeks prior to baseline and through Week 16.

- Anti-integrin inhibitors (eg, vedolizumab) within 14 weeks prior to baseline and through Week 16.

- Any use of natalizumab at any time.

- Interferon therapy within 8 weeks prior to baseline and through Week 16.

- Lymphocyte-depleting agents/therapies (eg, CamPath® [alemtuzumab], alkylating agents [eg, cyclophosphamide or chlorambucil], total lymphoid irradiation, etc) within 1 year of screening visit.

- Rituximab or other selective B lymphocyte-depleting agents within 1 year prior to baseline and through Week 16.

- Leukocyte apheresis, including selective lymphocyte, monocyte, or granulocyte apheresis, or plasma exchange within 6 months of baseline and through Week 16.

- Janus kinase (JAK) inhibitors within 3 months prior to baseline and through Week 16.

- Any investigational procedures(s) or product(s), such as immunomodulators used in transplantation (eg, mycophenolate mofetil, cyclosporine, rapamycin, or tacrolimus).

5.11. Rescue Medication

Rescue therapy should be provided by the investigator as deemed clinically appropriate. Subjects requiring rescue medication prior to the end of the study will be discontinued from IP (PF-06687234 or placebo) and will enter the follow-up period. Subjects requiring rescue medication after Week 11 (after last IP administration) should also complete the follow-up period.

6. STUDY PROCEDURES

6.1. Screening

After informed consent has been obtained, subjects have up to 4 weeks of a screening period to complete all of the screening procedures. Subject's eligibility for the study will be evaluated during this period based on medical history, physical examination, laboratory values, bowel movement diary data and additional tests. To prepare for study participation, subjects will be instructed on the use of Lifestyle Requirements (see Section 4.4) and Concomitant Medications (see Section 5.10).

Screening laboratory tests with abnormal results may be repeated **once** to confirm abnormal results; the last value will be used to determine eligibility. If results return to normal within the 4-week screening period, the subject may enter the study.

Subjects who do not meet eligibility criteria (eg, screen fail) may be re-screened **once** (with a new screening number).

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

The following procedures will be performed:

- ICD.
- Review of inclusion and exclusion criteria.
- Demography, complete medical history (including UC and smoking).
- Assessment of prior concomitant medications, including a complete history of all therapies for UC (eg, steroids, immunomodulators and/or anti-TNF-α and anti-integrin treatment) received since diagnosis (including treatment response), and detailed UC medications (including dose, frequency, and route) taken within 90 days prior to the screening visit. Complete history of all drugs (including nonprescription drugs, vitamins, and dietary or herbal supplements), taken within 4 weeks prior to screening procedures.

- Vital signs measurements including sitting blood pressure (BP) and pulse (after approximately 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 7.2.9 and Schedule of Activities).
- Chest x-ray (See Section 7.2.10 and Schedule of Activities). Negative results must be documented prior to Baseline (Day 1) randomization.
- Collect blood, urine and 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, urinalysis and prothrombin time (PT), partial thromboplastin time (PTT)/international normalized ratio (INR);
    - HbA1c;
    - Immunogenicity: HAFAs and NAb against PF-06687234;
    - PK sample: Serum infliximab concentration;
    - 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) will be performed by the central laboratory and HIV as per local regulations and to be assayed locally. Confirmation and 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 7.2.6 for *Clostridium difficile*);
    - Stool specimen for exploratory biomarkers (microbiome) (prior to initiation of any bowel preparation for endoscopy);

  - Stool specimen for fecal calprotectin (prior to initiation of any bowel preparation for endoscopy);
  - Blood for gene expression profiling.
- Subjects will be instructed on the use of the Bowel Movement Diary (e-diary) for daily collection.
- Dispense labeled stool container and plastic bag (for refrigerated or frozen stool sample at subsequent visit).
- UC Assessments:
  - Endoscopy: All subjects may undergo either a colonoscopy or a video flexible sigmoidoscopy at the discretion of the investigator. Subjects who undergo colonoscopy do not require a separate sigmoidoscopy. If subjects undergo a colonoscopy for screening, flexible sigmoidoscopy for exam at Week 12 is allowed;
  - Endoscopy (flexible sigmoidoscopy or colonoscopy) should be performed within approximately 14 days (preferably 5 to 7 days) of 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;
  - Geboes score provided by Central Reader;
  - Ulcerative colitis endoscopic index of severity (UCEIS) provided by Central Reader;
  - Endoscopic tissue biopsies for exploratory mRNA, tissue protein, tissue concentration PF-06687234, tissue epigenetic and/or cytometry/microbiome and tissue histology (central imaging reader) (See Section 7.3.2 and Schedule of Activities).
- Contraception check.
- Serious and non-serious adverse event monitoring.

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.

6.2.1. Baseline – Day 1

The baseline visit must occur on the projected visit date within approximately 28 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 approximately 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 and urine samples for the following laboratory tests:

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

    - Urine pregnancy test (WOCBP only);

    - Collect genomic banked biospecimens. If missed, collect at the next available time point when biospecimens are being collected in conjunction with a subject visit;

    - Collect other exploratory banked specimens (Prep B1.5, Prep B2.5, Prep R1);

    - PD Biomarkers: hsCRP;

    - Serum for exploratory protein biomarkers;

    - Blood for gene expression profiling;

- Blood for epigenetic testing of immune cells;
- Pre-dose PK: Serum PF-06687234 concentration should be collected approximately 30 minutes prior to dosing;
- Immunogenicity: HAFAs and Nab against PF-06687234, and infliximab ADA.

- UC Assessment: Provide PGA to obtain baseline total and partial Mayo score and review subject bowel movement e-diary data (See Sections 7.3.3, 7.3.4 and Schedule of Activities).
- Review bowel movement e-diary completion instructions.
- Review prior and concomitant medications/treatments.
- Contraception check.
- Serious and non-serious adverse event monitoring.

Randomization/Dosing may occur after all screening procedures are completed and results reviewed. Note for WOCBP, the urine pregnancy test must be negative prior to dosing.

- Administer Remicade® as per instructions in relevant geographic region Remicade® Package Insert or protocol specific infliximab biosimilar (See Appendix 5) approved for the treatment of UC as per instructions in relevant geographic region infliximab biosimilar package insert and as described in Section 5.5.
- Administration of PF-06687234 or placebo should occur approximately 1 hour but not exceed 3 hours after the completion of the administration of Remicade® or protocol specific infliximab biosimilar (See Appendix 5) approved for the treatment of UC and as described in Section 5.5.
- Measure vital signs including sitting BP and pulse (after approximately 5 minutes of rest) and temperature (oral, tympanic or axillary). Vital sign measurement should occur approximately 30 minutes post dosing and approximately 1 hour post dosing of PF-06687234 or placebo. If subject experiences no safety issues (eg, severe injection site reactions, severe elevations BP and/or pulse) at Weeks 2-12 BP and pulse will be collected approximately 30 minutes prior to dosing and approximately 30 minutes post dosing.
- Monitor for AEs and injection site reaction (ISRs). Subjects should be monitored during and post Remicade® or protocol specific infliximab biosimilar (See Appendix 5) approved for the treatment of UC administration as per local standard of care and for a minimum of 1 hour following administration of PF-06687234 or placebo.

6.2.2. Additional PK Sampling Day 1, Day 2 and Day 4

Subjects who agree and provide consent will have the following additional PK samples collected post-dosing:

- Serum PF-06687234 concentration sample collected approximately 6 hours (±15 min), 24 hours (±3 hours) and 72 hours (±7 hours).

6.2.3. Week 1 (±2 days)

There is a ±2 day window for this study visit. However, at no point during the study can consecutive IP administration be given <4 consecutive days apart. During the course of the study consecutive IP administrations within the same calendar week are not permitted on more than 3 occasions.

Prior to dosing the following procedures will be completed:

- Measure vital signs including sitting BP and pulse (after approximately 5 minutes of rest) and temperature (oral, tympanic or axillary). Vital signs measurement should occur approximately 30 minutes prior to dosing.
- Collect blood and urine samples for the following laboratory tests:
  - Safety laboratory tests for blood chemistry, hematology and urinalysis;
  - Urine pregnancy test (WOCBP only);
  - Pre-dose PK: Serum PF-06687234 concentration sample should be collected approximately 30 minutes prior to dosing.
- Review of bowel movement e-diary completion instructions (See Schedule of Activities).
- Review subject bowel movement e-diary data (See Section 7.3.4 and Schedule of Activities).
- Review concomitant medications/treatments.
- Contraception check.
- Serious and non-serious adverse event monitoring.

Dosing may occur after all pre-dosing procedures are performed. For WOCBP, the urine pregnancy test must be negative prior to dosing.

- **Administer PF-06687234** or placebo as described in Section 5.5.

- Measure vital signs including sitting BP and pulse (after approximately 5 minutes of rest) and temperature (oral, tympanic or axillary). Vital sign measurement should occur approximately 30 minutes post dosing and approximately 1 hour post dosing. If subject experiences no safety issues (eg, severe injection site reactions, severe elevations BP and/or pulse) at Weeks 2-12 BP and pulse will be collected approximately 30 minutes prior to dosing and approximately 30 minutes post dosing.

- Monitor for AEs and ISRs. Subjects should be monitored for a minimum of 1 hour following administration of PF-06687234 or placebo.

6.2.4. Week 2 (±2 days)

There is a ±2 day window for this study visit. However, at no point during the study can consecutive IP administration be given <4 consecutive days apart. During the course of the study consecutive IP administrations within the same calendar week are not permitted on more than 3 occasions.

Prior to dosing the following procedures will be completed:

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

- Targeted physical examination.

- Collect blood and urine samples for the following laboratory tests:

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

  - Urine pregnancy test (WOCBP only);

  - Collect other exploratory banked specimens (Prep B1.5, Prep B2.5, Prep R1).

- UC Assessment: Partial Mayo score and review subject bowel movement e-diary data (See Sections 7.3.3, 7.3.4 and Schedule of Activities).

- Review bowel movement e-diary completion instructions.

- Review concomitant medications/treatments.

- Contraception check.

- Serious and non-serious adverse event monitoring.

Dosing may occur after all pre-dosing procedures are performed. For WOCBP, the urine pregnancy test must be negative prior to dosing.

- **Administer PF-06687234** or placebo as described in Section 5.5.

- Measure vital signs including sitting BP and pulse (after approximately 5 minutes of rest) and temperature (oral, tympanic or axillary). If subject experiences no safety issues then vital sign measurement should occur approximately 30 minutes post dosing.

- Monitor for AEs and ISRs. Subjects should be monitored for a minimum of 1 hour following administration of PF-06687234 or placebo.

6.2.5. Week 3 (±2 days)

There is a ±2 day window for this study visit. However, at no point during the study can consecutive IP administration be given <4 consecutive days apart. During the course of the study consecutive IP administrations within the same calendar week are not permitted on more than 3 occasions.

Prior to dosing the following procedures will be completed:

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

- Collect blood and urine samples for the following laboratory tests:

  - Urine pregnancy test (WOCBP only);

  - Pre-dose PK: Serum PF-06687234 concentration sample should be collected approximately 30 minutes prior to dosing;

  - Immunogenicity: HAFAs and Nab against PF-06687234.

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

- Review subject bowel movement e-diary data (See Section 7.3.4 and Schedule of Activities).

- Review concomitant medications/treatments.

- Dispense labeled stool container and plastic bag (for refrigerated or frozen stool sample at subsequent visit).

- Contraception check.

- Serious and non-serious adverse event monitoring.

Dosing may occur after all pre-dosing procedures are performed. For WOCBP, the urine pregnancy test must be negative prior to dosing.

- **Administer PF-06687234** or placebo as described in Section 5.5.
- Measure vital signs including sitting BP and pulse (after approximately 5 minutes of rest) and temperature (oral, tympanic or axillary). If subject experiences no safety issues then vital sign measurement should occur approximately 30 minutes post dosing.
- Monitor for AEs and ISRs. Subjects should be monitored for a minimum of 1 hour following administration of PF-06687234 or placebo.

6.2.6. Week 4 (±2 days)

There is a ±2 day window for this study visit. However, at no point during the study can consecutive IP administration be given <4 consecutive days apart. During the course of the study consecutive IP administrations within the same calendar week are not permitted on more than 3 occasions.

Prior to dosing the following procedures will be completed:

- Measure vital signs including sitting BP and pulse (after approximately 5 minutes of rest) and temperature (oral, tympanic or axillary). Vital signs measurement should occur approximately 30 minutes prior to dosing.
- Record subject's weight.
- Targeted physical examination.
- Collect blood, urine and 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 for exploratory protein biomarkers;
  - Stool sample for fecal calprotectin;
  - Blood for epigenetic testing of immune cells;
  - Blood for gene expression profiling;
  - Collect other exploratory banked specimens (Prep B1.5, Prep B2.5, Prep R1).

- UC Assessment: Partial Mayo score and review subject bowel movement e-diary data (See Sections 7.3.3, 7.3.4 and Schedule of Activities).
- Review bowel movement e-diary completion instructions.
- Review concomitant medications/treatments.
- Contraception check.
- Serious and non-serious adverse event monitoring.

Dosing may occur after all pre-dosing procedures are performed. For WOCBP, the urine pregnancy test must be negative prior to dosing.

- **Administer PF-06687234** or placebo as described in Section 5.5.
- Measure vital signs including sitting BP and pulse (after approximately 5 minutes of rest) and temperature (oral, tympanic or axillary). If subject experiences no safety issues then vital sign measurement should occur approximately 30 minutes post dosing.
- Monitor for AEs and ISRs. Subjects should be monitored for a minimum of 1 hour following administration of PF-06687234.

6.2.7. Week 5 (±2 days)

There is a ±2 day window for this study visit. However, at no point during the study can consecutive IP administration be given <4 consecutive days apart. During the course of the study consecutive IP administrations within the same calendar week are not permitted on more than 3 occasions.

Prior to dosing the following procedures will be completed:

- Measure vital signs including sitting BP and pulse (after approximately 5 minutes of rest) and temperature (oral, tympanic or axillary). Vital signs measurement should occur approximately 30 minutes prior to dosing.
- Collect urine sample for the following laboratory tests:
  - Urine pregnancy test (WOCBP only).
- Review of bowel movement e-diary completion instructions (See Schedule of Activities).
- Review subject bowel movement e-diary data (See Section 7.3.4 and Schedule of Activities).

- Review concomitant medications/treatments.
- Contraception check.
- Serious and non-serious adverse event monitoring.

Dosing may occur after all pre-dosing procedures are performed. For WOCBP, the urine pregnancy test must be negative prior to dosing.

- **Administer PF-06687234** or placebo as described in Section 5.5.
- Measure vital signs including sitting BP and pulse (after approximately 5 minutes of rest) and temperature (oral, tympanic or axillary). If subject experiences no safety issues then vital sign measurement should occur approximately 30 minutes post dosing.
- Monitor for AEs and ISRs. Subjects should be monitored for a minimum of 1 hour following administration of PF-06687234 or placebo.

6.2.8. Week 6 (±2 days)

There is a ±2 day window for this study visit. However, at no point during the study can consecutive IP administration be given <4 consecutive days apart. During the course of the study consecutive IP administrations within the same calendar week are not permitted on more than 3 occasions.

Prior to dosing the following procedures will be completed:

- Measure vital signs including sitting BP and pulse (after approximately 5 minutes of rest) and temperature (oral, tympanic or axillary). Vital sign measurement should occur approximately 30 minutes prior to dosing.
- Targeted physical examination.
- Standard 12-lead ECG (See Section 7.2.9 and Schedule of Activities).
- Collect blood, urine and stool samples for the following laboratory tests:
  - Safety laboratory tests for blood chemistry, hematology and urinalysis;
  - Urine pregnancy test (WOCBP only).
- UC Assessment: Partial Mayo score and review subject bowel movement e-diary data (See Sections 7.3.3, 7.3.4 and Schedule of Activities).
- Review bowel movement e-diary completion instructions.

- Review concomitant medications/treatments.
- Contraception check.
- Serious and non-serious adverse event monitoring.

Dosing may occur after all pre-dosing procedures are performed. For WOCBP, the urine pregnancy test must be negative prior to dosing.

- If applicable, for subjects on an infliximab dosing schedule of every 6 weeks, collect a trough sample and an ADA sample for infliximab 30 minutes before administration of infliximab and administer Remicade® or protocol specific infliximab biosimilar (See Appendix 5) as per instructions in relevant geographic region Remicade® or protocol specific infliximab biosimilar Package Insert and as described in Section 5.5.
- **Administer PF-06687234** or placebo as described in Section 5.5 (Administration of PF-06687234 or placebo should occur approximately 1 hour but not exceed 3 hours after the completion of the administration of Remicade® or protocol specific infliximab biosimilar (See Appendix 5) for subject with infliximab dosing every 6 weeks).
- Measure vital signs including sitting BP and pulse (after approximately 5 minutes of rest) and temperature (oral, tympanic or axillary). If subject experiences no safety issues then vital sign measurement should occur approximately 30 minutes post dosing.
- Monitor for AEs and ISRs. Subjects should be monitored for a minimum of 1 hour following administration of PF-06687234 or placebo.

6.2.9. Week 7 (±2 days)

There is a ±2 day window for this study visit. However, at no point during the study can consecutive IP administration be given <4 consecutive days apart. During the course of the study consecutive IP administrations within the same calendar week are not permitted on more than 3 occasions.

Prior to dosing the following procedures will be completed:

- Measure vital signs including sitting BP and pulse (after approximately 5 minutes of rest) and temperature (oral, tympanic or axillary). Vital sign measurement should occur approximately 30 minutes prior to dosing.
- Collect blood and urine samples for the following laboratory tests:
  - Urine pregnancy test (WOCBP only);

  - Pre-dose PK: Serum PK-06687234 concentration sample should be collected approximately 30 minutes prior to dosing;
  - Immunogenicity: HAFAs and Nab against PF-06687234, ADA against infliximab.

- Review of bowel movement e-diary completion instructions (See Schedule of Activities).
- Review subject bowel movement e-diary data (See Section 7.3.4 and Schedule of Activities).
- Review concomitant medications/treatments.
- Dispense labeled stool container and plastic bag (for refrigerated or frozen stool sample at subsequent visit).
- Contraception check.
- Serious and non-serious adverse event monitoring.

Dosing may occur after all pre-dosing procedures are performed. For WOCBP, the urine pregnancy test must be negative prior to dosing.

- **Administer PF-06687234** or placebo as described in Section 5.5.
- Measure vital signs including sitting BP and pulse (after approximately 5 minutes of rest) and temperature (oral, tympanic or axillary). If subject experiences no safety issues then vital sign measurement should occur approximately 30 minutes post dosing.
- Monitor for AEs and ISRs. Subjects should be monitored for a minimum of 1 hour following administration of PF-06687234 or placebo.

6.2.10. Week 8 (±2 days)

There is a ±2 day window for this study visit. However, at no point during the study can consecutive IP administration be given <4 consecutive days apart. During the course of the study consecutive IP administrations within the same calendar week are not permitted on more than 3 occasions.

Prior to dosing the following procedures will be completed:

- Measure vital signs including sitting BP and pulse (after approximately 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 stool samples for the following laboratory tests:
  - Safety laboratory tests for blood chemistry, hematology, urinalysis and PT, PTT/INR;
  - Urine pregnancy test (WOCBP only);
  - PD Biomarkers: hsCRP;
  - Stool sample for fecal calprotectin;
  - Stool specimen for exploratory biomarkers (microbiome);
  - Collect other exploratory banked specimens (Prep B1.5, Prep B2.5, Prep R1).
- UC Assessment: Partial Mayo score and review subject bowel movement e-diary data (See Sections 7.3.3, 7.3.4 and Schedule of Activities).
- Review bowel movement e-diary completion instructions.
- Review concomitant medications/treatments.
- Contraception check.
- Serious and non-serious adverse event monitoring.

Dosing may occur after all pre-dosing procedures are performed. For WOCBP, the urine pregnancy test must be negative prior to dosing.

- If applicable, for subjects on an infliximab schedule of every 8 weeks:
  - Collect a trough sample and an ADA sample for infliximab 30 minutes before administration of infliximab.
  - Administer Remicade® or protocol specific infliximab biosimilar (See Appendix 5) as per instructions in relevant geographic region Remicade® or protocol specific infliximab biosimilar Package Insert and as described in Section 5.5.
- Administration of PF-06687234 or placebo should occur approximately 1 hour but not exceed 3 hours after the completion of the administration of Remicade® or protocol specific infliximab biosimilar (See Appendix 5) and as described in Section 5.5.

- Measure vital signs including sitting BP and pulse (after approximately 5 minutes of rest) and temperature (oral, tympanic or axillary). If subject experiences no safety issues then vital sign measurement should occur approximately 30 minutes post dosing.

- Monitor for AEs and ISRs. Subjects should be monitored as per local standard of care during and following administration of Remicade® or protocol specific infliximab biosimilar (See Appendix 5) and a minimum of 1 hour following administration of PF-06687234 or placebo.

6.2.11. Week 9 (±2 days)

There is a ±2 day window for this study visit. However, at no point during the study can consecutive IP administration be given <4 consecutive days apart. During the course of the study consecutive IP administrations within the same calendar week are not permitted on more than 3 occasions.

Prior to dosing the following procedures will be completed:

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

- Collect urine sample for the following laboratory tests:

  - Urine pregnancy test (WOCBP only).

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

- Review subject bowel movement e-diary data (See Section 7.3.4 and Schedule of Activities).

- Review concomitant medications/treatments.

- Contraception check.

- Serious and non-serious adverse event monitoring.

Dosing may occur after all pre-dosing procedures are performed. For WOCBP, the urine pregnancy test must be negative prior to dosing.

- **Administer PF-06687234** or placebo as described in Section 5.5.

- Measure vital signs including sitting BP and pulse (after approximately 5 minutes of rest) and temperature (oral, tympanic or axillary). If subject experiences no safety issues then vital sign measurement should occur approximately 30 minutes post dosing.

- Monitor for AEs and ISRs. Subjects should be monitored for a minimum of 1 hour following administration of PF-06687234 or placebo.

6.2.12. Week 10 (±2 days)

There is a ±2 day window for this study visit. However, at no point during the study can consecutive IP administration be given <4 consecutive days apart. During the course of the study consecutive IP administrations within the same calendar week are not permitted on more than 3 occasions.

Prior to dosing the following procedures will be completed:

- Measure vital signs including sitting BP and pulse (after approximately 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 and urine samples for the following laboratory tests:

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

  - Urine pregnancy test (WOCBP only).

- UC Assessment: Partial Mayo score and review subject bowel movement e-diary data (See Sections 7.3.3, 7.3.4 and Schedule of Activities).

- Review bowel movement e-diary completion instructions.

- Review concomitant medications/treatments.

- Dispense labeled stool container and plastic bag (for refrigerated or frozen stool sample at subsequent visit).

- Contraception check.

- Serious and non-serious adverse event monitoring.

Dosing may occur after all pre-dosing procedures are performed. For WOCBP, the urine pregnancy test must be negative prior to dosing.

- **Administer PF-06687234** or placebo as described in Section 5.5.

- Measure vital signs including sitting BP and pulse (after approximately 5 minutes of rest) and temperature (oral, tympanic or axillary). If subject experiences no safety issues then vital sign measurement should occur approximately 30 minutes post dosing.

- Monitor for AEs and ISRs. Subjects should be monitored for a minimum of 1 hour following administration of PF-06687234 or placebo.

6.2.13. Week 11 (±2 days)

There is a ±2 day window for this study visit. However, at no point during the study can consecutive IP administration be given <4 consecutive days apart. During the course of the study consecutive IP administrations within the same calendar week are not permitted on more than 3 occasions.

Prior to dosing the following procedures will be completed:

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

- Collect blood, urine and stool sample for the following laboratory tests:

  - Urine pregnancy test (WOCBP only);

  - Pre-dose PK: Serum PF-06687234 concentration sample should be collected approximately 30 minutes prior to dosing;

  - Immunogenicity: HAFAs and Nab;

  - PD Biomarkers: hsCRP;

  - Stool sample for fecal calprotectin;

  - Stool specimen for exploratory biomarkers (microbiome).

- Review bowel movement e-diary completion instructions.

- Review subject bowel movement e-diary data (See Section 7.3.4 and Schedule of Activities).

- Review concomitant medications/treatments.

- Dispense labeled stool container and plastic bag (for refrigerated or frozen stool sample at subsequent visit).

- Contraception check.

- Serious and non-serious adverse event monitoring.

Dosing may occur after all pre-dosing procedures are performed. For WOCBP, the urine pregnancy test must be negative prior to dosing.

- **Administer PF-06687234** or placebo as described in Section 5.5.
- Measure vital signs including sitting BP and pulse (after approximately 5 minutes of rest) and temperature (oral, tympanic or axillary). If subject experiences no safety issues then vital sign measurement should occur approximately 30 minutes post dosing.
- Monitor for AEs and ISRs. Subjects should be monitored for a minimum of 1 hour following administration of PF-06687234 or placebo.

6.2.14. Additional PK Sampling Week 11 (Day 78), Day 79 and Day 81

Subjects who agree and provide consent will have the following additional PK samples collected post-dosing:

- Serum PF-06687234 concentration sample collected approximately 6 hours (±15 min), 24 hours (±3 hours) and 72 hours (±7 hours).

6.2.15. Week 12 (±2 days)/Early Withdrawal Visit

For subjects who discontinue early from the double-blind period prior to Week 12 visit, the procedures scheduled for Week 12 should be performed as an early withdrawal visit as soon as possible and then subjects should enter the follow up period.

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

- Measure vital signs including sitting BP and pulse (after approximately 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.
- Complete physical examination.
- Standard 12-lead ECG (See Section 7.2.9 and Schedule of Activities).
- Collect blood, urine and stool samples for the following laboratory tests:
  - Safety laboratory tests for blood chemistry, hematology and urinalysis;
  - Urine pregnancy test (WOCBP only);
  - Stool sample for *C-Difficile;*

  - Serum for exploratory protein biomarkers;
  - Blood for gene expression profiling;
  - Blood for epigenetic testing of immune cells;
  - Collect other exploratory banked specimens (Prep B1.5, Prep B2.5, Prep R1);
  - PK: Serum PF-06687234 concentration sample should be collected;
  - Immunogenicity: HAFAs and Nab against PF-06687234.
- UC Assessments:
  - Review subject bowel movement e-Diary data;
  - Endoscopy (video flexible sigmoidoscopy or colonoscopy as preferred by the investigator);
  - 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, 7.3.4 and Schedule of Activities);
  - Geboes provided by Central Reader;
  - UCEIS provided by Central Reader;
  - Endoscopic tissue biopsies for exploratory mRNA, tissue protein, tissue concentration PF-06687234, tissue epigenetics and/or cytometry/microbiome and tissue histology (central imaging reader) (See Section 7.3.2 and Schedule of Activities).
- Review concomitant medications/treatments.
- Contraception check.
- Serious and non-serious adverse event monitoring.
- If applicable, for subjects on an infliximab dosing schedule of every 6 weeks, perform the following procedures after all other study specified procedures for the visit are completed:
  - Collect a trough sample and an ADA sample for infliximab 30 minutes before administration of infliximab;

- Administer Remicade® or protocol specific infliximab biosimilar (See Appendix 5) as per instructions in the relevant geographic region Remicade® or protocol specific infliximab biosimilar Package Insert and as described in Section 5.5;

- Measure vital signs including sitting BP and pulse (after approximately 5 minutes of rest) and temperature (oral, tympanic or axillary). If subject experiences no safety issues then vital sign measurement should occur approximately 30 minutes post dosing;

- Monitor for AEs and ISRs. Subjects should be monitored as per local standard of care during and following administration of Remicade®.

6.2.16. Week 16 Onsite Follow-up (+2 days)

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

Follow-up contact will be completed at least 28 calendar days after the last IP administration to capture any potential adverse events (see Section 8.1.4) and to confirm appropriate contraception usage (see Section 4.4.1).

The following procedures will be performed:

- Measure vital signs including sitting BP and pulse (after approximately 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.

- Complete physical examination.

- Standard 12-lead ECG (See Section 7.2.9 and Schedule of Activities).

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

  - Safety laboratory tests for blood chemistry, hematology, urinalysis and PT, PTT/INR;

  - Urine pregnancy test (WOCBP only);

  - PK: Serum PF-06687234 concentration sample should be collected;

  - Immunogenicity: HAFAs and NAbs against PF-06687234.

- Review concomitant medications/treatments.

- Contraception check.

- Serious and non-serious adverse event monitoring.

Dosing may occur after all pre-dosing procedures are performed. For WOCBP, the urine pregnancy test must be negative prior to dosing.

- If applicable, for subjects with an infliximab dosing schedule of every 8 weeks, administer Remicade® or protocol specific infliximab biosimilar (See Appendix 5) as per instructions in the relevant geographic region Remicade® or protocol specific infliximab biosimilar Package Insert and as described in Section 5.5.

- Monitor for AEs and injection site reaction (ISRs). Subjects should be monitored as per local standard of care during and following administration of Remicade® or protocol specific infliximab biosimilar (See Appendix 5).

6.2.17. If applicable, Week 18 (±2 day) for Subjects on Infliximab Dosing Every 6 Weeks

There is a ±2 day window for this study visit. Subjects may use infusion centers outside of study sites for administration of infliximab; however, they should report any AE or ISR related to infliximab infusion to the designated study site personnel.

The following procedures will be performed:

- For subjects on an infliximab dosing schedule of every 6 weeks, administer Remicade® or protocol specific infliximab biosimilar (See Appendix 5) as per instructions in the relevant geographic region Remicade® or protocol specific infliximab biosimilar Package Insert and as described in Section 5.5.

- Monitor for AEs and injection site reaction (ISRs). Subjects should be monitored as per local standard of care during and following administration of Remicade®.

6.2.18. Week 22 Telephone Contact (+2 days)

After the Week 16 visit, one telephone contact will take place within 42 days to capture any potential SAEs (see Section 8.1.4), inform subjects of their immunogenicity status and complete the study disposition CRF (Subject status). Only SAEs will be collected on the CRF at the Week 22 telephone contact.

Subjects with no detectable HAFA or NAb against the IL-10 portion of PF-06687234 will require no further follow-up beyone the Week 22 telephone contact. However, subjects with detectable HAFA or NAb against the IL-10 portion of PF-06687234 will be required to return for an onsite visit at Week 28 for repeat immunogenicity testing. If these subjects have detectable HAFA or NAb against the IL-10 portion of PF-06687234 from the immunogenicity sample collection at Week 28, they will require one additional follow-up collection 3 months after Week 28 at approximately Week 40.

Note: Unscheduled visits should be arranged when possible in the event of an SAE, hospitalization and/or surgery, specified lab abnormalities or at discretion of investigator.

6.3. Subject Withdrawal

6.3.1. Withdrawal of Consent

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

6.3.2. Lost to Follow-up

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

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

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. All attempts to contact the subject and information received during contact attempts must be documented in the subject's medical record. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire

about the reason for withdrawal, request that the subject return for a final visit, if applicable, and follow up with the subject regarding any unresolved adverse events (AEs).

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

6.4. Guidelines for Monitoring and Discontinuations

The following laboratory abnormalities require monitoring and re-testing ideally within 1 week:

- Absolute neutrophil counts <1.2 x 10^9/L (<1200/ mm^3).
- Platelet counts <100 x 10^9/L (<100,000/mm^3).
- Any single AST and/or ALT elevation ≥3 times the upper limit of normal (repeat laboratory testing should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase (GGT), PT [prothrombin time] with INR [international normalized ratio], and alkaline phosphatase), regardless of the total bilirubin. (Please note that 3 times the upper limit of normal increases in ALT, AST need confirmation on separate blood draw before undertaking thorough evaluation for liver injury).
- For women of child-bearing potential with any positive urine beta-human chorionic gonadotropin (β-hCG) test, the subject will have study drug interrupted and a serum sample submitted to the central laboratory for β-hCG testing.

Treatment with investigational product will be discontinued for:

- Serious infections defined as any infection (viral, bacterial, and fungal) requiring parenteral antimicrobial therapy, hospitalization for treatment, or meeting other criteria that require the infection to be classified as serious adverse event (See Section 7.2.1).
- Serious signs/symptoms of injection or infusion reactions (See Section 5.6).
- Two sequential absolute neutrophil counts <1.0 x 10^9/L (<1000/mm^3).
- Two sequential hemoglobin values of <8.0 g/dL; <4.96 mmol/L; <80 g/L.
- Any anemia requiring a blood transfusion.
- Two sequential platelet counts <75 x 10^9/L (<75,000/mm^3).
- Two sequential lymphocyte counts <500/mm^3; <0.5x10^9/L.

- AST or ALT elevation >8 times the upper limit of normal.
- Two sequential AST or ALT elevation ≥3 times the upper limit of normal with at least one total bilirubin value ≥2 times the upper limit of normal.
- AST or ALT elevation ≥3 times the upper limit of normal combined with any one or more of the following; new onset of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia >5%, or INR >1.5.
- Two sequential AST or ALT elevation ≥5 times the upper limit of normal, regardless of total bilirubin or accompanying signs or symptoms.
- Female subjects found to be pregnant during the study.
- At the discretion of the PI, initiation of any new treatment for UC for disease progression.
- Surgery for UC.
- Other treatment related serious or severe AEs, after consultation with the Pfizer medical monitor or designee.
- Detected neutralizing antibody to IL-10 domain of the IP during the study.

In the event that ≥2 subjects on IP develop the same AE MEDRA Preferred Term graded as severe intensity as defined in Section 8.3 or if 1 subject develops an SAE as defined in Section 8.2.3, and the event(s) are assessed as potentially causally related to the IP and not clearly related to the underlying disease process or other causes, an ad-hoc internal review committee (IRC) meeting will be convened. At this time the IRC will make recommendations to the study team. These recommendations will be to stop the study, continue with modifications or continue with the study unchanged.

In addition, the Sponsor will notify all relevant regulatory authorities that such an ad-hoc IRC has been convened and will provide case details to all relevant regulatory authorities within 15 days of making the determination to convene the IRC meeting.

For early withdrawal subjects with detectable NAb against IL-10 of PF-06687432 and HAFA during the treatment period, their immunogenicity tests will be repeated at the Follow–up visit, and approximately every three months for a maximum of 6 months from the follow-up visit until the level of NAb against the IL-10 portion of PF-06687432 and HAFA return to baseline level, or for 6 months, or stabilize at a level acceptable to the investigator and sponsor. At the discretion of the sponsor, the subjects with positive NAb against IL-10 may be tested for immunogenicity at shorter intervals (<3 months) or followed for longer than 6 months duration.

7. ASSESSMENTS

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

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

7.1. Blood Volume

Total planned blood sampling for an individual subject that completes all currently scheduled assessments through Week 16 visit is approximately 400 mL. Additional blood samples may need to be taken at times not specified in the protocol (eg, replacement of clotted or compromised specimens or repeat clinically significant out of range laboratory results).

7.2. Safety

7.2.1. Infections

A subject who experiences a serious infection as defined in Section 6.4 should be discontinued from the study. A serious infection should be reported as an SAE and should be listed as the reason for discontinuation in the CRF. All serious infections occurring during the study should undergo appropriate laboratory investigations, including culture, and the results (eg, any identified organisms or absence of growth) be recorded in the CRF.

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

7.2.2. Laboratory

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

Table 2. Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hemoglobin Hematocrit RBC count Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs) Reticulocytes (% and Abs) PT/INR/PTT	BUN/Urea and Creatinine Glucose Calcium Sodium Potassium Chloride AST, ALT Total Bilirubin Direct bilirubin[a] Alkaline phosphatase Uric acid Albumin Total protein Creatine kinase (CK) CK fractionation[b]	pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Microscopy[c]	HbA1c[e] FSH[d, e] β-hCG[f] Hepatitis B, C and HIV[e] QFT-G or other IGRA[e] hsCRP Stool sample to detect enteric infections and C. difficile toxins A and B Stool sample for fecal calprotectin Stool sample for exploratory biomarkers (microbiome) Exploratory samples (serum, plasma, blood, RNA, DNA) Colonic tissue biopsies Systemic PF-06687234 and infliximab concentrations HAFA and Nab ADA against infliximab

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. Sponsor may request spot urine protein creatinine ratio for quantification if significant proteinuria is identified.
d. In females who are amenorrheic for at least 12 consecutive months.
e. Complete at screening.
f. Serum/Urine for women of childbearing potential. Serum pregnancy test must be performed at screening. If serum pregnancy test (for WOCBP) is borderline positive, the central lab will run a FSH test to confirm menopause.

7.2.3. 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, prior to investigational product administration at the baseline visit, and at all treatment visits to confirm the subject has not become pregnant during the study, at a follow-up visit, and at the early-withdrawal visit.

A negative pregnancy test 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). Pregnancy tests may also be repeated if requested by institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations.

Urine pregnancy tests must be sensitive to at least 25 mIU/mL and will be conducted with the test kit provided by the central laboratory in accordance with instructions provided in its package insert. Subjects who have missed a menstrual period or who show an indeterminate or positive result on the urine test may not further progress in the study until pregnancy is ruled out using further diagnostic testing (eg, a negative quantitative serum pregnancy test conducted at a certified laboratory).

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

7.2.4. Purified Protein Derivative (PPD) Tuberculin Test

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

7.2.5. Interferon Gamma Release Assay Tuberculin Test

Subjects can be screened for tuberculosis using an IGRA per local guidelines. IGRA will be tested locally 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. Refer to local lab for any additional processing information and shipping instructions. Testing may be performed by the central laboratory if necessary.

7.2.6. Screening for Clostridium Difficile

C. difficile testing is performed at screening and during the study at Week 12 or early withdrawal visit.

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 local lab or central lab manual for further guidance and instruction for *C. difficile* screening.

7.2.7. 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.

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

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

The same size BP cuff, which has been properly sized and calibrated, will be used to measure BP each time. The use of automated devices for measuring BP and pulse rate 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 (°C or °F) be collected using tympanic, oral, or axillary methods and that the same method be used consistently throughout the study.

7.2.8. 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).

7.2.9. 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.

7.2.10. 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. Endoscopy

Video flexible sigmoidoscopy (with visualization to at a minimum, the splenic flexure segment) or colonoscopy should be performed within approximately 14 days of baseline, preferably 5 to 7 days prior to the baseline, to allow total Mayo score calculation. Subjects with extensive UC of at least 8 years duration, with moderate or severe active inflammation (confirmed by endoscopy or histologically) who have not had a colonoscopy within 2 years prior to baseline will be excluded. However, such subjects may be rescreened after a colonoscopy with biopsies as part of standard of care has been completed. If visualization is not adequate for either colonoscopy or sigmoidoscopy due to suboptimal bowel prep, the procedure must be repeated.

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

A video flexible sigmoidoscopy or colonoscopy (as preferred by the investigator) is also performed at the Week 12 visit or at the early withdrawal visit where applicable. Bowel preparation should be conducted as per local routine. The position of the endoscope at the Week 12 visit 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 endoscopy 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 endoscopy component should be completed at the end of the procedure to document the endoscopic subscore.

7.3.2. Biopsy Collection from Colonic Mucosa for Histology, RNA, Epigenetic, Tissue Concentration PF-06687234 and Tissue Protein

Colonic tissue biopsies will be collected at Screening, Week 12 and early withdrawal visit during the endoscopy. Jumbo 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 endoscopy procedure, 9 biopsies (2 for histology, 1 for RNA, 3 for protein analysis and 3 biopsies for epigenetic and/or cytometry/microbiome analysis) should be taken from abnormally inflamed colonic mucosa and 3 biopsies (for protein analysis including PF-06687234) should be taken from normal appearing colonic mucosa, resulting in a total of 12 biopsies from each subject, if possible. All inflamed pre-treatment biopsies should be obtained in a targeted manner from the most affected are 15-30 cm from the anal verge. During post-treatment endoscopies, samples should be obtained from approximately the same anatomic location as the baseline assessment. Frankly ulcerated areas should be avoided. For all biopsies collected, record the colonic segment and approximate distance from the anal verge for each sample in the source documents. If 12 biopsies cannot be collected during the endoscopy, then samples from inflamed tissues should be prioritized in the order of histology, RNA analysis, protein analysis/tissue

concentration PF-06687234, and epigenetic and/or cytometry/microbiome analysis. During the baseline assessment, if increased inflammation is identified further than 15-30 cm, the location should be noted in the source documents (ie, colonic segment and approximate distance from anal verge) and additional 2 biopsies should be taken for histology both before and after treatment if possible. If these 2 additional inflamed biopsies are taken for histology, then the total biopsies taken at pre and post endoscopy procedure will be 14 biopsies (11 inflamed and 3 non inflamed biopsies).

Histological, gene expression (RNA), protein analysis/tissue concentration PF-06687234 and epigenetic and/or cytometry/microbiome analysis may be conducted on the biopsy samples that are obtained. Pfizer and the central laboratory vendor will provide sites with instructions for collection, processing, and shipment of biopsy samples. These samples may be used for the evaluation of exploratory biomarkers that may include markers related to UC, Crohn's disease and/or other inflammatory conditions and/or the mechanism of action of PF-06687234. Detailed processing, storage and shipment instructions will be provided in the Lab Manual.

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 (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 (partial, modified or total see Appendix 2 and Appendix 3) will be calculated based on the subject's stool diary recorded over 3 valid days closest to and prior to the visit date, where the invalid days are either the date of bowel preparation, date of endoscopy, any date between bowel preparation and endoscopy, or the date of endoscopy plus 1 day or 2 days prior to the endoscopy bowel preparation procedure. Investigator sites will be trained on the diary usage and will train subjects on use of the diary. Diary data entered by the subject will be reviewed by the site at each visit.

If there are missing stool diary data, the average will be taken from the 3 most recently available days reported within 5 days prior or 2 or more days after the endoscopy preparation for calculation of Mayo score.

If there only 2 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.

Note: If there is 1 day of diary data or no diary data recorded prior to the baseline (Day 1), then the subject cannot be randomized into the study.

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

The endoscopic appearance will be read by the Central Reader.

The physician's global assessment (PGA) acknowledges the other three criteria, the subject's abdominal discomfort and sense of general well-being. In addition, the investigator should consider other observations (eg, physical findings) and subject's performance status when making the PGA assessment. In consequence, the PGA should be recorded after all other components of the Mayo score and relevant interval medical history and physical examination have been completed. It is preferred that the same physician performs all such assessment for a given subject throughout the study.

The traditional total Mayo score at the screening visit must be ≥4 but no more than 9, with a traditional endoscopic subscore of ≥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 14 days.

7.3.4. Subject Bowel Movement Diary

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

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

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

7.3.5. Partial Mayo Score

A partial Mayo Score (total Mayo Score excluding the endoscopic subscore, ranging from 0 to 9 see Appendix 3) will be assessed at the times specified in the Schedule of Activities section. On dosing days, the partial Mayo Score should be assessed prior to administration of the IP.

7.3.6. Geboes Score

Colon biopsies obtained during screening and Week 12 endoscopies will be submitted for expert histology review. A histological activity grading system referred to as "Geboes" which has demonstrated good reproducibility, will be utilized by a central reader and will be the basis for assessing histological changes pre and post treatment.[29]

7.3.7. Ulcerative Colitis Endoscopic Index of Severity (UCEIS)

The UCEIS is a tool designed to measure disease activity for UC. The UCEIS scoring system uses vascular pattern, bleeding and erosions/ulceration to provide an overall score of endoscopic severity.

The UCEIS will be scored by the Central Reader.

7.4. Pharmacodynamics

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

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

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

As part of understanding the pharmacodynamics of the study drug and the disease under study, samples may be used for evaluation of the bioanalytical method. These data will be used for internal (ie, Pfizer) exploratory purposes and will not be included in the clinical report.

7.4.1. Exploratory Serum Protein Biomarkers

Blood samples (10 mL) for analysis of exploratory serum biomarkers will be collected into appropriately labeled glass tubes containing no preservatives; anticoagulant or serum separator according to the times specified in the Schedule of Activities and may be analyzed. Serum should be alliquotted before storing.

7.4.2. Exploratory Biomeasurement Immune Cells

Blood samples (2 ml) for epigenetic analysis and/or cytometry of immune cells will be collected into appropriately labelled tubes containing ethylenediaminetetraacetic acid (EDTA) according to the times specified in the Schedule of Activities and may be analyzed.

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

Blood samples for determination of hsCRP will be obtained at the times specified in the Schedules of Activities and will be analyzed at the same laboratory performing the safety laboratory analyses.

7.4.4. 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 as long as the sample is collected **prior to the subject initiating the bowel preparation for endoscopy**.

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.

7.4.5. Stool Samples for Exploratory Biomarkers (Microbiome)

A stool sample for microbiome analysis will be obtained at the times specified in the Schedule of Activities. Sequencing of the DNA present in the stool will be performed. DNA generally comes from microorganisms like bacteria, viruses, fungi and parasites that may be present in the stool. During this process, some human DNA may be inadvertently sequenced, but will not be used for the final microbiome analysis. The analysis vendors will analyze the DNA contained in the stool to better understand disease activity and response to therapy.

The study site personnel will provide appropriately labeled containers and instructions to the subject on how best to collect a sufficient stool 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 as long as the sample is taken **prior to the subject initiating the bowel preparation for endoscopy**.

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.

7.5. Pharmacokinetics

7.5.1. Serum for Analysis of PF-06687234 and Serum for Analysis of Infliximab

During the study blood samples (4 mL) to provide a minimum of approximately 1.5 mL serum for pharmacokinetic analysis of PF-06687234 will be collected into appropriately labeled tubes containing K_2 edetic acid EDTA at times specified in the SOA of the protocol.

Blood samples (approximately 3 mL whole blood) to provide at least 1 mL of serum for measurement of serum infliximab concentrations will be collected at time points specified in the Schedule of Activities. PK sampling schedule may be modified based on emerging PK data.

The actual sampling times for infliximab and PF-07787234 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). The testing of the PK samples for infliximab will depend upon the sponsor's decision and the results may not be reported in the clinical study report (CSR).

As part of understanding the PK of the study drug, samples may be used for metabolite identification and/or evaluation of the bioanalytical method, as well as for other internal exploratory purposes. These data will be used for internal exploratory purposes and will not be included in the clinical report. 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. Additional PK Sampling

To characterize the PK of PF-06687234 a more extensive sampling scheme may be obtained in a subgroup of approximately 12 subjects who provide consent. For these subjects undergoing the additional PK sampling, blood samples (4 mL) to provide a minimum of approximately 1.5 mL serum for pharmacokinetic analysis of PF-06687234 will be collected into appropriately labeled tubes containing K_2 edetic acid EDTA at times specified in the SOA of the protocol. The actual sampling times for these additional PK samples 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 SOPs. As part of understanding the PK of the study drug, samples may be used for metabolite identification and/or evaluation of the bioanalytical method, as well as for other internal exploratory purposes. These data will be used for internal exploratory purposes and will not be included in the clinical report. Samples collected for this purpose will be retained in accordance with local regulations and, if not used within this timeframe, will be destroyed.

7.5.3. Shipment of Serum Samples for Analysis of PF-06687234 and Serum for Analysis of Infliximab

The shipment address and assay lab contact information for analysis of PF-06687234 (including the additional PK samples) and infliximab will be provided to the investigator site prior to initiation of the study.

7.6. Immunogenicity

7.6.1. Plasma for Analysis of Human Anti-Fusion Antibodies (HAFA), Neutralizing Antibodies (NAb) Against PF-06687234 and Anti-Drug Antibodies Against Infliximab

To characterize immunogenicity against PF-06687234, blood samples (12 mL) to provide approximately 8 mL plasma for HAFA and NAb analyses will be collected into appropriately labeled tubes containing K_2 edetic acid [ethylenediaminetetraacetic acid] (EDTA) at times specified in the SOA of the protocol.

For PF-06687234, a tiered immunogenicity testing strategy will be used: all samples that are positive will be confirmed for domain specificity. The positive samples will be further characterized in the NAb assays, if bioanalytically feasible.

Anti-drug antibody against infliximab may be tested and would require blood samples (6 ml) to provide minimum of 2 mL of serum to be collected into appropriately labeled tubes with no preservative (no anticoagulant and no serum separator gel may be used) at times specified in the SOA. The testing of these immunogenicity samples for infliximab will depend upon the sponsor's decision and the results may not be reported in the clinical study report (CSR).

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. These data will be used for internal exploratory purposes and will not be included in the CSR. Samples collected for this purpose will be retained in accordance to local regulations and if not used within this timeframe will be destroyed.

7.7. Pharmacogenomics

7.7.1. Gene Expression Analysis

Blood samples for the assessment of gene expression (mRNA analysis) will be collected in appropriately labeled PAXgene Blood RNA Tubes. Samples will be collected according to the times outlined in the Schedule of Activities. These samples may be used for the evaluation of exploratory biomarkers that may include markers related to ulcerative colitis, Crohn's disease and/or other inflammatory conditions and/or the mechanism of action of PF-06687234. These samples are for biomarker analysis and will not be used for genetic testing. Detailed processing, storage and shipment instructions will be provided in the Lab Manual.

Colon tissue biopsies will also be taken and may be used for histology, gene expression, protein analysis and epigenetic and/or cytometry/microbiome and are described in Section 7.3.2.

7.8. Banked Biospecimens

Banked biospecimens will be collected from subjects for exploratory research relating to the drug response and disease/condition under study. These collections are not typically associated with a planned assessment described in the protocol. They will be handled in a manner that protects each subject's privacy and confidentiality. Banked biospecimens will be assigned the subject's study identification code (ID) at the site. The data generated from these banked biospecimens will also be indexed by this ID. Biospecimens will be kept until destruction in facilities with access limited to authorized personnel, and biospecimen-derived data will be stored on password-protected computer systems. The key between the subject's ID and the subject's direct personally identifying information (eg, name, address) will be held at the study site. Biospecimens will be used only for the purposes described in the protocol and informed consent document; any other uses require additional ethical approval. Unless a time limitation is required by local regulations or ethical requirements, biospecimens will be stored for many years (no time limit) to allow for research in the future, including research conducted during the lengthy drug-development process and also postmarketing research. Subjects may withdraw their consent for the use of their banked biospecimens at any time by making a request to the investigator; in this case, any remaining biospecimens will be destroyed, but data already generated from the biospecimens will continue to be available to protect the integrity of existing analyses.

Unless prohibited by local regulations or ethics committee decision, a 4-mL blood genomic banked biospecimen **Prep D1 (dipotassium edetic acid [ethylenediaminetetraacetic acid] [K_2EDTA] whole-blood collection optimized for DNA analysis)** will be collected at the time specified in the Schedule of Activities section of the protocol to be retained for potential pharmacogenomic/genomic/biomarker analyses related to drug response and disease/condition under study. For example, putative safety biomarkers, drug-metabolizing enzyme genes, drug-transport protein genes, or genes thought to be related to the mechanism of drug action may be examined. The primary purpose is to examine DNA; however, the biospecimen may also be used to study other molecules (eg, RNA, proteins, and metabolites).

Additional banked biospecimens to be retained for such exploratory analyses in this study include the following:

- **Prep B1.5 (K2EDTA plasma collection optimized for biomarker/proteomic/metabonomic analysis):** A 4-mL blood biospecimen will be collected at times specified in the Schedule of Activities section of the protocol.

- **Prep B2.5 (serum collection optimized for biomarker/proteomic/metabonomic analysis):** a 4-mL blood biospecimen will be collected at times specified in the Schedule of Activities section of the protocol.

- **Prep R1 (PAXGene whole-blood collection optimized for RNA analysis):** A 2.5-mL blood biospecimen will be collected at times specified in the Schedule of Activities section of the protocol.

The banked biospecimens will be collected from all subjects unless prohibited by local regulations or IRB/EC decision.

It is possible that the use of these biospecimens may result in commercially viable products. Subjects will be advised in the informed consent document that they will not be compensated in this event.

7.8.1. Additional Research

Unless prohibited by local regulations or IRB/EC decision, subjects will be asked to indicate on the consent form whether they will allow banked biospecimens to also be used to design and conduct research in order to gain a further understanding of other diseases and to advance science, including development of other medicines for patients.

Subjects need not provide additional biospecimens for the uses described in this section; the biospecimens specified in the Banked Biospecimens section will be used. Subjects may still participate in the study if they elect not to allow their banked biospecimens to be used for the additional purposes described in this section.

8. ADVERSE EVENT REPORTING

8.1. Requirements

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

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

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

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

For each event, the investigator must pursue and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE (see the Serious Adverse Events section below). In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the CRF. In general, this will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety. Any pertinent additional information must be reported on the CT SAE Report Form; additional source documents (eg, medical records, CRF, laboratory data) are to be sent to Pfizer Safety **ONLY** upon request.

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

8.1.1. Additional Details on Recording Adverse Events on the CRF

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

8.1.2. Eliciting Adverse Event Information

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

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

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

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

8.1.4. Time Period for Collecting AE/SAE Information

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

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

8.1.4.1. Reporting SAEs to Pfizer Safety

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

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

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

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

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

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

8.1.5. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship on the CRF, and report such an assessment in accordance with the SAE reporting requirements, if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts

(evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor. If the investigator's causality assessment is "unknown but not related" to investigational product, this should be clearly documented on study records.

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

8.1.6. Sponsor's Reporting Requirements to Regulatory Authorities

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

8.2. Definitions

8.2.1. Adverse Events

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

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

Additionally, AEs may include signs and symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;

- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure.

8.2.2. Abnormal Test Findings

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

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

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

8.2.3. Serious Adverse Events

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

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

Or that is considered to be:

- An important medical event.

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

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

8.2.4. Hospitalization

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

Hospitalization does not include the following:

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

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

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for workup of a persistent pretreatment laboratory abnormality);
- Social admission (eg, subject has no place to sleep);
- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);

- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual subject.

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

8.3. Severity Assessment

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

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

8.4. Special Situations

8.4.1. Protocol-Specified Serious Adverse Events

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

8.4.2. Potential Cases of Drug-Induced Liver Injury

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

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

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

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

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

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

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

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

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

In addition to repeating measurements of AST and ALT and TBili, laboratory tests should include albumin, creatine kinase (CK), direct and indirect bilirubin, GGT, PT/INR, total bile acids, alkaline phosphatase and acetaminophen drug and/or protein adduct levels. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous

analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen (either by itself or as a co-formulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) may be warranted.

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

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

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

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

8.4.3.1. Exposure During Pregnancy

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

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

If a subject or subject's partner becomes or is found to be pregnant during the subject's treatment with the investigational product, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP supplemental form, regardless of whether an SAE has occurred. In addition, the investigator must submit information

regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) to Pfizer Safety using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP supplemental form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

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

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

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

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

8.4.3.2. Exposure During Breastfeeding

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

accord with authorized use. However, if the infant experiences an SAE associated with such a drug's administration, the SAE is reported together with the exposure during breastfeeding.

8.4.3.3. Occupational Exposure

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

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

8.4.4. Medication Errors

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

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

8.4.4.1. Medication Errors

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

Medication errors include:

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

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

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

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

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

9. DATA ANALYSIS/STATISTICAL METHODS

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

9.1. Sample Size Determination

The sample size calculation was based on the primary efficacy endpoint, proportion of subjects in clinical remission at Week 12.

It is anticipated that 22% of placebo subjects and 52% of subjects assigned to receive PF-06687234 will achieve a clinical remission rate at Week 12. The placebo rate of 22% was selected based on published literature[23] and internal meta-analysis of previous biological agents for ulcerative colitis. A sample size of 32 subjects in each treatment group (64 in total) is required to detect a treatment advantage of 30% in clinical remission with at least 80% power and a Type I error at 0.05 in a one-sided test. Assuming a 15% dropout rate, the target sample size for recruitment is 38 per group.

Treatment failure approach will be used for missing value imputation from drop out subjects, ie, subjects who have missing value for any reasons will be considered as treatment failures.

If the recruitment rate is very slow, an interim analysis for futility will be done with approximately 20% and 40% randomized subjects for 12-week treatment. Since the interim analysis is for futility only, type I error rate will not be affected.

9.2. Efficacy Analysis

The primary analysis population will be based on a modified intent to treat (mITT) analysis set, which is defined as all randomized subjects who received at least one dose of randomized treatment. A supportive analysis population will be based on a per-protocol (PP) population, which excludes those subjects who are identified as key protocol violators from mITT population. Treatment failure approach will be used for missing value imputation from the subjects who drop out.

All endpoints will be evaluated at the 0.05 level of significance level (2-sided).

9.2.1. Analysis of the Primary Endpoint

The primary objective is to establish the superiority of treatment to placebo for the primary efficacy endpoint of the proportion of subjects in clinical remission at Week 12. The primary endpoint will be analyzed using exact Chan and Zhang method.[22] The difference between treatment groups in the proportion of subjects in remission at Week 12 will be presented along with its 95% confidence interval. Subjects with missing remission data at Week 12

will be treated as treatment failure. As sensitivity analyses, the primary endpoint will also be analyzed using other methods for handling missing data which will be described in the SAP.

9.2.2. Analysis of Secondary Endpoints

The binary secondary endpoints, such as the proportion of subjects achieving endoscopic improvements or the proportion of subjects achieving clinical response, will be analyzed using the same approach as described for the primary endpoint. Subjects with missing data at Week 12 will be treated as treatment failure.

For continuous secondary endpoints that are only measured at baseline and Week 12, such as change from baseline at Week 12 in Geboes histology score will be analyzed using an analysis of covariance (ANCOVA) model with treatment group and baseline scores. For binary/continuous secondary endpoints that are measured repeatedly over time, such as proportions of subjects with partial Mayo Score of ≤2 with no individual subscore >1, will be analyzed using generalized linear mixed effect model with treatment group, visit, treatment group by visit interaction and subjects as the random effect. An unstructured covariance matrix will be assumed.

9.3. Analysis of Other Endpoints

All other continuous and binary data will be similar to the primary and secondary endpoints. The biomarker data, such as hsCRP data, fecal calprotectin data, the mean change from baseline and the corresponding confidence interval will be summarized by treatment group. Exploratory biomarkers will be summarized by dose group and may be graphically displayed; appropriate analysis may be performed as needed. The analysis population will be based on a mITT analysis set and will not account for missing values.

9.3.1. Pharmacokinetic Analysis

The PK concentration population for PF-06687234 is defined as all enrolled subjects who received at least one dose of PF-06687234 and in whom at least one concentration value is reported.

PK concentrations will be summarized and presented with summary statistics. Data permitting exploratory non-compartmental analysis of the additional PK samples may be conducted and non-compartmental PK parameters AUCτ, C_{max}, T_{max}, $t_{1/2}$, CL/F and Vz/F may be generated from these patients with additional PK sampling. Details of the non-compartmental analysis method used for this exploratory analysis will be captured in the SAP. Data permitting, concentration of PF-06687234 in the biopsy tissues will be summarized and presented with summary statistics.

A population PK model may be developed for the purpose of estimating population 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 mild to moderate 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.

Additionally, infliximab serum concentrations may be reported from all subjects enrolled in study.

9.3.2. Immunogenicity Analysis

The immunogenicity assessment population for PF-06687234 is defined as all enrolled subjects who received at least one dose of PF-06687234 with at least one post-treatment HAFA determination.

Overall incidence of development of HAFA 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 HAFA and NAb assays by time points samples would be collected. Data permitting, the impact of HAFA and NAb on PK, PD, safety and efficacy profiles may be explored.

Additionally, ADA against infliximab may be reported from all subjects enrolled in study.

9.4. Safety Analysis

All clinical AEs, SAEs, treatment emergent adverse events (TEAEs), withdrawal due to AEs, ECGs, vital signs and safety laboratory data will be reviewed and summarized on an ongoing basis in a blinded manner during the study to evaluate the safety of subjects.

The safety analysis will be based on a safety population, defined as all randomized subjects who received at least one dose of study treatment and all subjects will be analyzed according to the treatment which they actually received. 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. Demographic data, medical history, physical examination, discontinuation and incidence of development of anti-drug antibodies and neutralizing antibody will be tabulated. Safety lab parameters and vital signs will be summarized with absolute value and change from baseline. Subject listings will be produced for these safety endpoints accordingly.

9.5. Interim Analysis

Interim analysis for futility may be performed after approximately 20% (about 15 subjects) and 40% (about 30 subjects) randomized subjects for 12-week treatment period, respectively. Additional interim analysis may be conducted. If futility analysis criteria are reached, additional screening activities and enrollment/randomization will stop immediately. However, all subjects who are still participating in the active portions (treatment or follow-up periods) of the study will continue to completion.

Interim analysis results may be used for internal business decisions regarding future study planning and stopping for futility. Before any interim analysis is instigated, the details of the objectives, decision criteria, dissemination plan and method of maintaining the study blind as per Pfizer's standard operating procedures (SOPs) will be documented and approved in an internal review committee (IRC) charter. In addition, the analysis details will be documented and approved in an interim analysis SAP or final SAP.

9.6. Data Monitoring Committee (Internal Review Committee)

This study will use an internal review committee (IRC) which will be comprised of internal Pfizer experts, independent of the study team.

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

Additional information will be provided in the IRC charter.

10. QUALITY CONTROL AND QUALITY ASSURANCE

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

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

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

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

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

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

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

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

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

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

11.2. Record Retention

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

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

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

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

12. ETHICS

12.1. Institutional Review Board/Ethics Committee

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

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

12.2. Ethical Conduct of the Study

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

12.3. Subject Information and Consent

All parties will 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 numerical codes based on a numbering system provided by Pfizer in order to de-identify study subjects. The investigator site will maintain a confidential list of subjects who participated in the study, linking each subject’s numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subjects’ personal data consistent with applicable privacy laws.

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

The investigator must ensure that each study subject is fully informed about the nature and objectives of the study and possible risks associated with participation.

The investigator, or a person designated by the investigator, will obtain written informed consent from each subject before any study-specific activity is performed, unless a waiver of informed consent has been granted by an IRB/EC. The investigator will retain the original of each subject's signed consent.

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

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

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

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in a Member State

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

13.2. End of Trial in All Other Participating Countries

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

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or investigational product safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of PF-06687234 at any time.

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

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

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

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

www.clinicaltrials.gov

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

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

EudraCT

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

www.pfizer.com

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

15.2. Publications by Investigators

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

publication or other type of disclosure of the results of the study (collectively, "publication") before it is submitted or otherwise disclosed.

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

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

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

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

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

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

16. REFERENCES

1. Loftus EV et al., Clin Epi of IBD Gastroenterology 126(6):1504-1517(2004).

2. Hanauer S.B., Present, D.H., and Rubin, D.T. Emerging Issues in Ulcerative colitis and Ulcerative Proctitis. Gastroenterol Hepatol (N Y). 2009 Jun; 5(6 Suppl 15): 4–16.

3. Strik AS et al. Optimization of anti-TNF therapy in patients with Inflammatory Bowel Disease, Expert Review of Clinical Pharmacology, 2016 VOL. 9, NO. 3; 429-439.

4. Saraiva M, O'Garra A. The regulation of IL-10 production by immune cells. Nat Rev Immunol. 2010 Mar;10(3):170-81.

5. Schrieber S, Fedorak R, Nielsen O, et al. Safety and Efficacy of Human Recombinant InterLeukin-10 in Chronic Active Crohn's Disease, Gastroenterology 2000; 119:1461-1472.

6. Taxonera C, Olivares D, Mendoza JL, Diaz-Rubio M, Rey E. Need for infliximab dose intensification in Crohn's disease and ulcerative colitis. World J Gastroenterol. 2014; 20(27):9170–7.

7. Rostholder E, Ahmed A, Cheifetz AS, Moss AC. Outcomes after escalation of infliximab therapy in ambulatory patients with moderately active ulcerative colitis. Aliment Pharmacol Ther. 2012; 35(5):562–7.

8. Yamada S, Yoshino T, Matsuura M, Minami N, Toyonaga T, Honzawa Y, et al. Long-term efficacy of infliximab for refractory ulcerative colitis: results from a single center experience. BMC Gastroenterol. 2014; 14:80.

9. Panaccione R, Ghosh S, Middleton S, Marquez JR, Scott BB, Flint L, et al. SUCCESS TRIAL - Combination therapy with infliximab and azathioprine is superior to monotherapy with either agent in ulcerative colitis. Gastroenterology. 2014; 146(2):392–400.

10. Fedorak, R.N., et al., Recombinant human interleukin 10 in the treatment of patients with mild to moderately active Crohn's disease. The Interleukin 10 Inflammatory Bowel Disease Cooperative Study Group. Gastroenterology, 2000. 119(6): p. 1473-82.

11. Schreiber, S., et al., Safety and efficacy of recombinant human interleukin 10 in chronic active Crohn's disease. Crohn's Disease IL-10 Cooperative Study Group. Gastroenterology, 2000. 119(6): p. 1461-72.

12. Colombel, J.F., et al., Interleukin 10 (Tenovil) in the prevention of postoperative recurrence of Crohn's disease. Gut, 2001. 49(1): p. 42-6.

13. Asadullah, K., W. Sterry, and H.D. Volk, Interleukin-10 therapy—review of a new approach. Pharmacol Rev. 2003, 55(2): p. 241-69.

14. Tilg, H., et al., Treatment of Crohn's disease with recombinant human interleukin 10 induces the pro-inflammatory cytokine interferon gamma. Gut 2002. 50(2): p. 191-5.

15. Doll F, Schwager K, Hemmerle T, & Neri D. Murine analogues of enanercept and of F8-IL10 inhibit the progression of collagen-induced arthritis in the mouse. Arthritis Research & Therapy, 2013; 15: R138.

16. Samaan et al., An Update on Anti-TNF Agents in Ulcerative Colitis. Gastroenterol N Am. 2014; 43: p. 479-494.

17. Kim Kwang-Nam, Watanabe S, Ma Y, Thorton S, Giannini EH and Hirsch R. Viral IL-10 and Soluble TNF Receptor Act Synergistically to Inhibit Collagen Induced Arthritis Following Adenovirus Mediated Gene Transfer. J Immunol 2000;164:1576-1581.

18. Nagy Z, Karadi O, Rumi G, Rumi Jr G, Par A, Mozsik , Czirjak Z, Suto G. Crohn's disease is associated with polymorphism of CARD15/NOD2 gene in a Hungarian population. Annals of the New York Academy of Sciences, 2005; 1051:45-51.

19. Ogura Y, Bonen DK, Inohara N, Nicolae DL, Chen FF, Ramos R, Britton H, Moran T, Karaliuskas R, Duerr RH, Achkar JP, Brant SR, Bayless TM, Kirschner BS, Hanauer SB, Nunez G & Cho JH. A frameshift mutation in NOD2 associated with susceptibility to Crohn's disease. Letters to Nature, 2001, 411: 603-606.

20. Shouval DS, Ouahed J, Biswas A, Goettel JA, Horwitz BH, Klein C, Muise AM & Snapper SB. Interleukin 10 receptor signaling: master regulator of intestinal mucosal homeostasis in mice and humans. Advances in Immunology, 2014; Vol. 122, chapter 5.

21. Genovese MC, Cohen S, Moreland L, Lium D, Robbins S, Newmark R and Bekker P. Combination therapy with etanercept and anakinra in the treatment of patients with rheumatoid arthritis who have been treated unsuccessfully with methotrexate. Arthritis and Rheumatism; Vol 50:No5. May 2004. Pp 1412-1419.

22. Chan ISF., Zhang Z. Test-based exact confidence intervals for the difference of two binomial proportions. Biometrics, 1999; 55: 1201–1209.

23. Jairath V, Zou G, Parker CE, et al. Systematic review with meta-analysis: placebo rates in induction and maintenance trials of ulcerative colitis. J Crohns and Colitis 2016; 10(5): 607-618.

24. Walmsley M, Katsikis PD, Abney E, Parry S, Williams RO, Maini RN, Feldmann M. Interleukin-10 inhibition of the progression of established collagen-induced arthritis. Arthritis Rheum 1996, 39: 495-503.

25. Draft Guidance for Industry: Ulcerative Colitis Clinical Trials Endpoints. August 2016.

26. Guideline in the development of New Medicinal Products for the Treatment of Ulcerative Colitis: EMA Draft Guideline Rev. 1 (August 2016).

27. Huhn et al. Pharmacodynamics and Immunomodulatory Properties of Intravenously Administered Recombinant Human Interleukin-10 in Healthy Volunteers. Blood 1996; 87: 699-705.

28. McInnees et al. IL-10 Improves Skin Disease and Modulates Endothelial Activation and Leukocytes Effector Function in Patients with Psoriatic Arthritis. The Journal of Immunology 2001; 167: 4075-4082.

29. Geboes K.*Gut* 2000;**47**:404–409.

30. Sampson HA, Munoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: Summary Report-Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Symposium. J Allergy Clin Immunol 2006;117(2):391-97.

31. Gorski J et al. In vivo effects of interleukin-10 on human cytochrome P450 activity. Clinical Pharmacology & Therapeutics 2000; 67: 32-43.

32. Taxonera C et al. Infliximab dose escalation as an effective strategy for managing secondary loss of response in ulcerative colitis. Digestive Diseases and Sciences 2015; 60 (10): 3075-3084.

33. Cesarini M et al. Dose optimization is effective in ulcerative colitis patients losing response to infliximab:A collaborative multicentre retrospective study. Dig Liver Dis. 2014; 46(2): 135-139.

34. Yamada S et al. Long- term efficacy of infliximab for refractory ulcerative colitis: results from a single center experience. BMC Gastroenterology 2014;14 (80):1471-1480.

35. Fernández-Salazar L et al. Frequency, predictors and consequences of maintenance infliximab therapy intensification in ulcerative colitis. Rev Esp Enferm dig. 2015; 107 (9): 527-533.

36. Kornbluth A et al. Ulcerative Colitis Practice Guidelines in Adults: American College of Gastroenterology, Practice Parameters Committee. Am J Gastroenterol 2010;105:501–523.

Appendix 1. Abbreviations

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

Abbreviation	Term
ADA	Anti-drug antibodies
AE	adverse event
ALT	alanine aminotransferase
ANC	Absolute neutrophil count
ANCOVA	Analysis of covariance
5-ASA	5-aminosalicylic acid
AST	aspartate aminotransferase
AUC	Area under the curve
AZA	azathioprine
BBS	Biospecimen Banking System
BCG	Bacillus Calmette-Guerin
β-hCG	Beta-human chorionic gonadotropin
BP	Blood pressure
CD	Crohn's disease
CK	creatine kinase
C_{max}	Maximum observed concentration
CL/F	Apparent clearance
CMH	Cochran-Mantel Haenszel
CRF	case report form
CSA	clinical study agreement
CSF	cerebrospinal fluid
CSR	clinical study report
CT	Computerized tomography
CTA	clinical trial application
CTCAE	Common Terminology Criteria for Adverse Events
DILI	drug-induced liver injury
DLT	dose limiting toxicity
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DU	dispensable unit
EC	ethics committee
ECG	electrocardiogram
EDA	Extra-domain A
EDP	exposure during pregnancy
EDTA	ethylenediaminetetraacetic acid
eGFR	Estimated glomerular filtration rate
EU	European Union
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration

Abbreviation	Term
FMV	Fisrt morning void
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GDH	Glutamate dehydrogenase
GGT	Gamma-glutamyl transferase
GLP	Good Lab Practices
HAFA	Human Anti Fusion Antibody
HbA1c	Glycosylated hemoglobin
HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
HCVAb	Hepatitis C antibody
HCV	Hepatitis C virus
HEENT	Head eyes ears nose throat
HGB	hemoglobin
HIV	human immunodeficiency virus
hsCRP	high sensitivity C-reactive protein
IB	Investigator's brochure
IBD	Inflammatory bowel disease
ICD	Immune complex deposition
ICD	Informed consent document
ICH	International Conference on Harmonisation
ID	identification
IGRA	interferon gamma release assay
IHC	immunohistology
IL-10	Interleukin-10
IND	investigational new drug application
INR	international normalized ratio
IP	investigational product
IRB	institutional review board
IRC	internal review committee
IRT	interactive response technology
ISRs	Injection site reactions
IUD	intrauterine device
IUS	Intrauterine system
IV	intravenous
IWR	interactive web response
JAK	Janus kinase
JAK-STAT	Janus kinase signal transducers and activators of transcription
K_2EDTA	dipotassium ethylenediaminetetraacetic acid
LFT	liver function test
LSLV	last subject last visit
MAD	Mutual acceptance of data
MHC	Major histocompatibility complex

Abbreviation	Term
mITT	Modified intent to treat
MTD	maximum tolerated dose
MTX	methotrexate
N/A	not applicable
Nabs	neutralizing antibodies
NK	Natural killer
NOAEL	no-observed adverse effect level
OECD	Organization for economic cooperation and development
PCD	primary completion date
PCR	polymerase chain reaction
PD	Pharmacodynamics(s)
PEF	Peak expiratory flow
PFS	prefilled syringe
PGA	Physicians global assessment
PGx	Pharmacogenomics(s)
PI	principal investigator
PK	pharmacokinetic
PP	Per protocol
PPD	purified protein derivative
PT	prothrombin time
PTT	Partial thromboplastin time
PV	Peripheral venous
QFT-G	QuantiFERON
QFT-GIT	QuantiFERON – Gold In-Tube
RA	Rheumatoid arthritis
RBC	red blood cells
RCTC	rheumatology common toxicity criteria
Rh	Recombinant human
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SADR	serious adverse drug reaction
SC	subcutaneous
scFv	fully human single chain variable fragment
SOA	Schedule of activities
SOP	standard operating procedure
SRSD	single reference safety document
sTNFR-Ig	soluble tumor necrosis factor receptor immunoglobulin
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
TDM	Therapeutic drug monitoring
TEAE	Treatment emergent adverse event
$T_{½}$	Terminal half-life

Abbreviation	Term
TBili	total bilirubin
T_{max}	Time to reach maximum concentration
TNF	Tumor necrosis factor
UA	urinalysis
UC	Ulcerative colitis
UCEIS	Ulcerative Colitis Endoscopic Index of Severity
ULN	upper limit of normal
US	United States
Vz/F	Apparent volume of distribution
WBC	White blood cells
WOCBP	Women of childbearing potential
WONCBP	Women of non-childbearing 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.

Reference: Schroeder KW, Tremaine WJ and Listrup DM. NEJM 1987;24;317(26) 1625-1629.

Appendix 3. Glossary of Terms for Mayo Score Used in B7581002 Study

Traditional Total Mayo Score: 4 domains (Physicians global assessment, endoscopic, stool frequency, rectal bleeding)

Modified Total Mayo Score; 3 domains (Endoscopic, stool frequency, rectal bleeding)

Partial Mayo Score: 3 domains (Stool frequency, rectal bleeding and physicians global assessment

Traditional Endoscopic subscore - mild friability = 1, moderate or severe friability = 2

Modified Endoscopic subscore - ANY friability = 2

Appendix 4. Clinical Criteria for Diagnosing Anaphylaxis Guidance[30]

Anaphylaxis is highly likely when any <u>one</u> of the following 3 criteria are fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)

AND AT LEAST ONE OF THE FOLLOWING

   a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)

   b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)

2. Two or more of the following that occur rapidly after exposure *to a <u>likely</u> allergen for that patient* (minutes to several hours):

   c. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)

   d. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)

   e. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)

   f. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)

3. Reduced BP after exposure to *<u>known</u> allergen for that patient* (minutes to several hours):

   g. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP*

   h. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

PEF, Peak expiratory flow; *BP*, blood pressure.

*Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg + [2 X age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.

Appendix 5. Protocol Specific Infliximab Biosimilars

The following infliximab biosimilar are approved for treatment in this protocol:

1. Inflectra™
2. Remsima®

The Sponsor may add other infliximab biosimilars to the list if needed.