CLINICAL PROTOCOL

A MULTICENTER OPEN-LABEL EXTENSION STUDY TO ASSESS LONG-TERM SAFETY OF PF-00547659 IN SUBJECTS WITH ULCERATIVE COLITIS (TURANDOT II)

Compound:	PF-00547659*
Compound Name:	N/A
US IND Number:	100,222
European Clinical Trial Database (EudraCT) Number:	2012-002031-28
Protocol Number:	A7281010
Phase:	2
Principal/Coordinating Investigator:	Walter Reinisch, MD
Protocol History:	Original Protocol: 26 Jun 2012 Amendment 5: 14 Nov 2016 Amendment 4: 04 Dec 2015 Amendment 3: 24 Feb 2015 Amendment 2: 21 Mar 2013 Amendment 1: 04 Mar 2013

*Sponsorship of this study is transferred to Shire. The compound name has been modified from PF-00547659 to SHP647 (MAdCAM) or SHP647. PF-00547659 and SHP647 (MAdCAM) refer to the same compound and are interchangeable wherever they appear.

PROTOCOL SIGNATURE PAGE

Sponsor's (Shire) Approval

Signature: PPD **Date:** PPD

Prabhakar Viswanathan, MD, PhD
PPD

Investigator's Acknowledgement

I have read this protocol for Shire Study A7281010.

Title: A Multicenter, Open-label Extension Study to Assess Long-term Safety of PF-00547659 in Subjects with Ulcerative Colitis (TURANDOT II)

I have fully discussed the objective(s) of this study and the contents of this protocol with the sponsor's representative.

I understand that the information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the scientific/ethical review of the study, without written authorization from the sponsor. It is, however, permissible to provide the information contained herein to a subject in order to obtain their consent to participate.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with International Conference on Harmonisation guidelines on Good Clinical Practice and with the applicable regulatory requirements.

I understand that failure to comply with the requirements of the protocol may lead to the termination of my participation as an investigator for this study.

I understand that the sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study I will communicate my intention immediately in writing to the sponsor.

Investigator Name and Address: _____

(please hand print or type) _____

_____

Signature: _____ **Date:** _____

SUMMARY OF CHANGES FROM PREVIOUS VERSION

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **5**	**Amendment Date** **14 November 2016**	**Global/Country/Site Specific** **Global**
Description of Change and Rationale		**Section(s) Affected by Change**
Added Principal/Coordinating Investigator name; Listed prior protocol amendments		Cover page
Added footnote indicating that sponsorship of study was transferred to Shire and that the compound name has been modified from PF-00547659 to SHP647 (MAdCAM).		Cover page
Updated confidentiality statement with standard Shire language.		Cover page
Updated header to include Shire compound name.		Cover page
Updated footer from “Pfizer Confidential” to “Shire Confidential”.		Cover page
Inserted Protocol Signature page updated with Medical Monitor name consistent with Shire’s Standard Operating Procedure (SOP) for protocols		Protocol Signature Page
Inserted Emergency Contact page updated with Medical Monitor name and contact information consistent with Shire’s SOP for protocols		Emergency Contact Page
Inserted Product Quality Complaint page consistent with Shire’s SOP for protocols		Product Quality Complaint Page
Updated Sponsor from Pfizer to Shire		Globally
Updated footnote for clarity		Schedule of Activities
Updated languge citing investigator’s brochure as the most current source of overall risk/benefit assessment of PF 00547659/SHP647.		Section 1.2.6. Risk Benefit
Removed text describing the details of the contact card as Shire does not provide a help desk contact.		Section 4.3 Sponsor Qualified Medical Personnel
Clarified text describing packaging.		Section 5.2.1 Formulation and Packaging
Updated text to be consistent with Shire’s standard processes for drug storage and temperature monitoring of storage facility.		Section 5.3 Drug Storage and Drug Accountability
Updated text to be consistent with Shire’s standard processes for reporting and follow-up of pregnancies of female study participants or partners of male study participants.		Section 8.10 Exposure During Pregnancy
Updated text to be consistent with Shire’s standard processes for reporting and follow-up of serious adverse events.		Section 8.14.1 Serious Adverse Event Reporting Requirements
Updated text to be consistent with Shire’s standard timeline for posting clinical study report synopses in which identifying patient information has been redacted.		Section 15.1 Communication of Results by Shire

EMERGENCY CONTACT INFORMATION

In the event of a serious adverse event (SAE), the investigator must fax or e-mail the Shire Clinical Study Adverse Event Form for Serious Adverse Events (SAEs) and Non-serious AEs as Required by Protocol within 24 hours to Shire Global Drug Safety. Applicable fax numbers and e-mail address can be found on the form (sent under separate cover). A copy of this form must also be sent to the contract research organization (CRO)/Shire medical monitor by fax or e-mail using the details below.

PPD , MD, PhD, PPD

Email: PPD

Fax: PPD

For protocol- or safety-related issues <u>during normal business hours (8 am to 5 pm, Eastern Standard Time)</u>, the investigator must contact the Shire medical monitor:

PPD , MD, PhD, PPD

Phone: PPD

Mobile: PPD

Email: PPD

Fax: PPD

PPD , MD, PPD

Office Phone: PPD

Mobile: PPD

Email: PPD

Fax: PPD

For protocol- or safety-related issues <u>outside of normal business hours</u>, the investigator must contact the Medical monitor:

PPD , MD, PhD, PPD

Mobile: PPD

Email: PPD

PPD , MD, PPD

Office Phone: PPD

Mobile: PPD

Email: PPD

Fax: PPD

PRODUCT QUALITY COMPLAINTS

Investigators are required to report investigational product quality complaints to Shire within 24 hours. This includes any instances wherein the quality or performance of a Shire product (marketed or investigational) does not meet expectations (eg, inadequate or faulty closure, product contamination) or that the product did not meet the specifications defined in the application for the product (eg, wrong product such that the label and contents are different products). For instructions on reporting AEs related to product complaints, see Section 8.

Please use the information below as applicable to report the Product Quality Complaint:

Origin of Product Quality Complaint	**E-mail Address**
North and South America	PPD
European Union and Rest of World	PPD

Telephone numbers (provided for reference if needed):

Shire, Lexington, MA (USA)

PPD

Summary of Changes From Prior Versions

Document	Version Date	Summary of Changes

Amendment 4	04 December 2015	• Revised Risk Benefit Section 1.2.6 to reflect current available biologic treatment for subjects with inflammatory bowel disease.
		• Changed the 24-month follow-up period to a 6 month follow-up period. Specific changes include:
		  • Removing Study Weeks 148, 152, 160 and 164. Visits at study Weeks 156 and 168 remained and collection of blood samples for PK and ADA and Nab have been added to Week 156 visit.
		  • Removing the 18 month telephone follow-up. Specific protocol sections affected by the change include:
		  • Protocol Summary, Schedule of Activities, Section 3.0, Section 3.1, Section 3.2, Section 6.3, Section 6.4.1, Section 7.1, and Section 7.3.
		• Updated Section 8 of the Protocol to be consistent with current Pfizer standards.

Amendment #3	24 February 2015	• Addition of a Open Label Treatment Period 2 in which subjects will receive 75 mg PF-00547659 for an additional 18 months. Specific protocol sections changed to support this addition include:
		  • Protocol Summary, Schedule of Activities, Section 1.2.3.1, Section 3.1, Section 3.2, Section 3.3, Section 5.1, Section 5.2.3, Section 6.2.19, Section 6.2.20, Section 6.3, Section 6.4, Section 7.2, Section 7.2.1, Section 7.2.2.1, Section 7.2.2.2, Section 7.2.3, Section 7.2.4, Section 7.2.5 and Section 7.3.
		• Changed language pertaining to the feeder study to A7281009 study. Specific protocol sections affected by the change include:
		  • Protocol Summary, Section 3.0, Section 3.4. 4.1 and Section 6.1.
		• Removed language “Study drug will be stopped for discontinued Non-Responders who will then enter the follow-up period” from the Protocol Summary and Section 2.2.3.1 Efficacy.
		• Updated Protocol throughout to be consistent with current Pfizer standards, which include Section 5.1, Section 5.2.4 (now Section 8.4), Section 5.4, Section 5.5, Section 6.4, Section 7.1, and Section 15.1.
		  • Specific changes include:
		  • Legal representative revised to acceptable

		representative. • Medication Errors moved from Section 5.2.4 to Section 8.4. • Medication(s) changed to Treatment(s). • Addition of Withdraw Consent and Lost to Follow-up language. • Pregnancy testing regarding cases of a positive result. • Removed all language pertaining to Dose Escalation as results from A7281009 study did not show additional benefit 225 mg dose. Specific sections affected include the following: • Protocol Summary, Section 3.1, Section 5.6, Section 6.2.2, Section 6.2.4, Section 6.2.6, Section 6.2.8, Section 6.2.10, Section 6.2.12, Section 6.2.14 and Section 6.2.16. • Removed Figure 1 Study Schematic due to removal of Dose Escalation from study design. • Additional language added in Section 3.1 regarding guidance on Dose Interruption. • In Section 5.5.5 Oral Corticosteroid Rescue Therapy changed one additional course of oral corticosteroid rescue therapy to three additional course of oral corticosteroid rescue therapy. • Section 7.2.2.1 Complete Physical Examination clarified that the external genitalia examination is optional. • In sections 7.4.1.2., 7.4.1.3.9., and 7.4.1.4 included clarification regarding the term baseline. • Added clarification regarding definition of immediately in Section 7.5.3 Subjectr Stool Diary.
Amendment #2	21 March 2013	• Introduction of the feeder study throughout the protocol. • Updated Protocol Summary. • Updated Rationale for Discontinuing Immunosuppressive Therapy Section 1.2.2. • Updated Section 2.2.3.3 to clarify specimen collection. • Updated Approximate Number of Subjects Section 3.4. • Updated Inclusion Criteria 1 and 3 Section 4.1. • Added Sponsor Qualified Medical Personnel Section 4.3. • Removed Antidiarrheal language from Sections 5.5.1 and

		5.5.3. • Blood Sample from RNA removed from Visit 2, Section 6. • Soluble MAdCAM testing removed from Visit 2 Section 6. • JC virus DNA testing removed from Visits 2-6, 8-12, 14-18 and 20-24 Section 6. • JC virus antibody testing added to Vists 7, 13, 19, 25 and Early Withdrawal Section 6. • Updated Early Withdrawal Section 6.4. • Added footnote e to Laboratory Assessments Table 3 to include creatinine clearance calculation by central lab (C&G method). • Added JC Virus Antibody to Table 3. • Clarified JC virus sampling Section 7.4.1.6. • Updated Optional Endoscopic Biopsy Substudy Section 7.5.2. • Updated SCCAI Section 7.5.6. • Updated Exploratory Biomarkers Section 7.7.3. • Revised Adverse Event Reporting Section 8.2 to align with current protocol template • Updated Section 8.12.2 to clarify halting treatment with study medication for unexplained neurological signs or symptoms and undergoing further neurological evaluation. • Removed Pop-PK and PK/PD modeling references from Sections 9.3 and 9.4. • Updated Plasma to Serum in Section 9.4. • Removed the statement Subjects with a positive antibody status at any time during the study will be defined as having an overall positive antibody status while subjects with a negative antibody status throughout the study will be defined as having an overall negative antibody status from Section 9.5. • Minor administrative changes/corrections
Amendment #1	04 March 2013	• Updated withdrawal criteria as defined for Week 16 Section 6.2.4.

		• Revised language for Early Withdrawal Section 6.4.
Original Protocol	26 June 2012	N/A

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

Abbreviations

This is a list of abbreviations that may or may not be used in the protocol.

Abbreviation	Term
5-ASA	5-aminosalicylic acid derivative
6-MP	6-mercaptopurine
9-HPT	9-Hole Peg Test
ADA	anti-drug antibodies
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AZA	Azathioprine
BUN	blood urea nitrogen
BNP	B-type Natriuretic Peptide
CD	Crohn's Disease
CD4	Cluster of differentiation; glycoprotein on T-cell surface
CDS	Core data sheet
CNS	Central nervous system
CPK	Creatinine phosphokinase
CRF	case report form
CRP	C-reactive protein
CSR	Clinical study report
CTA	Clinical trial application
cTnI	Cardiac Troponin I
DMC	data monitoring committee
DNA	deoxyribonucleic acid
EC	Ethics committee
ECG	Electrocardiogram
ECHO	Echocardiogram
EDP	Exposure during pregnancy
ELISA	enzyme-linked immunosorbent assay
EOS	end of study
EudraCT	European Clinical Trial Database
FDA	Food and Drug Administration (US)
FS	Feeder Study
GCP	Good Clinical Practice
GDH	Glutamate Dehydrogenase
GI	Gastrointestinal
HEENT	head, eyes, ears, nose, and throat
hs-CRP	high-sensitivity C-reactive protein
IBD	inflammatory bowel disease
ICD	informed consent document
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IHC	Immunohistochemistry

This is a list of abbreviations that may or may not be used in the protocol.

Abbreviation	Term
IND	investigational new drug application
IRB	institutional review board
LSLV	Last subject last visit
MTX	Methotrexate
MS	Multiple Sclerosis
MSFC	Multiple Sclerosis Functional Composite
MSNQ	Multiple Sclerosis Neuropsychological Questionnaire
Nab	Neutralizing antibody
NT-proBNP	N-terminal B-type Natriuretic Peptide
OL/OLE	open-label/open-label extension
PCR	Polymerase Chain Reaction
PD	pharmacodynamic(s)
PhRMA	Pharmaceutical Research and Manufacturers of America
PK	Pharmacokinetic(s)
PML	Progressive Multifocal Leukoencephalopathy
POC	proof-of-concept
PRO	Patient Reported Outcome
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous, subcutaneously
SCCAI	Simple clinical colitis activity index
SDMT	Symbol Digit Modality Test
SOA	Schedules of Activities
TNF	tumor necrosis factor
T25FW	Timed 25-Foot Walk
UC	Ulcerative colitis
US	United States
ULN	upper limit of normal
WOCBP	women of childbearing potential
WONCBP	women of non-childbearing potential

PROTOCOL SUMMARY

PF-00547659 is a fully human $IgG_{2\kappa}$ anti-MAdCAM-1 monoclonal antibody that binds to human MAdCAM to reduce lymphocyte homing to the gut and GI inflammation and is under development for the treatment of Crohn's Disease (CD) and Ulcerative Colitis (UC).

PF-00547659 has been shown to block the MAdCAM pathway which decreases leukocyte homing to gut by inhibiting the key interactions between MAdCAM and the $\alpha_4\beta_7$+integrin expressed on lymphocytes. Although the selectively targeting of the MAdCAM receptors is a novel approach, the basic interference of lymphocyte homing by preventing the binding of these $\alpha_4\beta_7$+ lymphocytes to the MAdCAM receptor and the resultant efficacy in UC is well established. The main differentiation being that PF-00547659 blocks the interaction of $\alpha_4\beta_7$+ lymphocytes to the MAdCAM receptor by selectively binding to the receptor. Principal sites of the MAdCAM expression on normal tissue includes intestine, pancreas, stomach, esophagus, spleen and to a lesser extent lung, liver, and bladder but not in the central nervous system (CNS).[1] PF-00547659 also does not bind to VCAM and is therefore not expected to be effective for the treatment of Multiple Sclerosis or affect lymphocyte homing or surveillance in the CNS.

Subjects who participate in this study will have completed the A7281009 Study.

Objectives:

Primary Objective

- The primary objective of this study is to monitor the safety and tolerability of PF-00547659 during long-term treatment.

Secondary Objective

- The secondary objective is to assess pharmacokinetics and immunogenicity of PF-00547659.

Exploratory Objectives

- Exploratory objectives include an assessment of the durability of response with long-term treatment with PF-00547659 based upon Clinical Remission and Clinical Response based upon the Mayo Score performed at Week 16 in Clinical Responders from study A7281009.

- Explore relationships between PK of PF-00547659, PD and clinical endpoints.

Endpoints:

Primary Endpoint

- **Safety**
  - Frequency of on-treatment adverse events (AEs), AEs leading to withdrawal, and SAEs.

Secondary Endpoints

- **Immunogenicity**
  - Frequency of the development of anti-drug antibodies (ADAs) and neutralizing antibodies (Nabs).
- **Pharmacokinetics**
  - Serum trough concentrations of PF-00547659 via listings and plots.

Mucosal Healing

- Proportion of subjects with mucosal healing at Week 16 (defined as absolute Mayo subscore for endoscopy of 0 or 1).

Exploratory Efficacy Endpoints

- Assessment of the durability of response based upon Clinical Remission and Clinical Response based upon Total Mayo score assessed at Week 16 [28 weeks from initial dose] in subjects with a Clinical Response in study A7281009.
- Non-Responders from study A7281009 will also be assessed at Week 16 for Clinical Remission and Clinical Response.
- Assessment of Clinical Remission and Clinical Response based upon the partial Mayo Score in all subjects at Week 40, Week 92 and Week 144.
- Simple Clinical Colitis Activity Index (SCCAI) will be assessed at monthly visits.
- Partial and Mayo subscores will also be assessed.

Exploratory Pharmacodynamic Endpoints

- Blood samples will be collected prior to dosing at baseline and every 4 weeks to Week 24, Week 32 and Week 72 to measure hsCRP. Also, stool samples will be collected at the time points noted above to measure fecal calprotectin.

Exploratory Biomarkers (Blood/stool)

- Soluble MAdCAM in blood may be assessed at baseline and Week 16.
- Gene expression profiling (mRNA) in blood and protein associated with UC, inflammation and mechanism of drug activity may be assessed at baseline, Week 16 and Week 72.
- Analyses relevant to the understanding and treatment of UC may be conducted on the portion of stool samples remaining after calprotectin analysis.

- **Optional Exploratory Endoscopic Substudy:**
  - Endoscopic biopsies at Week 16 for immunohistochemistry (IHC) that may include different subsets of lymphocytes, hematopoietic cells and/or protein biomarkers and assessment of RNA transcripts associated with UC, inflammation and mechanism of drug activity (all sites).
  - Effect of PF-00547659 on mucosal healing (all sites).
  - Change in biomarkers in endoscopic biopsy specimens (at selected centers).

Study Design:

This is a multi-center Phase 2, open-label, safety extension study for the A7281009 study which evaluates PF-00547659 in subjects with moderate to severe ulcerative colitis. Subjects eligible for this study will have completed the 12-week double-blind induction period in study A7281009 and must have discontinued immunosuppressant therapy. They will then enter into the Active Treatment period which consists of two consecutive 18 month periods. The first active period is called Open Label Treatment Period 1 (Weeks 0-72). All subjects will be randomly assigned to receive either 75 mg or 225 mg subcutaneously every 4 weeks without unblinding treatment assignment from the A7281009 study, and without regard to responder status in that study.

After completion of Open Label Treatment Period 1, all subjects will be permitted to continue in Open Label Treatment Period 2 (Weeks 76-144) and will receive the 75 mg dose on a every four weeks basis for a further 18 months.

Subjects entering this study will be given assigned treatment at the baseline visit and then every 4 weeks through Week 144. After the active treatment period, the subjects will enter a 6-month follow-up period including 2 visits 3 months apart. At the last onsite visit (Week 168), subjects will undergo an End of Study visit.

In some cases, due to Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approval, regulatory-specific, or other administrative delays, a subject may rollover into this study after the 12-week induction period but no later than the first follow-up visit of the A7281009 study with sponsor approval.

Dosing

The Active Treatment Period will be comprised of Open Label Treatment Period 1 and Open Label Treatment Period 2. During Open Label Treatment Period 1 treatment of 75 mg or 225 mg SC, will be administered at baseline and then every 4 weeks through Week 72 (Visit 19). Once the Open Label Treatment Period 1 has been completed, subjects may continue for Open Label Treatment Period 2 and will be assigned to the 75 mg dose.

After the active treatment period, the subjects will enter a 6-month follow-up period. At Week 168, subjects will undergo the Final Onsite Study Visit (see Section 6.3.2).

Dose Interruption

In the event of unforeseen circumstances or life events a dose may be delayed or missed up to a period of one month. If dosing cannot be resumed, the subject should discontinue active treatment and will then undergo the Early Withdrawal procedures (Section 6.4) and enter a 6 month follow-up period which includes 2 follow-up visits each separated by 3 months. If the subject has a dose held and the reason resolves within a one month period, the subject should be dosed as soon as possible after resolution and the original study schedule should be maintained.

Early Withdrawal from OLE Treatment

Subjects may withdraw from active treatment for a variety of reasons including: serious adverse event, loss of response or withdrawal of consent among others. Subjects may be discontinued from treatment if they fail to respond. In such cases, study drug will be withdrawn, the subject will complete early withdrawal procedures (see Section 6.4), and then enter the 6-month follow-up period beginning with Visit 38 (Week 156).

Study Treatments:

Doses of PF-00547659 will be evaluated in subjects with UC. Doses will be administered following the completion of study procedures at baseline (results of laboratory evaluations for samples collected at Week 12 of A7281009 are not required prior to dosing) and then every 4 weeks (±7 Days of the Projected Visit Date) through Week 144. Subjects will have study medication administered subcutaneously in the anterolateral right or left thigh(s). Alternatively, the study drug may be injected into the deltoid area or the abdomen. Subjects assigned to receive 75 mg will get a single injection, while those assigned to receive 225 mg will get 3 injections. Location of the study drug administration should be noted in the source documentation. If there are clinical reasons why multiple injections cannot be administered in the same leg, the drug may be administered in two (2) of these locations. Location of the study drug administration should be noted in the source documentation.

Injection site and allergic reaction monitoring should be completed by a member of the study staff and observed for a period of at least 30-60 minutes (but the total duration should be determined at the discretion of the investigator).

Statistical Analysis:

Sample Size Determination

All eligible subjects, based on inclusion/exclusion criteria, from the feeder study may be enrolled. It is estimated that approximately 90% of the subjects (about 270 subjects) from study A7281009 are likely to enroll into this open label extension study A7281010. The sample size is chosen based on clinical outcome of the feeder study rather than statistical consideration.

Safety Analysis

Safety data may be reviewed and summarized on an ongoing basis as needed during the study since this is an open-label study. A set of safety summary tables will be produced to evaluate potential risks associated with the safety and tolerability of administering the study medication. All clinical AEs, SAEs, on-treatment AEs, as well as discontinuations due to AEs will be summarized with frequency and percentage. Continuous outcomes (eg, vitals, safety lab parameters, etc) will be summarized using n, mean, median, standard deviation etc. Change from baseline on selected safety endpoints may be additionally summarized. Subject listings may also be produced for these safety endpoints.

The safety endpoints will be listed and summarized in accordance with Shire Data Standards. Detailed methodologies of these analyses will be described in the SAP.

Interim Analysis

Two interim analyses (IAs) may be performed for this study when 50% of subjects from the Phase 2 study (A7281009) have been enrolled in this study (A7281010), and the last subject from the Phase 2 study (A7281009) has been enrolled in this study (A7281010). The purpose of the IAs is to provide additional data on the durability of response, remission, and safety from A7281009 to facilitate the decision-making process of initiating future studies. Summary statistics for safety, efficacy as well as subject demographics will be provided at IA. Detailed analysis will be described in the SAP.

Additional interim analyses may also be performed when it is deemed necessary to evaluate safety and efficacy during the trial.

Pharmacokinetic Analysis

Blood samples will be collected prior to dosing for analysis of plasma trough concentrations of PF-00547659. Plasma concentration data obtained from all subjects in this study will be tabulated and plotted to assess average steady state concentrations following repeat subcutaneous (SC) dosing of PF-00547659. As subjects enrolled in this study will have previously been followed in a separate protocol where more PK sampling may have been performed, the trough PK data collected from this study may be combined with data from the previous study into a single database.

Exploratory Efficacy Analysis

Descriptive statistics will be provided for the exploratory efficacy analysis. The binary endpoints such as clinical remission, clinical response will be summarized with frequency and percentage by time point; and the continuous variables will be summarized with n, mean, median, standard deviation etc. These summaries may be provided by the strata of responder status at entry based on the feeder study.

All subjects who have received at least one dose of planned investigational product in the open label extension study will be included into the exploraty efficacy analysis. Detailed methodologies of these analyses will be described in the SAP.

Exploratory Pharmacodynamic Analysis

Fecal calprotectin, hsCRP and exploratory biomarkers will be listed and summarized by visit, and change from baseline for these endpoints will also be summarized at specific time points as reported in the Schedule of Activities (SOA).

Appropriate regression models may be used to look at association between these endpoints and any covariates of clinical interests.

Data Monitoring Committee

An external Data Monitoring Committee will be in place to review the safety of subjects on an ongoing basis and to adjudicate any subjects with unexplained neurological or cardiac findings. Membership of this committee shall include at least one neurologist with expertise in Progressive Multifocal Leukencephalopahty (PML) and one cardiologist with expertise in heart failure and/or myocarditis. Work-up of such suspected PML cases will include a neurology consultation as well as an MRI scan, and a lumbar puncture, if clinically indicated. Additional procedures may be deemed necessary. Given the lack of therapeutic options for subjects who have failed at least 1 conventional therapy, PF-00547659 with its distinct mechanism of action and known safety profile appears to have a favorable Risk-Benefit profile.

Additional cardiac monitoring will be implemented in this study. Serum samples for CPK (with reflex isoenzymes), troponin I and NT-proBNP will be drawn with the safety labs. Elevation of cardiac troponin I (cTnI) >0.05 ng/mL or CPK with MB should prompt a cardiology consult. Any subject who experiences an initial on-study elevation of NTproBNP to >300 pg/mL shall have an echocardiogram and cardiology consult. All subjects who have had an echocardiogram, in whom the NTproBNP remains >124 pg/mL at the Week 144 visit, shall have a repeat echocardiogram and cardiology consultation ordered no later than the following visit. All cases of on-study elevation of NTproBNP to >300 pg/mL, elevation in cardiac troponin I (cTnI) or CK/MB or new electrocardiogram (ECG) changes will be reviewed by the DMC.

The DMC will be responsible for ongoing monitoring of safety of subjects in the study according to the Charter. The recommendations made by the DMC to alter the conduct of the study or amend the protocol will be forwarded to Shire for final decision. Shire will notify investigative sites and regulatory authorities as appropriate.

Table 1. Schedule of Activities Open Label Treatment Period 1

The Schedule of Activities table provides an overview of the protocol visits and procedures. Refer to the Study Procedures (Section 6) and Assessments (Section 7) for detailed information on each procedure and assessment required for compliance with the protocol.

Protocol Activity	Open-label Treatment Period 1																		
Study Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Study Week	0/Day 1 Baseline[a]	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72
Visit Window	±7 Days	±7 Days based on Baseline Visit																	
Enrollment Procedures																			
Informed Consent	X																		
Eligibility Assessment	X																		
Determine Responder/Non-Responder Status[r]	X																		
Open-Label Treatment Assignment	X																		
Medical Procedures																			
Vital Signs																			
Blood pressure, pulse, respirations	a	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Temperature [°C-or °F]	a	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight (lbs or kg) without shoes	a	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height (in or cm) without shoes	X																		
Complete Physical Exam	b					X					X					X			X
Targeted Physical Exam		X	X	X	X		X	X	X	X		X	X	X	X		X	X	
ECG (12-lead)	b		X		X		X		X		X		X		X		X		X
Laboratory Assessments																			
Clinical Laboratory Evaluations																			
Blood chemistry (to include cTn1 and NTproBNP), hematology, urinalysis[e]	b	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine Pregnancy test[f]	b	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Flexible Sigmoidoscopy or Colonoscopy (if recommended)[g]	b				X						X	----------							X

Protocol Activity	Open-label Treatment Period 1																		
Study Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**
Study Week	**0/Day 1 Baseline[a]**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**60**	**64**	**68**	**72**
Visit Window	±7 Days	**±7 Days based on Baseline Visit**																	
Optional Endoscopic tissue biopsy[h]	b				X														
Laboratory Pharmacodynamics																			
hs CRP	b	X	X	X	X	X	X		X										X
Soluble MAdCAM	b				X														
Stool sample for fecal calprotectin	b	X	X	X	X	X	X		X										X
Stool sample for enteric pathogens[i]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood gene expression profiling (mRNA) and proteins	b				X														X
Pharmacokinetics																			
PK blood sample collection[j]	b	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ADA and Nab	b		X		X		X				X		X				X		
Disease Activity Analysis																			
Stool Diary data[s]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Total Mayo Score[u]	b				X						X	----------							X
SCCAI	b	X	X	X		X	X	X	X	X									
Partial Mayo Score[u]		X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Trial Treatment Procedures																			
Study Drug Administration	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Confrontational Visual Fields[k]	b	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Timed 25-foot walk (T25-FW)[l]	b	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
9-hole peg test (9-HPT)[m]	b	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Symbol Digit Modality Test (SDMT)[n]	b	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
MSNQ[o]	b	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense stool specimen container and bag[t]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
JC virus DNA sample taken[p]	b						X						X						X
JC virus antibody testing	b						X						X						X
AE Assessment	X----------																		----------X

Protocol Activity	Open-label Treatment Period 1																		
Study Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Study Week	0/Day 1 Baseline[a]	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72
Visit Window	±7 Days	±7 Days based on Baseline Visit																	
Concomitant treatments	X----------X																		

Abbreviations: 9-HPT=nine hole peg test; ADA=anti-drug antibodies; AE=adverse event; cTnI=cardiac troponin I; DNA=deoxyribonucleic acid; ECG=electrocardiogram; ECHO=echocardiogram; eCRF=electronic case report form; EOS=end of study; GDH=glutamate dehydrogenase; hsCRP=high-sensitivity C-reactive protein; ICD=informed consent document; IS=immunosuppressants; MAdCAM=mucosal addressin cell adhesion molecule; MSFC=Multiple Sclerosis Functional Composite; MSNQ=Multiple Sclerosis Neuropsychological Questionnaire; Nab=neutralizing antibody; NT-proBNP=N-terminal B-type Natriuretic Peptide; PCR=polymerase chain reaction; PD=pharmacodynamic; PK=pharmacokinetic; SCCAI= Simple Clinical Colitis Activity Index; SDMT=Symbol Digit Modality Test; T25FW=timed 25-foot walk; UC=Ulcerative Colitis

a. Baseline (Day 1, Visit 1) procedures will correspond with the procedures conducted at the Week 12 (Day 84) or final visit in study A7281009. Data transferred from study A7281009 and recorded on the appropriate eCRF will be captured after the ICD is signed. The ICD for this study must be signed and dated before protocol-related procedures are performed. All baseline assessments and procedures must be completed prior to administration of the open label investigational product.
b. Responder/nonresponder analysis will be determined at the Week 12 (Day 84) or final visit of study A7281009. This determination will be made based on the Total Mayo score.
c. Vital signs (single sitting blood pressure [BP], pulse rate, and respirations [measured after 5 minute rest], temperature (oral or tympanic [ºC or ºF]), and weight (lbs or kg; measured without shoes) do not need to be repeated; however, the information must be entered into the eCRF. Source documentation supporting this data previously obtained at the Week 12 (Day 84) or final visit of the study A7281009 must be available in the subject's record for this study.
d. Baseline evaluations/assessments that were previously obtained at the Week 12 (Day 84) or final visit of study A7281009 do not need to be repeated, nor any information entered into the eCRF. Source documentation supporting this data previously obtained at the Week 12 (Day 84) or final visit of the study A7281009 must be available in the subject's record for this study. Adverse events (AEs) and concomitant treatment(s) that are continuing from study A7281009 will be recorded on the source documents and the respective AE and CM eCRFs at the baseline visit. Note: No blood or urine samples will be collected for the baseline visit of this study unless there is a need to repeat a safety laboratory test or tests.
e. To include NT-proBNP and troponin I levels for additional cardiac monitoring. ECHO and cardiology consult will be performed locally only under specified conditions. These conditions are:
    - At *baseline* visit: if NTproBNP value is >300 pg/mL if no prior ECHO.
    - At the *on-treatment visits up to Week 144*: If no prior ECHO, the first time NTproBNP is >300 pg/mL.
    - At the *Week 144 or early withdrawal* visit: If there has been any prior ECHO AND the NTproBNP is >124 pg/mL or if there has been no prior ECHO, and the NTproBNP is >300 pg/mL.
    - At the *post-week 144* visits: if there has been no prior ECHO and NTproBNP is >300 pg/mL.
f. For women of childbearing potential only. A negative urine pregnancy test result is required beginning at baseline before investigational product administration, and at all subsequent visits during the open-label treatment period, the follow-up visit, and at early withdrawal (if necessary).
g. Flexible sigmoidoscopy or Colonoscopy if recommended. Colonoscopy will be performed at Visits 11-19 for subjects undergoing routine cancer surveillance.

h. Eligible subjects will be asked if they would like to continue participation in an optional endoscopic substudy that will characterize the effect of PF-00547659 on mucosal healing and tissue biology. Participation in this part of the study will not affect participation in the main study (see Section 7.4.2).
i. 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 PCR for detection of toxin RNA are also acceptable alternatives. Refer to the lab manual for further guidance and instruction for *C. difficile* testing. This test will be mandatory for subjects who experience a disease flare and/or dose de-escalate.
j. PK samples will be collected before dosing at visits where study drug will be administered.
k. As part of the complete physical examination and targeted physical examination. A confrontation visual field test will be performed to measure overall field of vision as a basic screening tool.
l. The timed 25-foot time walk (T25-FW) test is part of the neurologic assessment and measures quantitative mobility and leg function.
m. The nine-hole peg test (9-HPT) is part of the neurologic assessment and measures upper extremity function.
n. The Symbol Digit Modality Test (SDMT) is part of the neurologic assessment and assesses cognitive functioning over time and in response to treatment. To help score the test, subjects must enter level of education completed onto the Social Status CRF page.
o. The patient-MSNQ (Multiple Sclerosis Neuropsychological Questionnaire) is part of the neurologic assessment and assesses cognitive functioning over time.
p. Samples may be stored and batched for analysis. At a minimum, baseline and end-of-study sample will be tested.
q. Responder analysis will be determined at Week 12 of study A7281009. This determination will be made based on the Total Mayo Score.
r. The subject stool diary to collect stool frequency and rectal bleeding will be collected via paper diary. Subjects will be required to enter diary data for 3 days immediately preceding the flexible sigmoidoscopy visit prior to Week 16. Should any subject be required to perform bowel preparation prior to the flexible sigmoidoscopy at Week 16, the subject should be instructed to complete the diary 1 day prior to initiating bowel preparation. Diaries to be completed by the subject will be distributed during the baseline visit [Week 12 of study A7281009 (for collection at the flexible sigmoidoscopy visit prior to Week 16)].
s. At Visits 7 and 9-17, dispense stool specimen container and bag to subjects who have had a disease flare **only**.
t. A Total Mayo Score will be calculated for subjects undergoing routine cancer surveillance at Visits 11-19. A Partial Mayo Score will be calculated for all other subjects at these visits.
u. Does not include endoscopic biopsies performed at selected centers (see Section 7.4.2). However, mucosal healing may be assessed.

SCHEDULE OF ACTIVITIES: Open Label Treatment Period 2 and Follow-Up Period

Protocol Activity	Open Label Treatment Period 2																		Follow up		Early withdrawal
																				EOS	
Study Visit	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**32**	**33**	**34**	**35**	**36**	**37**	**38**	**39**	
Study Week	**76**	**80**	**84**	**88**	**92**	**96**	**100**	**104**	**108**	**112**	**116**	**120**	**124**	**128**	**132**	**136**	**140**	**144**	**156**	**168**	
Visit Window	**±7 Days based on Baseline Visit**																				
Enrollment Procedures																					
Amendment Informed Consent	X																				
Open-Label 75 mg Treatment Assignment	X																				
Medical Procedures																					
Vital Signs																					
Blood pressure, pulse,	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight (lbs or kg) without shoes	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Targeted Physical Exam	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG (12-lead)[0]			X			X			X			X			X			X		X	X
Laboratory Assessments																					
Clinical Laboratory Evaluations																					
Blood chemistry (to include troponin I and NTproBNP), hematology, urinalysis[b]			X			X			X			X			X			X		X	X
Urine Pregnancy test[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Pharmacodynamics																					
Stool sample for enteric pathogens[d]	X----------X																				
Pharmacokinetics																					
PK blood sample collection[e]																			X		X
ADA and Nab																			X		X
Disease Activity Analysis																					
Stool Diary data	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X
SCCAI	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X
Partial Mayo Score	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Study Drug Administration	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Confrontational Visual Fields	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Timed 25-foot walk (T25-FW)[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
9-hole peg test (9-HPT)[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Protocol Activity	Open Label Treatment Period 2																		Follow up		Early withdrawal
																				EOS	
Study Visit	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**32**	**33**	**34**	**35**	**36**	**37**	**38**	**39**	
Study Week	**76**	**80**	**84**	**88**	**92**	**96**	**100**	**104**	**108**	**112**	**116**	**120**	**124**	**128**	**132**	**136**	**140**	**144**	**156**	**168**	
Visit Window	**±7 Days based on Baseline Visit**																				
Symbol Digit Modality Test (SDMT)[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
MSNQ[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
JC virus DNA sample taken							X						X					X		X	X
JC virus antibody testing							X						X					X		X	X
AE Assessment	X----------X																				
Concomitant treatments	X----------X																				
End of Study CRF[j]																				X	X

Abbreviations: 9-HPT=nine hole peg test; ADA=anti-drug antibodies; AE=adverse event; cTnI=cardiac troponin I; DNA=deoxyribonucleic acid; ECG=electrocardiogram; ECHO=echocardiogram; eCRF=electronic case report form; EOS=end of study; GDH=glutamate dehydrogenase; hsCRP=high-sensitivity C-reactive protein; ICD=informed consent document; IS=immunosuppressants; MAdCAM=mucosal addressin cell adhesion molecule; MSFC=Multiple Sclerosis Functional Composite; MSNQ=Multiple Sclerosis Neuropsychological Questionnaire; Nab=neutralizing antibody; NT-proBNP=N-terminal B-type Natriuretic Peptide; PCR=polymerase chain reaction; PD=pharmacodynamic; PK=pharmacokinetic; SCCAI= Simple Clinical Colitis Activity Index; SDMT=Symbol Digit Modality Test; T25FW=timed 25-foot walk; UC=Ulcerative Colitis

a. A single ECG will be collected starting at Week 84, every 12 weeks and at EOS (Week 168).

b. To include NT-proBNP and cTn1 levels for additional cardiac monitoring. ECHO and cardiology consult will be performed locally only under specified conditions. These conditions are:
   - At *baseline* visit: if NTproBNP value is >300 pg/mL if no prior ECHO.
   - At the *on-treatment visits up to Week 144*: If no prior ECHO, the first time NTproBNP is >300 pg/mL.
   - At the *Week 144 or early withdrawal* visit: If there has been any prior ECHO AND the NTproBNP is >124 pg/mL or if there has been no prior ECHO, and the NTproBNP is >300 pg/mL.
   - At the *post-week 144* visits: if there has been no prior ECHO and NTproBNP is >300 pg/mL.

c. For women of childbearing potential only. A negative urine pregnancy test result is required beginning at baseline before investigational product administration, and at all subsequent visits during the open-label treatment period, the follow-up visit, and at early withdrawal (if necessary).

d. A stool sample for enteric pathogens will only be collected if subject is symptomatic.

e. A serum sample for PK analysis will be collected only at the first Follow-up visit (Week 156) and/or Early withdrawal visit.

f. The timed 25-foot time walk (T25-FW) test is part of the neurologic assessment and measures quantitative mobility and leg function.

g. The nine-hole peg test (9-HPT) is part of the neurologic assessment and measures upper extremity function.

h. The Symbol Digit Modality Test (SDMT) is part of the neurologic assessment and assesses cognitive functioning over time and in response to treatment. To help score the test, subjects must enter level of education completed onto the Social Status CRF page.

i. The patient-MSNQ (Multiple Sclerosis Neuropsychological Questionnaire) is part of the neurologic assessment and assesses cognitive functioning over time.

j. Complete End of Study CRF when subjects withdraw from the study at Early withdrawal visit or when the subject completes participation in the study (Week 168).

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APPENDICES

1. INTRODUCTION

Ulcerative Colitis (UC) is a chronic, relapsing disease marked by ulceration and inflammation of the colonic mucosa and submucosa. Initially it usually involves the rectum but may extend proximally to involve a portion of or the entire colon. In the early stages hemorrhagic and erythematous tissue is observed, progressing to mucosal ulceration with purulent exudates in severe cases. The ulceration pattern is continuous and may extend the entire length of the colon. Perforation of the bowel wall causing ileus and peritonitis can occur with transmural extension of the ulceration. Bloody diarrhea with or without mucus and lower abdominal pain with periods of remission and exacerbation are the most common symptoms.

The incidence of UC in the United States (US) is 10-12 cases per 100,000 person years. It occurs more frequently in Caucasians and affects 30% more females than males. Although UC can occur at any age, the incidence peaks between 15 to 25 years and 55 to 65 years.[2] UC is a lifelong condition with a serious effect on the quality of life. Current treatment primarily consists of symptomatic management with dietary modifications, 5-aminosalicylic acid (5-ASA), opiates such as loperamide, systemic corticosteroids, immunosuppressive agents (azathioprine/6-mercaptopurine, cyclosporine), and most recently anti-tumor necrosis factor (TNF) agents. However, despite recent advances, effective pharmacological treatment is needed which will induce and maintain remission.

While colectomy cures the disease and removes the possibility of colon cancer, the long-term postoperative course may require adjustment to an ileostomy, ileoanal anastomosis, or management of the chronic inflammation of an ileoanal pouch (pouchitis). A significant number of patients are refractory or unresponsive to conventional medical therapy, in addition to those patients who need more effective and tolerable therapy to maintain remissions and avoid surgery.

1.1. Indication

PF-00547659, also referred to as SHP647 (MAdCAM) or SHP647, is a fully human $IgG_{2\kappa}$ anti-MAdCAM-1 monoclonal antibody, which is being developed by Shire as a treatment for the induction and maintenance of remission of Crohn's disease (CD) and Ulcerative Colitis (UC).

1.2. Background and Rationale

PF-00547659 is a fully human $IgG_{2\kappa}$ anti-MAdCAM-1 monoclonal antibody that binds to MAdCAM with high affinity and selectivity to reduce lymphocyte homing to the gut and GI inflammation.

The selectivity of lymphocyte homing to specialized lymphoid tissue and mucosal sites of the gastrointestinal tract is determined by the endothelial expression of the mucosal addressin cell adhesion molecule (MAdCAM). MAdCAM is a member of the immunoglobulin super family of cell adhesion molecules and is mostly expressed on the cell surface of high endothelial venules of organized intestinal lymphoid tissue such as Peyer's patches and mesenteric lymph nodes.[3] MAdCAM plays a role in gut immune surveillance, and also appears to facilitate excessive lymphocyte infiltration under conditions of chronic gastrointestinal inflammation. The $\alpha_4\beta_7^+$ integrin is the recognized ligand for MAdCAM and expression of this ligand on populations of CD4+ and CD8+ T cells that distinguishes them as unique gut homing lymphocytes.

PF-00547659 is an anti-MAdCAM monoclonal antibody with high affinity and selectivity that prevents the binding of $\alpha_4\beta_7$+ lymphocytes to MAdCAM expressing sites in the high endothelial venules of the gastrointestinal tract.

1.2.1. Study Rationale

The rationale for conducting this open-label extension (OLE) study is primarily to evaluate long-term safety of PF-00547659. This protocol also provides the opportunity for continued treatment for subjects who completed study A7281009.

1.2.2. Rationale for Discontinuing Immunosuppressive Therapy

The greatest concern for the safety of subjects receiving therapy that acts on the integrin/CAM axis of lymphocyte trafficking is the risk of progressive multifocal leukoencephalopathy (PML). This risk was first identified in subjects treated with natalizumab, an agent that targets the α4 integrin on lymphocytes and is used to treat subjects with Multiple Sclerosis (MS) or Crohn's disease.

As of January 2012, three risk factors associated with increased risk of PML have been identified: prolonged use of natalizumab (2-4 years), JC virus seropositivity, and prior therapy with immunosuppressant agents. While no data have been presented for subjects who are JC virus seronegative, the PML incidence in JC virus seropositive subjects is shown in the table below:

Estimated PML Incidence Stratified by Risk Factor[2]

	Anti-JCV Antibody Positive*	**Anti-JCV Antibody Positive***
Tysabri Exposure†	No Prior Immunosuppressant Use	Prior Immunosuppressant Use
1-24 months	<1/1,000	2/1,000
25-48 months	4/1,000	11/1,000

Notes: Based on postmarketing PML data and Tysabri use data as of September 1, 2011.
†Data beyond 4 years of treatment are limited.
* Risk in anti-JCV antibody positive patients was estimated based on the assumptions that 18% of Tysabri-treated MS patients have a history of prior immunosuppressant treatment and that 55% of Tysabri-treated MS patients are anti-JCV antibody positive.
* The anti-JCV antibody status was determined using an anti-JCV antibody test (ELISA) that has been analytically and clinically validated and is configured with detection and inhibition steps to confirm the presence of JCV-specific antibodies with a false negative rate of 3%.

The maximum duration of study drug treatment anticipated at present is 3 months for subjects who receive active drug in study A7281009 plus 18 months for those who choose to enter this open label extension study, A7281010, for a total of 21 months. Subjects receiving Tysabri who had prior immunosuppressant therapy would be expected to have a PML risk of 0.2% if they were seropositive for JC virus, while the risk in seronegative individuals is not known.

The causative infectious agent of PML is the JC virus, a polyoma virus that is asymptomatically present in the majority of adults in whom the prevalence of seropositivity increases with age.

The mechanism of increased risk for PML in subjects treated with natalizumab is not known, but may involve reduced immune surveillance of the central nervous system. The JC virus appears to cause PML only in subjects with significant immune compromise, such as that associated with HIV infection, transplant-associated immunosuppression or treated leukemia.

In order to minimize the potential risk of excessive immunosuppression in study subjects, it is important to discontinue immunosuppressant therapy. Subjects entering this OLE study, regardless of disease activity, will have discontinued all immunosuppressant therapy. Subjects entering this trial will have received 3 doses of investigational therapy, but 25% of those subjects will have received placebo in study A7281009. Since immunosuppressants were withdrawn during the previous study, there may be an increased risk of disease exacerbation in subjects who have not received any treatment with PF-00547659. Subjects will therefore be allowed to treat any disease exacerbations with oral corticosteroids for 6 months in clinically appropriate doses and durations. Immunosuppressants are not allowed in this study.

1.2.3. Dose Selection Rationale

Study A7281001, a single and multiple dose study in Ulcerative Colitis (UC) was conducted with multiple IV and 3 subcutaneous (SC) doses in 60 subjects including: Single dose from 0.03-10.0 mg/kg IV; Multiple dose 0.1-3.0 mg/kg IV; Single dose 3.0 mg/kg SC; Multiple dose 0.3 and 1.0 mg/kg SC. Results of the study indicate that PF-00547659 was well-tolerated with adverse reaction rates similar to placebo. Approximately half of the subjects received background azathioprine. There was no pattern of adverse events suggestive of increased risk of opportunistic infections or CNS effects. SAEs and adverse events (AEs) leading to withdrawal were due to exacerbations of the underlying UC unrelated to dose or treatment assignment. There was no evidence of adverse effects on laboratory parameters, electrocardiogram (ECG), vital signs, or neurological function.

Preliminary efficacy findings (Mayo Score) in the Study A7281001 were promising with higher response and remission rate for PF-00547659 as compared to Placebo; however, no dose-response relationship was observed in part due to the small sample size limitations. Results of biomarker assays (fecal calprotectin) supported the clinical findings of this study.

PF-00547659 exhibited nonlinear pharmacokinetics (PK) with higher clearance at lower doses. The PK profile can be described using a mathematic model which depicts drug-binding to MAdCAM causing nonlinear clearance of PF-00547659, also called target-mediated drug disposition (TMDD) model. Availability of pharmacokinetic data covering a wide range of doses, made possible the development of a TMDD. A population PK model adequately described the nonlinear PK of PF-00547659 in A7281001.

The two doses from study A7281009, considered most likely to be effective, 75 and 225 mg SC every 4 weeks, have been selected as the starting doses in this study. It is predicted that 75 mg SC every 4 weeks will provide >98% MAdCAM suppression in >90% of subjects over a 4-week interval. Escalation from 75 mg to 225 mg SC every 4 weeks will be allowed, at the Investigator's discretion, for subjects that experience a relapse or who have had no response by Week 8. A 225 mg SC dose is expected to provide >99% MAdCAM suppression in >90% of the population at the end of a 4-week interval.

1.2.3.1. Active Treatment Period

The Active Treatment Period will be comprised of an Open Label Treatment Period 1 (Weeks 0-72) and an Open Label Treatment Period 2 (Weeks 76-144). During the Open Label Treatment Period 1 subjects will be randomized to 75 mg or 225 mg SC starting at baseline and then every 4 weeks through Week 72 (Visit 19). After completion of the Open Label Treatment Period 1 randomized subjects will be permitted to continue to receive treatment in an Open Label Treatment Period 2 for a further 72 weeks (18 months) at a dose of 75 mg every 4 weeks through Week 144. This dose was selected based upon the results of the A7281009 study that indicated no additional benefit associated with the 225 mg dose.

1.2.4. Safety Data

1.2.4.1. Non-Clinical Safety

Non-clinical pharmacology data indicate that blockade of the MAdCAM pathway decreases leukocyte homing to the gut by inhibiting the key interaction between MAdCAM and the $\alpha_4\beta_7$ integrin expressed on lymphocytes. PF-00547659 binds to recombinant human MAdCAM with a K_D of 16.1 pM, and was shown to inhibit the adhesion of $\alpha_4\beta_7$ expressing cells (human JY, B-cell line) to human and cynomolgus MAdCAM. PF-00547659 does not bind to the closely related VCAM adhesion molecule, or Fcγ receptor, and does not stimulate the in vitro release of pro-inflammatory cytokines from human whole blood. When administered to cynomolgus monkeys, PF-00547659 caused a dose-dependent increase in blood levels of β_7^+ central memory T cells with concurrent increases in CD_4^+ β_7^+ effector and naïve cells, by presumably reducing MAdCAM-mediated lymphocyte homing to the gut.

Repeat-dose toxicity studies, dosing once every 10 days, were conducted with PF-00547659 in cynomolgus monkeys for up to 6 months. In all studies, the drug was generally well-tolerated at doses up to 100 mg/kg. The exception was one high dose female receiving 100 mg/kg in the 1-month IV study that became moribund starting on study Day 15 in the period between the second and third doses. This animal's clinical condition required euthanasia, and at post-mortem this animal was diagnosed with myocardial inflammation of unknown etiology resulting in heart failure. A recent expert diagnostic opinion on this animal suggested that myocarditis was a component of Systemic Inflammatory Response Syndrome (SIRS), triggered by ulcerative gingivitis, and not a primary myocardial inflammation. Ultimately, it was unknown whether inflammation in the heart in this single animal was related to the pharmacological activity of PF-00547659 or was the result of spontaneous disease. It is notable that myocardial inflammation in this animal was an isolated occurrence and did not occur in any other animal in this study, nor in the subsequent 1-month SC or 6-month SC and IV repeat-dose studies at doses up to 100 mg/kg. Other notable findings in repeat-dose toxicology studies included sporadic local or systemic hypersensitivity reactions such as anaphylaxis (1 animal,10 mg/kg, 1-month IV study), nonadverse self-limiting skin rash/injection site reactions (sporadic at doses of 10 mg/kg and greater across studies), and glomerulonephropathy (2 animals receiving 100 mg/kg SC in the 6-month studies). Hypersensitivity reactions were not unexpected in nonhuman primates receiving repeated large doses of foreign (ie, human) protein. For detailed summaries of the findings in the toxicology studies, please refer to Section 5.3 of the Investigator's Brochure.

1.2.5. Anticipated Risks

A total of 60 subjects have received single doses up to 10 mg/kg (24 subjects) or 3 doses of up to 3 mg/kg (36 subjects) of PF-00547659 or placebo (20 subjects) in the Phase I clinical study (A7281001) with adverse events comparable to placebo. The majority of withdrawals due to AEs or SAEs were related to lack of efficacy particularly with single or subtherapeutic doses.

Since April 2011, study drug has been under investigation for the treatment of patients with moderate to severe Crohn's disease. As of 31 March 2012, 31 subjects have entered the induction study, 11 have entered the open label extension study and 148 monthly doses of study drug have been administered. 3 subjects experienced a single episode of injection site pain or burning (2% of injections).

During the CD induction study (OPERA, A7281006) three subjects reported Serious Adverse Events (SAEs): 2 small bowel obstructions, 1 with ileus, and one subject had electrolyte abnormalities that required hospitalization. None of these was considered related to study drug. Seven subjects reported nonserious adverse events related to study drug; none of these events occurred in more than one subject. 18 subjects reported unrelated adverse events; 3 reported mild to moderate nausea and vomiting, and 2 each reported blurred vision, fever, elevated neutrophil count, flatulence, and frequent bowel movements.

In the CD Open Label Extension study (OPERA 2, A7281007) 3 subjects reported 6 SAEs, none related to study drug: worsening Crohn's disease, viral gastroenteritis, rectal hemorrhage, viral upper respiratory tract infection, tooth abscess and a urinary tract infection. One subject reported a SAE related to study drug: a left hydrocele with cellulitis that resolved without treatment. 7 subjects reported nonserious AEs related to study drug. 2 subjects reported vomiting, while the other AEs were reported only by one subject. 6 subjects reported unrelated AEs. 3 reported arthralgia, and 2 (the same 2 as in OPERA) reported blurred vision. All other AEs were reported only by single subjects.

The mechanism of action of PF-00547659, an anti-MAdCAM receptor antibody, is distinct from natalizumab in that it does not directly bind to $\alpha_4\beta_7$+ T-lymphocytes. It prevents the binding of $\alpha_4\beta_7$ + T-lymphocytes to the MAdCAM receptor but does not affect binding to ICAM or VCAM. Therefore, it is not expected to affect CNS lymphocyte surveillance. However, since the drug is early in development and due to some overlap of the mechanisms, additional prudence is warranted.

In addition to routine safety, additional surveillance will be in place to look for potential cases of Progressive Multifocal Leukoencephalopathy (PML) as a precaution due to the increased risk seen with natalizumab.[4] Subjects with unexplained neurological changes, new onset seizures, sensory or motor neuropathy, cognitive or behavior changes observed during the treatment period will undergo neurologic evaluation and if appropriate discontinue treatment and enter the follow-up period. Samples for JC virus testing will be taken every 6 months throughout the study until the final onsite visit.

The following neurological assessments will be performed monthly throughout the Open Label Treatment Period 1 and the Open Label Treatment Period 2:

- Confrontational Visual Fields will be performed as part of the physical exam.
- Timed 25-Foot Walk (T25FW).
- 9-Hole Peg Test (9-HPT).
- Symbol Digit Modality Test (SDMT-written).
- Patient-Multiple Sclerosis Neuropsychological Questionnaire (MSNQ). (Does not trigger a neurology consult (refer to Special Safety Assessments Section 7.3).

1.2.6. Risk Benefit

The subjects that roll-over into this study from A7281009 will have completed Week 12 (Day 84). These subjects have failed at least 1 conventional therapy. This open-label extension study will provide additional treatment for these subjects with limited therapeutic options.

Beyond anti-TNFs, patients with inflammatory bowel disease have limited options for biologic therapy. One agent, approved for Crohn's disease only in the US is natalizumab, which has a 0.1% (1:1000) incidence of progressive multifocal leukoencephalopathy (PML)[5] which makes it unacceptable to most subjects with Crohn's disease and their physicians.

PF-00547659, an anti-MAdCAM monoclonal antibody under investigation for the treatment of both CD and UC, provides a novel mechanism of action that is distinct from natalizumab. There is no interference with central nervous system lymphocyte surveillance since the drug binds to the MAdCAM receptor which is primarily located to venules of the GI tract and to a lesser extent lung, liver and spleen but is not present in the central nervous system. Natalizumab binds to the $\alpha_4\beta_7$+ and $\alpha_4\beta_1$+ lymphocytes and prevents their binding to MAdCAM in the GI tract. Therefore, for subjects with ulcerative colitis the efficacy may be similar. However, natalizumab also prevents these lymphocytes from binding to VCAM[6] in the choroid plexus which is responsible for its efficacy in Multiple Sclerosis.

PF-00547659 demonstrated a favorable safety profile in the Phase 1 single and multiple dose study conducted in subjects with ulcerative colitis. However, due to the limited safety database, additional precautions will be taken to ensure the safety of subjects. Subjects will not be allowed long-term co-administration with immunosuppressives since IS use has been associated with increased risk of PML in MS patients taking Tysabri. However, the type of IS used is quite different from those used in IBD and it is not known whether or not inflammatory CNS disease makes patients more prone to PML. Since subjects may have stopped immunosuppressives shortly before entering into this study, they may be at increased risk for exacerbation or flare of their ulcerative colitis, especially subjects who enroll from the placebo-treatment arm of study A7281009.

Monitoring of subjects will include standardized focused neurological assessments, and JC virus testing throughout the study and follow-up period. Any new unexplained neurological finding will trigger an immediate neurologic consultation with appropriate actions. Samples for JC virus testing will be taken every 6 months throughout the study until the final onsite visit. In addition,

an external Data Monitoring Committee will be in place to adjudicate any subjects with unexplained neurological findings.

Given the lack of therapeutic options for subjects who have failed at least 1 conventional therapy, PF-00547659 with its distinct mechanism of action and known safety profile appears to have a favorable Risk-Benefit profile. The added precautions regarding Progressive Multifocal Leukoencephalopathy (PML) are probably unnecessary but will serve to increase the confidence in PF-00547659 in future development.

Always refer to the latest version of the investigator's brochure for the overall risk/benefit assessment and the most accurate and current information regarding the drug metabolism, pharmacokinetics, efficacy and safety.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

2.1.1. Primary Objective

- The primary objective of this study is to monitor the safety and tolerability of PF-00547659 during long-term treatment.

2.1.2. Secondary Objective

- The secondary objective is to assess pharmacokinetics and immunogenicity of PF-00547659.

2.1.3. Exploratory Objectives

- Exploratory objectives include an assessment of the durability of response with long term treatment with PF-00547659 based upon Clinical Remission and Clinical Response based upon the Mayo Score performed at Week 16 in Clinical Responders from study A7281009.

- Explore relationships between PK of PF-00547659, PD and clinical endpoints.

2.2. Endpoints

2.2.1. Primary Endpoints

2.2.1.1. Safety

- Frequency of on-treatment AEs, AEs leading to withdrawal, and SAEs.

2.2.2. Secondary Endpoints

2.2.2.1. Immunogenicity

- Frequency of the development of anti-drug antibodies (ADAs) and neutralizing antibodies (Nabs).

2.2.2.2. Pharmacokinetics

- Serum trough concentrations of PF-00547659 via listings and plots.

2.2.2.3. Mucosal Healing

- Proportion of subjects with mucosal healing at Week 16 (defined as absolute Mayo subscore for endoscopy of 0 or 1).

2.2.3. Exploratory Efficacy Endpoint

2.2.3.1. Efficacy

- Assessment of the durability of response based upon Clinical Remission and Clinical Response based upon Total Mayo score assessed at Week 16 (28 weeks from initial dose) in subjects with a Clinical Response in study A7281009.

- Non-Responders from study A7281009 will also be assessed at Week 16 for Clinical Remission and Clinical Response.

- Assessment of Clinical Remission and Clinical Response based upon the partial Mayo Score in all subjects at Week 40, Week 92 and Week 144.

- Simple Clinical Colitis Activity Index (SCCAI) will be assessed at monthly visits.

- Partial and Mayo subscores will also be assessed.

Table 2. Total Mayo Score

Clinical Remission	Total Mayo Score of 2 points or lower with no individual subscore exceeding 1 point and rectal bleed subscore of 0 or 1.
Clinical Response	A decrease from baseline in Total Mayo Score by at least 3 points and at least 30% decrease in subscore for rectal bleeding of at least 1 point or absolute subscore of 0 or 1.
Relapse	In a subject who was previously in Clinical Remission, an increase in the Partial Mayo Score to >4 without evidence of enteric infection.

2.2.3.2. Exploratory Pharmacodynamic Endpoints

- Blood samples will be collected prior to dosing at baseline and every 4 weeks to Week 24, Week 32 and Week 72 to measure hsCRP. Also, stool samples will be collected at the same time points to measure fecal calprotectin.

2.2.3.3. Exploratory Biomarkers (Blood/Stool):

- Soluble MAdCAM in blood may be assessed at baseline and Week 16

- Gene expression profiling (mRNA) in blood and protein associated with UC, inflammation and mechanism of drug activity may be assessed at baseline, Week 16 and Week 72

- Analyses relevant to the understanding and treatment of UC may be conducted on the portion of stool samples remaining after calprotectin analysis.

- **Optional Exploratory Endoscopic Substudy:**

  - Endoscopic biopsies at Week 16 for immunohistochemistry (IHC) that may include different subsets of lymphocytes, hematopoietic cells and/or protein biomarkers and assessment of RNA transcripts associated with UC, inflammation and mechanism of drug activity (all sites).

  - Effect of PF-00547659 on mucosal healing (all sites).

  - Change in biomarkers in endoscopic biopsy specimens (at selected centers).

3. STUDY DESIGN

This is a multi-center Phase 2, open-label, safety extension study for the A7281009 study which evaluates PF-00547659 in subjects with moderate to severe ulcerative colitis. Subjects eligible for this study will have completed the 12-week double-blind induction period in study A7281009 and must have discontinued immunosuppressant therapy. They will then enter into the Active Treatment period which consists of two consecutive 18 month periods. The first active period is called Open Label Treatment Period 1 (Weeks 0-72). All subjects will be randomly assigned to receive either 75 mg or 225 mg subcutaneously every 4 weeks without unblinding treatment assignment from the A7281009study, and without regard to responder status in that study.

After completion of Open Label Treatment Period 1, all subjects will be permitted to continue in Open Label Treatment Period 2 (Weeks 76-144) and will receive the 75 mg dose every four weeks for a further 18 months.

After the active treatment period, the subjects will enter a 6-month follow-up period including 2 visits 3 months apart. At the last onsite visit (Week 168), subjects will undergo an End of Study visit.

In some cases, due to Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approval, regulatory-specific, or other administrative delays, a subject may rollover into this study after the 12-week induction period but no later than the first follow-up visit of Study A7281009 with sponsor approval.

3.1. Dosing

The Active Treatment Period will be comprised of Open Label Treatment Period 1 and Open Label Treatment Period 2. During the Open Label Treatment Period 1, 75 mg or 225 mg SC, will be administered at baseline and then every 4 weeks through Week 72 (Visit 19). Once the Open Label Treatment Period 1 has been completed, subjects may continue for Open Label Treatment Period 2 and will be assigned to the 75 mg dose.

After the active treatment period, the subjects will enter a 6-month follow-up period. At Week 168, subjects will undergo the Final Onsite Study Visit (see Section 6.3.2).

Dose Interruption

In the event of unforeseen circumstances or life events a dose may be delayed or missed up to a period of one month. If dosing cannot be resumed, the subject should discontinue active treatment and will then undergo the Early Withdrawal procedures (Section 6.4) and enter a 6-month follow-up period which includes 2 follow-up visits separated by 3 months. If the subject has a dose held and the reason resolves within a one month period, the subject should be dosed as soon as possible after resolution and the original study schedule should be maintained.

Early Withdrawal from OLE Treatment

Subjects may withdraw from active treatment for a variety of reasons including: serious adverse events, loss of response or widrawal of consent among others. Subjects will be discontinued from treatment, if they fail to respond. Investigational product will be withdrawn, the subject will complete early withdrawal procedures (see Section 6.4), and then enter the 6-month follow-up period beginning with Visit 38 (Week 156).

3.2. Approximate Duration of Subject Participation

Subjects will actively participate in this study for up to 43 months. This includes a 37 month treatment period and a 6 month follow-up period. Dosing of eligible subjects will begin at the baseline visit and continue every 4 weeks through Week 144. Subjects will return to the study site for visits every 4 weeks from their baseline visit (Week 0) through the treatment and follow-up periods until Visit 39 [Week 168 (End of Study visit)] unless they withdraw early.

3.3. Approximate Duration of Study

This study will be clinically complete in approximately 78 months.

3.4. Approximate Number of Subjects

All eligible subjects, based on inclusion/exclusion criteria, from the A7281009 study may be enrolled.

Approximately 331 subjects (estimated as 90% of the subjects in A7281009) are anticipated to be eligible for this study at Week 12 of study A7281009 at approximately 100 sites worldwide.

4. SUBJECT SELECTION

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

4.1. Inclusion Criteria

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

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

1. Subjects previously enrolled in study A7281009 who have completed the blinded 84-day (12-week) induction period.

2. Evidence of a personally signed and dated informed consent document indicating that the subject (or a legally acceptable representative) has been informed of all pertinent aspects of the study.

3. Male and/or female subjects between the ages of ≥18 and ≤66 years at the time of informed consent if they were previously enrolled in study A7281009.

4. All women of childbearing potential (WOCBP) as determined during the feeder study (data must be available as source documents for this study) must have a negative urine pregnancy test result at the Baseline visit and throughout the duration of this study (defined as the time of the signing of the ICD through the end of this study).

5. Male and female subjects of childbearing potential must agree to use a highly effective method of contraception throughout the duration of the study (defined as the time of the signing of the ICD through the conclusion of onsite subject participation or for approximately 6 months from the last dose of investigational product for any subject who discontinues early from the study). A subject is of childbearing potential if, in the opinion of the investigator, he/she is biologically capable of having children and is sexually active.

    - Women of childbearing potential (WOCBP) must have a negative urine pregnancy test result at baseline. WOCBP are defined as women who are biologically capable of becoming pregnant, including women who are using contraceptives or whose sexual partners are either sterile or using contraceptives.

    - Women of non-childbearing potential (WONCBP) do not require a urine pregnancy test and must meet at least one of the following criteria:

        - Have undergone hysterectomy or bilateral oophorectomy;

        - Have medically confirmed ovarian failure; or

        - Are medically confirmed to be post-menopausal (cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause).

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

4.2. Exclusion Criteria

Subjects presenting with any of the following will not be included in this study:

1. Subjects that have completed Day 84 (Week-12) of study A7281009 but have experienced serious event(s) related to the investigational product, an unstable medical condition, or any other reason, in the opinion of the investigator, would preclude entry or participation in this study.

2. Subjects who are taking any dose of AZA, 6-MP or MTX.

3. Pregnant or breastfeeding women.

4. Males and females of childbearing potential not using highly effective contraception or not agreeing to continue highly effective contraception through the conclusion of onsite subject participation or for approximately 6 months from the last dose of investigational product for any subject who discontinues early from the study).

5. Evidence of right or left heart failure based on echocardiographic assessments conducted as part of a prior study of PF-00547659.

6. Other severe acute or chronic medical or psychiatric condition 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 entry into this study.

7. Received any prohibited treatment during the feeder study that, in the opinion of the investigator, compromised the safety or efficacy of this study.

8. Planned live (attenuated) vaccination during the course of the study.

9. Planned major elective medical or surgical procedure during the course of this study.

10. Participation in other interventional studies during participation in this study.

11. The inability to complete any of the five neurological assessments without a clear explanation (eg, broken leg, sprained wrist, etc).

4.3. Sponsor 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 coordinator's manual.

5. STUDY TREATMENTS

5.1. Allocation to Treatment

This is an open-label study and the investigator's knowledge of the treatment should not influence the decision to enroll a particular subject or affect the order in which subjects are enrolled. All subjects will be assigned either 75 mg or 225 mg of the investigational product

upon study entry for the first 18 month treatment period. The allocation ratio to treatment will be 1:1. Subsequently all subjects will be assigned to the 75 mg dose for an additional 18 month treatment period.

5.2. Drug Supplies

5.2.1. Formulation and Packaging

Investigational product is packaged in the followed labeled containers: Active PF-00547659 Injection, approximately 75 mg/mL will be presented as a ready to use sterile solution in a vial.

5.2.2. Preparation and Dispensing

A pharmacist or other qualified person (eg, registered nurse with previous experience in drug preparation and withdrawing solution from sterile vials via a syringe) at the Clinical Site, will prepare each dose of investigational product according to the Dosing an Administration Instructions (DAI), supplied under a separate cover.

5.2.3. Administration

Doses of PF-00547659 (75 mg SC [and 225 mg SC, if required]) will be evaluated in subjects with UC. Doses will be administered following the completion of study procedures at baseline (results of laboratory evaluations for samples collected at Week 12 of A7281009 are not required prior to dosing) and then every 4 weeks (±7 Days of the Projected Visit Date) through Week 144. Subjects will have study medication administered subcutaneously in the anterolateral right or left thigh(s). Alternatively, the study drug may be injected into the deltoid area, or the abdomen. If there are clinical reasons why multiple injections cannot be administered in the same leg, the drug may be administered in two (2) of these locations. Location of the study drug administration should be noted in the source documentation.

Drug product will be administered according to Dosage and Administration Instructions (DAI) provided under separate cover as a 75 mg/ml solution at a maximum of 1.0 mL per injection. The administration format for a given dose for the Open Label Treatment Period 1 described in the followingtable:

Dose	75 mg	225 mg
Administration	1 injection of 1.0 mL	3 injections of 1.0 mL

The administration format for a given dose for the Open Label Treatment Period 2 is described in the below table:

Dose	75 mg
Administration	1 injection of 1.0 mL

Injection site and allergic reaction monitoring should be completed by a member of the study staff and observed for a period of at least 30-60 minutes (but the total duration should be determined at the discretion of the investigator).

Investigator directed delays in dosing due to abnormal labs or AEs should be discussed with the sponsor to determine whether the subject should remain in the study.

The investigator, or an approved representative (eg, pharmacist), will ensure that all investigational product is dispensed by qualified staff members.

5.2.4. Compliance

All doses of the investigational product will be administered under the supervision of investigator site personnel and recorded on source documents and CRFs.

5.3. Drug Storage and Drug Accountability

Storage conditions stated in the SRSD (ie, Investigator Brochure [IB], Core Data Sheet [CDS], United States Package Insert [USPI], Summary of Product Characteristics [SPC], or Local Product Document [LPD]) may be superseded by the label storage.

Investigators and site staff are reminded to ensure that thermometers are working correctly as required for proper storage of investigational products. These include thermometers for both the room storage and refrigerator storage. The sponsor must be notified immediately upon discovery of any excursion from the established range. Temperature excursions will require site investigation as to cause and remediation. The sponsor will determine the ultimate impact of excursions on the investigational product and will provide supportive documentation as necessary. Under no circumstances should the product be dispensed to subjects until the impact has been determined and the product is deemed appropriate for use by the sponsor.

All investigational product is stored in refrigerated temperatures (2-8°C) and in accordance with applicable regulatory requirements.

Unless otherwise authorized by Shire, all unallocated or drug supplies unused by the subjects must be returned to Shire or its appointed agent (eg, CRO) at the end of the clinical trial. If Shire authorizes destruction at the study site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Shire. Destruction must be adequately documented.

5.4. Prior Treatment(s)

Medication data from the A7281009 study may be used as data for this study, but these data must be included in the subject file and source documentation for this study as well. The start date, stop date, indication, total daily dose, route, and unit of all concomitant treatments including vitamins, herbals, and dietary supplements must be recorded on the appropriate CRF.

5.5. Concomitant Treatment(s)

Subjects will abstain from all concomitant treatments as described in the Exclusion Criteria section of this protocol. Medications taken after the first dose of study medication will be documented as concomitant treatments.

The start date, stop date, and indication for all concomitant treatments received will be recorded on the CRF. The start date, stop date and indication for all non-drug therapies received will be recorded on the CRF.

The start date, stop date and indication for all other concomitant treatments and/or therapies given because of an AE, from the first dose until the last scheduled onsite visit will be recorded on the CRF.

5.5.1. Steroids Taken During This Study

Any steroids taken during this study will be recorded on a separate CRF page. The CRF page will capture start and stop dates, total daily dose and unit.

5.5.2. Prohibited During This Study

- Any live (attenuated) vaccines.
- Use of AZA, 6-MP or MTX.
- Any investigational or marketed biologic immunosuppressive drugs.
- Bismuth subsalicylate products. Concomitant use of mesalamine with bismuth subsalicylate can lead to salicylate over dosage.

5.5.3. Permitted During This Study

- Mesalamine and related 5-ASA compounds.
- Oral steroids through the Week 24 visit.
- Stable doses of statins.
- Any drugs or classes of drugs not listed in the Prohibited During This Study (Section 5.5.2).

5.5.4. Tapering of Corticosteroids

Steroids should be tapered slowly per local guidelines in all subjects entering the OLE in remission or with a clinically significant response. Subjects who have not achieved a clinical response in the induction study, should begin tapering when they achieve remission or a clinically significant response and should be off steroids if possible by Week 40 (Week 16 + 24 Weeks). Subjects unable to taper should be considered treatment failures.

5.5.5. Oral Corticosteroid Rescue Therapy

Oral corticosteroids (max of 1 mg/kg) may be administered for rescue but the subjects should be tapered off steroids within 12 weeks. Similarly budesonide up to 9 mg may be used. Typically 9 mg of budesonide is given over 8 weeks and then reduced to 6 mg for 2 weeks and then 3 mg for 2 weeks and then stopped.

Alternate tapering regimens may be used as long as the duration for an individual rescue treatment does not exceed 12 weeks.

Subjects unable to taper or who relapse within 2 months should be considered treatment failures and should withdraw from active treatment and enter the follow-up phase. Similarly, if subjects require IV steroids, they will be considered treatment failures.

Beyond 2 months, three additional course of oral corticosteroid rescue therapy as described above will be allowed.

5.6. Permitted During Follow-up

Subjects may receive IV steroids and other previously prohibited rescue therapies during the follow-up period. Within 6 months of the last dose of investigational product, other immunosuppressants should be used with caution since the investigational product will still be present for up to 6 months from the last dose. Biologic therapies should not be started without discussion with the sponsor.

6. STUDY PROCEDURES

Refer to the Schedule of Activity (SOA) for a detailed list of study procedures as they should be conducted at each respective visit.

6.1. Visit 1, Baseline

Visit 1, Baseline for this study refers to the Week-12 visit date of the A7281009 study. Therefore, Week 12 visit date of the A7281009 study = Visit 1, Baseline of A7281010.

Most evaluations/assessments obtained at the Week-12 visits of the A7281009 study, will serve as baseline evaluations in this extension study and will not need to be repeated or entered into the eCRFs. No blood or urine samples will be collected for the baseline visit of this study unless there is a need to repeat a safety laboratory test or tests. Source documentation supporting data from evaluations/assessments from the previous studies may be used as data for the Baseline visit in this study, but this data must be included in the subject file and source documentation for this study.

The ICD for this study must be signed and dated before protocol-related procedures are performed. Data transferred from the feeder study and recorded on the appropriate CRF will be captured after the ICD is signed. All baseline procedures and tests that must be completed at this visit must be completed prior to administration of the open-label investigational product.

The following procedures will be performed at the Baseline visit of this study:

- Informed consent: to participate in the study, subjects must meet all of the inclusion criteria and none of the exclusion criteria. This study begins with the signing and dating of the ICD.

- Eligibility Assessment.

- Responder/Non-responder determination for subjects entering from study A7281009 – Responder/Non-Responder analysis will be determined at the final visit (Week 12) of study A7281009. This determination will be made based on the Total Mayo score.

- Open-Label Treatment assignment.

- Height (in or cm) (measured without shoes) (see Section 7.2.1) will also be measured.

- Drug dispensing: administer SC PF-00547659 to subject as described in the Study Drug and Administration (Section 5.2.2, 5.2.3 and SOA). **After all eligibility criteria have been confirmed and other baseline procedures and tests are completed. Observe for injection site and allergic reactions for a period of at least 30-60 minutes (but total duration should be determined at the discretion of the investigator).**

- Dispense labeled stool container and plastic bag to subject to provide a refrigerated or frozen stool specimen at the subsequent visit.

- Dispense paper stool diaries (See Section 7.4.3, Appendix 3 and the SOA).

- Monitoring of adverse events: as described in the Adverse Event, Serious Adverse Event Recording and Reporting Sections (see Section 8.14.1 and the SOA). AEs that are continuing from the previous study will be recorded on the source documents and the AE CRF at the baseline visit for this study.

- Concomitant treatment and/or therapies and medications: as described in the Concomitant Medications Sections (see Section 5.5 and the SOA). Concomitant treatment(s) continuing from the previous study will be recorded on the source documents and the appropriate CM CRF at the baseline visit for this study.

- Vital signs and temperature: single sitting blood pressure (BP), pulse rate, and respirations (measured after 5 minute rest), temperature (oral or tympanic [°C or °F]) and weight (lbs or kg) (measured without shoes) will be conducted at the Week 12 visit in study A7281009, therefore, do not need to be repeated. However, this information must be entered into the eCRF and the source documents supporting this data must be available in the subject's record for this study.

The following data will be transferred from the Day 84 (Week 12) visit of Study A7281009:

- Complete physical examination: To include confrontational visual fields for neurologic assessment (see Section 7.2.2.1).

- Single, standard 12-lead electrocardiogram (see Section 7.2.3).

- Laboratory testing: blood chemistry to include cTnI and NTproBNP, hematology and urinalysis (see Section 7.2.5 and the SOA).

Note: if NTproBNP >300 pg/mL order repeat NTproBNP, echocardiogram (ECHO) and cardiology consult prior to Visit 2 unless there has already been an ECHO and cardiology consult for NTproBNP >300 pg/mL during the prior study of PF-00547659.

- Urine pregnancy test (see Section 7.2.5 and Table 3).

- Peripheral blood gene expression profiling (mRNA) and proteins associated with UC, inflammation and mechanism of drug activity (see Section 7.4 and SOA).

- Optional endoscopicbiopsy to assess RNA transcripts and proteins associated with UC, inflammation and mechanism of drug activity (see Section 7.4.2 and the SOA).

- Flexible sigmoidoscopy or colonoscopy (if preferred).

- Calculation of total Mayo Score (includes flexible sigmoidoscopy or colonoscopy results, stool frequency, rectal bleeding, and physician's global assessment) (see Section 7.4, Appendix 1, and SOA).

- Complete SCCAI (see Section 7.4, Appendix 2, and SOA).

- Laboratory Pharmacodynamics: hsCRP, Soluble MAdCAM, and stool sample for fecal calprotectin (see SOA and Section 7.6).

- Pharmacokinetics: PF-00547659 and ADAs (see SOA and Section 7).

- Neurological Assessments: Timed 25-Foot Walk (T25FW), 9-Hole Peg Test (9-HPT), Symbol Digit Modality Test (SDMT), and Multiple Sclerosis Neuropsychological Questionnaire (MSNQ) (see Section 7.3.1 and SOA).

- JC virus deoxyribonucleic acid (DNA) testing (see Section 7.3.1.6 and SOA).

- JC virus Antibody testing (see Section 7.3.1.6 and SOA).

6.2. Study Period

6.2.1. Visit 2, Week 4 (±7 Days of the Projected Visit Date)

The following procedures will be performed at this visit:

- Vital signs and temperature: single sitting blood pressure, pulse rate, respiratory rate (after 5 minute rest), and temperature (oral or tympanic [°C or °F]); weight (lbs or kg) (see Section 7.2.1).

- Review ECHO/Cardiology consult if applicable (see Section 7.2.4 and SOA).

- Targeted physical examination: To include confrontational visual fields for neurologic assessment (see Section 7.2.2.2).

- Laboratory testing: blood chemistry to include cTnI and NTproBNP, hematology and urinalysis (see Section 7.2.5 and the SOA).

Note: if NTproBNP >300 pg/mL order repeat NTproBNP, ECHO and cardiology consult prior to Visit 3 unless there has already been an ECHO and cardiology consult for NTproBNP >300 pg/mL.

- Urine pregnancy test (see Section 7.2.5 and Table 3).

- Partial Mayo Score (see Section 7.4, Appendix 1 and SOA).

- Complete SCCAI (see Section 7.4, Appendix 2, and SOA).

- Complete Stool Diary (see Section 7.4, Appendix 3, and SOA).

- Drug dispensing: administer the appropriate dose of SC PF-00547659 to subject as described in the Study Drug and Administration (Section 5.2.2 and 5.2.3). **Observe for injection site and allergic reactions for a period of at least 30-60 minutes (but total duration should be determined at the discretion of the investigator).**

- Dispense labeled stool container and plastic bag to subject to provide a refrigerated or frozen stool specimen at the subsequent visit.

- Pharmacokinetics: PF-00547659 (see SOA, Section 7.5).

- Laboratory Pharmacodynamics: hsCRP, and stool sample for fecal calprotectin (see SOA and Section 7.6).

- Neurological Assessments: Timed 25-Foot Walk (T25FW), 9-Hole Peg Test (9-HPT), Symbol Digit Modality Test (SDMT), and Multiple Sclerosis Neuropsychological Questionnaire (MSNQ) (see Section 7.3.1 and SOA).

- Monitoring of adverse events: as described in the Adverse Event, Serious Adverse Event Recording and Reporting Sections (see Section 8.14.1 and the SOA).

- Concomitant treatment and/or therapies and medications: as described in the Concomitant Medications Sections (see Section 5.5 and the SOA).

6.2.2. Visit 3, Week 8 (±7 Days of the Projected Visit Date)

At this visit, the serum samples for PK, ADAs and Nabs, and PD biomarkers must be collected prior to investigational product administration. Disease activity should also be reviewed to establish each subject's response and relapse status.

The following procedures will be performed at this visit:

- Vital signs and temperature: single sitting blood pressure, pulse rate, respiratory rate (after 5 minute rest), and temperature (oral or tympanic [°C or °F]); weight (lbs or kg) (see Section 7.2.1).
- Review ECHO/Cardiology Consult if applicable (see Section 7.2.4).
- Targeted physical examination: To include confrontational visual fields for neurologic assessment (see Section 7.2.2.2).
- Single, standard 12-lead electrocardiogram (see Section 7.2.3).
- Laboratory testing: blood chemistry to include cTnI and NTproBNP, hematology and urinalysis. (see Section 7.2.5 and SOA).

Note: if NTproBNP >300 pg/mL order repeat NTproBNP, ECHO and cardiology consult prior to Visit 4 unless there has already been an ECHO and cardiology consult for NTproBNP >300 pg/mL.

- Pharmacokinetics: PF-00547659, ADAs and Nabs (see Section 7 and SOA).
- Urine pregnancy test (see Section 7.2.5 and Table 3).
- Laboratory Pharmacodynamics: hsCRP and stool sample for fecal calprotectin (see SOA and Section 7.6).
    - Partial Mayo Score (see Section 7.4, Appendix 1 and SOA).
    - Complete SCCAI (see Section 7.3, Appendix 2, and SOA).
    - Complete Stool Diary (see Section 7.3, Appendix 3, and SOA).
    - Collect stool sample for enteric pathogens (see Section 7.3.2).
- Drug dispensing: administer the appropriate dose of SC PF-00547659 to subject as described in the Investigational Product Administration section of this protocol (see Sections 5.2.2 and 5.2.3). **Observe for injection site and allergic reactions for a period of at least 30-60 minutes (but total duration should be determined at the discretion of the investigator).**

- Neurological Assessments: Timed 25-Foot Walk (T25FW), 9-Hole Peg Test (9-HPT), Symbol Digit Modality Test (SDMT), and Multiple Sclerosis Neuropsychological Questionnaire (MSNQ) (see Section 7.3.1 and SOA).

- Dispense labeled stool container and plastic bag to subject to provide a refrigerated or frozen stool specimen at the subsequent visit.

- Monitoring of adverse events: as described in the Adverse Event, Serious Adverse Event Recording and Reporting Sections (see Section 8.14.1 and the SOA).

- Concomitant treatment and/or therapies and medications: as described in the Concomitant Medications Sections (see Section 5.5 and the SOA).

6.2.3. Visit 4, Week 12 (±7 Days of the Projected Visit Date)

The following procedures will be performed at this visit:

- Vital signs and temperature: single sitting blood pressure, pulse rate, respiratory rate (after 5 minute rest), and temperature (oral or tympanic [°C or °F]); weight (lbs or kg) (see Section 7.2.1).

- Review ECHO/Cardiology Consult if applicable (see Section 7.2.4 and SOA)

- Targeted physical examination: To include confrontational visual fields for neurologic assessment (see Section 7.2.2.2).

- Laboratory testing: blood chemistry to include cTnI and NTproBNP, hematology and urinalysis (see SOA and Section 7.2.5).

  Note: if NTproBNP >300 pg/mL order repeat NTproBNP, ECHO and cardiology consult prior to Visit 5 unless there has already been an ECHO and cardiology consult for NTproBNP >300 pg/mL.

- Urine pregnancy test (see Section 7.2.5 and Table 3).

- Pharmacokinetics: PF-00547659 (see SOA, and Section 7.5).

- Laboratory Pharmacodynamics: hsCRP and stool sample for fecal calprotectin (see SOA and Section 7.6).

- Partial Mayo Score (see Section 7.4, Appendix 1 and SOA).

- Complete SCCAI (see Section 7.4, Appendix 2, and SOA).

- Complete Stool Diary (see Section 7.4, Appendix 3, and SOA).

- Collect stool sample for enteric pathogens (see Section 7.3.2).

- Drug dispensing: administer the appropriate dose of SC PF-00547659 to subject as described in the Investigational Product Administration section of this protocol (see Sections 5.2.2 and 5.2.3). **Observe for injection site and allergic reactions for a period of at least 30-60 minutes (but total duration should be determined at the discretion of the investigator).**

- Dispense labeled stool container and plastic bag to subject to provide a refrigerated or frozen stool specimen at the subsequent visit.

- Neurological Assessments: Timed 25-Foot Walk (T25FW), 9-Hole Peg Test (9-HPT), Symbol Digit Modality Test (SDMT), and Multiple Sclerosis Neuropsychological Questionnaire (MSNQ) (see Section 7.3.1 and SOA).

- Monitoring of adverse events: as described in the Adverse Event, Serious Adverse Event Recording and Reporting Sections (see Section 8.14.1 and the SOA).

- Concomitant treatment and/or therapies and medications: as described in the Concomitant Medications Sections (see Section 5.5 and the SOA).

6.2.4. Visit 5, Week 16 (±7 Days of the Projected Visit Date)

At this visit, the serum samples for PK, ADAs and Nabs, and PD biomarkers must be collected prior to investigational product administration. Disease activity should also be reviewed to establish each subject's relapse status and/or treatment failure.

The following procedures will be performed at this visit:

- Vital signs and temperature: single sitting blood pressure, pulse rate, respiratory rate (after 5 minute rest), and temperature (oral or tympanic [°C or °F]); weight (lbs or kg) (see Section 7.2.1).

- Review ECHO/Cardiology Consult if applicable (see Section 7.2.4).

- Targeted physical examination: To include confrontational visual fields for neurologic assessment (see Section 7.2.2.2).

- Single, standard 12-lead electrocardiogram (see Section 7.2.3).

- Laboratory testing: blood chemistry to include cTnI and NTproBNP, hematology and urinalysis (see Section 7.2.5 and SOA).

  Note: if NTproBNP >300 pg/mL order repeat NTproBNP, ECHO and cardiology consult prior to Visit 6 unless there has already been an ECHO and cardiology consult for NTproBNP >300 pg/mL.

- Urine pregnancy test (see Section 7.2.5 and Table 3).

- Flexible sigmoidoscopy or colonoscopy (if preferred).
- Pharmacokinetics: PF-00547659, ADAs and Nabs (see SOA and Section 7).
- Laboratory Pharmacodynamics: hsCRP, Soluble MAdCAM, and stool sample for fecal calprotectin (see SOA and Section 7.6).
- Calculation of total Mayo Score (includes flexible sigmoidoscopy or colonoscopy results, stool frequency, rectal bleeding, and physician's global assessment) (see Section 7.4, Appendix 1 and SOA).
- Complete Stool Diary (see Section 7.4, Appendix 3, and SOA).
- Collect stool sample for enteric pathogens (see Section 7.3.2).
- Drug dispensing: administer the appropriate dose of SC PF-00547659 to subject as described in the Investigational Product Administration section of this protocol (see Sections 5.2.2 and 5.2.3). **Observe for injection site and allergic reactions for a period of at least 30-60 minutes (but total duration should be determined at the discretion of the investigator).**
- Neurological Assessments: Timed 25-Foot Walk (T25FW), 9-Hole Peg Test (9-HPT), Symbol Digit Modality Test (SDMT), and Multiple Sclerosis Neuropsychological Questionnaire (MSNQ) (see Section 7.3.1 and SOA).
- Optional endoscopic biopsy to assess RNA transcripts and proteins associated with UC, inflammation and mechanism of drug activity (see Section 7.4 and the SOA).
- Peripheral blood gene expression profiling (mRNA) and proteins associated with UC, inflammation and mechanism of drug activity (see Section 7.4 and the SOA).
- Dispense labeled stool container and plastic bag to subject to provide a refrigerated or frozen stool specimen at the subsequent visit.
- Monitoring of adverse events: as described in the Adverse Event, Serious Adverse Event Recording and Reporting Sections (see Section 8.14.1 and the SOA).
- Concomitant treatment and/or therapies and medications: as described in the Concomitant Medications Sections (see Section 5.5 and the SOA).

6.2.5. Visit 6, Week 20 (±7 Days of the Projected Visit Date)

The following procedures will be performed at this visit:

- Vital signs and temperature: single sitting blood pressure, pulse rate, respiratory rate (after 5 minute rest), and temperature (oral or tympanic [°C or °F]); weight (lbs or kg) (see Section 7.2.1).

- Review ECHO/Cardiology Consult if applicable (see Section 7.2.4 and SOA).

- Complete physical examination: To include confrontational visual fields for neurologic assessment (see Section 7.2.2.1).

- Laboratory testing: blood chemistry to include cTnI and NTproBNP, hematology and urinalysis (see SOA and Section 7.2.5).

Note: if NTproBNP >300 pg/mL order repeat NTproBNP, ECHO and cardiology consult prior to Visit 7 unless there has already been an ECHO and cardiology consult for NTproBNP >300 pg/mL.

- Urine pregnancy test (see Section 7.2.5 and Table 3).

- Drug dispensing: administer the appropriate dose of SC PF-00547659 to subject as described in the Investigational Product Administration section of this protocol (see Sections 5.2.2 and 5.2.3). **Observe for injection site and allergic reactions for a period of at least 30-60 minutes (but total duration should be determined at the discretion of the investigator).**

- Dispense labeled stool container and plastic bag to subject to provide a refrigerated or frozen stool specimen at the subsequent visit.

- Pharmacokinetics: PF-00547659 (see SOA, and Section 7.5).

- Laboratory Pharmacodynamics: hsCRP and stool sample for fecal calprotectin (see SOA and Section 7.6).

- Partial Mayo Score (see Section 7.4, Appendix 1 and SOA).

- Complete SCCAI (see Section 7.4, Appendix 2, and SOA).

- Complete Stool Diary (see Section 7.4, Appendix 3, and SOA).

- Collect stool sample for enteric pathogens (see Section 7.3.2).

- Neurological Assessments: Timed 25-Foot Walk (T25FW), 9-Hole Peg Test (9-HPT), Symbol Digit Modality Test (SDMT), and Multiple Sclerosis Neuropsychological Questionnaire (MSNQ) (see Section 7.3.1 and SOA).

- Monitoring of adverse events: as described in the Adverse Event, Serious Adverse Event Recording and Reporting Sections (see Section 8.14.1 and the SOA).

- Concomitant treatment and/or therapies and medications: as described in the Concomitant Medications Sections (see Section 5.5 and the SOA).

6.2.6. Visit 7, Week 24 (±7 Days of the Projected Visit Date)

At this visit, the serum samples for PK, ADAs and Nabs, and PD biomarkers must be collected prior to investigational product administration. Disease activity should also be reviewed to establish each subject's relapse status and/or treatment failure.

The following procedures will be performed at this visit:

- Vital signs and temperature: single sitting blood pressure, pulse rate, respiratory rate (after 5 minute rest), and temperature (oral or tympanic [°C or °F]); weight (lbs or kg) (see Section 7.2.1).
- Review ECHO/Cardiology Consult if applicable (see Section 7.2.4).
- Targeted physical examination: To include confrontational visual fields for neurologic assessment (see Section 7.2.2.2).
- Single, standard 12-lead electrocardiogram (see Section 7.2.3).
- Laboratory testing: blood chemistry to include cTnI and NTproBNP, hematology and urinalysis (see Section 7.2.5 and SOA).

Note: if NTproBNP >300 pg/mL order repeat NTproBNP, ECHO and cardiology consult prior to Visit 8 unless there has already been an ECHO and cardiology consult for NTproBNP >300 pg/mL.

- Urine pregnancy test (see Section 7.2.5 and Table 3).
- Pharmacokinetics: PF-00547659, ADAs and Nabs (see SOA and Section 7).
- Laboratory Pharmacodynamics: hsCRP and stool sample for fecal calprotectin (see SOA and Section 7.6).
- Partial Mayo Score (see Section 7.4, Appendix 1 and SOA).
- Complete SCCAI (see Section 7.4, Appendix 2, and SOA).
- Complete Stool Diary (see Section 7.4, Appendix 3, and SOA).
- Collect stool sample for enteric pathogens (see Section 7.3.2).
- Drug dispensing: administer the appropriate dose of SC PF-00547659 to subject as described in the Investigational Product Administration section of this protocol (see Sections 5.2.2 and 5.2.3). **Observe for injection site and allergic reactions for a period of at least 30-60 minutes (but total duration should be determined at the discretion of the investigator).**

- Dispense labeled stool container and plastic bag to subject to subjects who have had a disease flare **only.**

- Neurological Assessments: Timed 25-Foot Walk (T25FW), 9-Hole Peg Test (9-HPT), Symbol Digit Modality Test (SDMT), and Multiple Sclerosis Neuropsychological Questionnaire (MSNQ) (see Section 7.3.1 and SOA).

- JC virus DNA sample (see Section 7.3.1.6).

- JC virus Antibody testing (see Section 7.3.1.6).

- Monitoring of adverse events: as described in the Adverse Event, Serious Adverse Event Recording and Reporting Sections (see Section 8.14.1 and the SOA).

- Concomitant treatment and/or therapies and medications: as described in the Concomitant Medications Sections (see Section 5.5 and the SOA).

6.2.7. Visit 8, Week 28 (±7 Days of the Projected Visit Date)

The following procedures will be performed at this visit:

- Vital signs and temperature: single sitting blood pressure, pulse rate, respiratory rate (after 5 minute rest), and temperature (oral or tympanic [°C or °F]); weight (lbs or kg) (see Section 7.2.1).

- Review ECHO/Cardiology Consult if applicable (see Section 7.2.4).

- Targeted physical examination: To include confrontational visual fields for neurologic assessment (see Section 7.2.2.2).

- Laboratory testing: blood chemistry to include cTnI and NTproBNP, hematology and urinalysis (see SOA and Section 7.2.5).

Note: if NTproBNP >300 pg/mL order repeat NTproBNP, ECHO and cardiology consult prior to Visit 9 unless there has already been an ECHO and cardiology consult for NTproBNP >300 pg/mL.

- Urine pregnancy test (see Section 7.2.5 and Table 3).

- Pharmacokinetics: PF-00547659 (see SOA and Section 7.5).

- Partial Mayo Score (see Section 7.4, Appendix 1 and SOA).

- Complete SCCAI (see Section 7.4, Appendix 2, and SOA).

- Complete Stool Diary (see Section 7.4, Appendix 3, and SOA).

- Collect stool sample for enteric pathogens (see Section 7.3.2).

- Drug dispensing: administer the appropriate dose of SC PF-00547659 to subject as described in the Investigational Product Administration section of this protocol (see Sections 5.2.2 and 5.2.3). **Observe for injection site and allergic reactions for a period of at least 30-60 minutes (but total duration should be determined at the discretion of the investigator).**

- Dispense labeled stool container and plastic bag to subject to provide a refrigerated or frozen stool specimen at the subsequent visit.

- Neurological Assessments: Timed 25-Foot Walk (T25FW), 9-Hole Peg Test (9-HPT), Symbol Digit Modality Test (SDMT), and Multiple Sclerosis Neuropsychological Questionnaire (MSNQ) (see Section 7.3.1 and SOA).

- Monitoring of adverse events: as described in the Adverse Event, Serious Adverse Event Recording and Reporting Sections (see Section 8.14.1 and the SOA).

- Concomitant treatment and/or therapies and medications: as described in the Concomitant Medications Sections (see Section 5.5 and the SOA).

6.2.8. Visit 9, Week 32 (±7 Days of the Projected Visit Date)

At this visit, the serum samples for PK and PD biomarkers must be collected prior to investigational product administration. Disease activity should also be reviewed to establish each subject's relapse status and/or treatment failure.

The following procedures will be performed at this visit:

- Vital signs and temperature: single sitting blood pressure, pulse rate, respiratory rate (after 5 minute rest), and temperature (oral or tympanic [°C or °F]); weight (lbs or kg) (see Section 7.2.1).

- Review ECHO/Cardiology Consult if applicable (see Section 7.2.4).

- Targeted physical examination: To include confrontational visual fields for neurologic assessment (see Section 7.2.2.2).

- Single, standard 12-lead electrocardiogram (see Section 7.2.3).

- Laboratory testing: blood chemistry to include cTnI and NTproBNP, hematology and urinalysis (see Section 7.2.5 and SOA).

Note: if NTproBNP >300 pg/mL order repeat NTproBNP, ECHO and cardiology consult prior to Visit 10 unless there has already been an ECHO and cardiology consult for NTproBNP >300 pg/mL.

- Urine pregnancy test (see Section 7.2.5 and Table 3).
- Pharmacokinetics: PF-00547659 (see SOA, and Section 7.5).
- Laboratory Pharmacodynamics: hsCRP and stool sample for fecal calprotectin (see SOA and Section 7.6).
- Partial Mayo Score (see Section 7.4, Appendix 1 and SOA).
- Complete SCCAI (see Section 7.4, Appendix 2, and SOA).
- Complete Stool Diary (see Section 7.4, Appendix 3, and SOA).
- Collect stool sample for enteric pathogens (see Section 7.3.2).
- Dispense labeled stool container and plastic bag to subject to subjects who have had adisease flare **only.**
- Drug dispensing: administer the appropriate dose of SC PF-00547659 to subject as described in the Investigational Product Administration section of this protocol (see Sections 5.2.2 and 5.2.3). **Observe for injection site and allergic reactions for a period of at least 30-60 minutes (but total duration should be determined at the discretion of the investigator).**
- Neurological Assessments: Timed 25-Foot Walk (T25FW), 9-Hole Peg Test (9-HPT), Symbol Digit Modality Test (SDMT), and Multiple Sclerosis Neuropsychological Questionnaire (MSNQ) (see Section 7.3.1 and SOA).
- Monitoring of adverse events: as described in the Adverse Event, Serious Adverse Event Recording and Reporting Sections (see Section 8.14.1 and the SOA).
- Concomitant treatment and/or therapies and medications: as described in the Concomitant Medications Sections (see Section 5.5 and the SOA).

6.2.9. Visit 10, Week 36 (±7 Days of the Projected Visit Date)

The following procedures will be performed at this visit:

- Vital signs and temperature: single sitting blood pressure, pulse rate, respiratory rate (after 5 minute rest), and temperature (oral or tympanic [°C or °F]); weight (lbs or kg) (see Section 7.2.1).
- Review ECHO/Cardiology Consult if applicable (see Section 7.2.4).
- Targeted physical examination: To include confrontational visual fields for neurologic assessment (see Section 7.2.2.2).

- Laboratory testing: blood chemistry to include cTnI and NTproBNP, hematology and urinalysis (see SOA and Section 7.2.5).

Note: if NTproBNP >300 pg/mL order repeat NTproBNP, ECHO and cardiology consult prior to Visit 11 unless there has already been an ECHO and cardiology consult for NTproBNP >300 pg/mL.

- Urine pregnancy test (see Section 7.2.5 and Table 3).
- Pharmacokinetics: PF-00547659 (see SOA, and Section 7.5).
- Partial Mayo Score (see Section 7.4, Appendix 1 and SOA).
- Complete SCCAI (see Section 7.4, Appendix 2, and SOA).
- Complete Stool Diary (see Section 7.4, Appendix 3, and SOA).
- Collect stool sample for enteric pathogens (see Section 7.3.2).
- Dispense labeled stool container and plastic bag to subject to subjects who have had a disease flare **only.**
- Drug dispensing: administer the appropriate dose of SC PF-00547659 to subject as described in the Investigational Product Administration section of this protocol (see Sections 5.2.2 and 5.2.3). **Observe for injection site and allergic reactions for a period of at least 30-60 minutes (but total duration should be determined at the discretion of the investigator).**
- Neurological Assessments: Timed 25-Foot Walk (T25FW), 9-Hole Peg Test (9-HPT), Symbol Digit Modality Test (SDMT), and Multiple Sclerosis Neuropsychological Questionnaire (MSNQ) (see Section 7.3.1 and SOA).
- Monitoring of adverse events: as described in the Adverse Event, Serious Adverse Event Recording and Reporting Sections (see Section 8.14.1 and the SOA).
- Concomitant treatment and/or therapies and medications: as described in the Concomitant Medications Sections (see Section 5.5 and the SOA).

6.2.10. Visit 11, Week 40 (±7 Days of the Projected Visit Date)

At this visit, the serum samples for PK, ADAs and Nabs, and PD biomarkers must be collected prior to investigational product administration. Disease activity should also be documented to establish each subject's relapse status and/or treatment failure.

From this visit through Visit 19 (Week 72), any subject who has a routine screening colonoscopy should have a Total Mayo Score documented at the first visit after the procedure. All other visits for which no colonoscopy is performed should have a Partial Mayo Score documented.

The following procedures will be performed at this visit:

- Vital signs and temperature: single sitting blood pressure, pulse rate, respiratory rate (after 5 minute rest), and temperature (oral or tympanic [°C or °F]); weight (lbs or kg) (see Section 7.2.1).

- Review ECHO/Cardiology Consult if applicable (see Section 7.2.4).

- Complete physical examination: To include confrontational visual fields for neurologic assessment (see Section 7.2.2.1).

- Single, standard 12-lead electrocardiogram (see Section 7.2.3).

- Laboratory testing: blood chemistry to include cTnI and NTproBNP, hematology and urinalysis (see Section 7.2.5 and SOA).

Note: if NTproBNP >300 pg/mL order repeat NTproBNP, ECHO and cardiology consult prior to Visit 12 unless there has already been an ECHO and cardiology consult for NTproBNP >300 pg/mL.

- Urine pregnancy test (see Section 7.2.5 and Table 3).

- Colonoscopy will be performed for subjects undergoing routine cancer surveillance (see Section 7.4.1 and SOA).

- Partial Mayo Score (see Section 7.4, Appendix 1 and SOA).

    - Calculation of total Mayo Score (includes flexible sigmoidoscopy or colonoscopy results, stool frequency, rectal bleeding, and physician's global assessment) (see Section 7.4, Appendix 1, and SOA footnote t). Only for subjects undergoing routine cancer surveillance. Total Mayo Score should be calculated only for the first study visit following the surveillance colonoscopy.

- Dispense labeled stool container and plastic bag to subject to subjects who have had a disease flare **only.**

- Drug dispensing: administer the appropriate dose of SC PF-00547659 to subject as described in the Investigational Product Administration section of this protocol (see Sections 5.2.2 and 5.2.3). **Observe for injection site and allergic reactions for a period of at least 30-60 minutes (but total duration should be determined at the discretion of the investigator).**

- Pharmacokinetics: PF-00547659, ADAs and Nabs (see SOA and Section 7).

- Complete Stool Diary (see Section 7.4, Appendix 3, and SOA).

- Collect stool sample for enteric pathogens (see Section 7.3.2).

- Neurological Assessments: Timed 25-Foot Walk (T25FW), 9-Hole Peg Test (9-HPT), Symbol Digit Modality Test (SDMT), and Multiple Sclerosis Neuropsychological Questionnaire (MSNQ) (see Section 7.3.1 and SOA).

- Monitoring of adverse events: as described in the Adverse Event, Serious Adverse Event Recording and Reporting Sections (see Section 8.14.1 and the SOA).

- Concomitant treatment and/or therapies and medications: as described in the Concomitant Medications Sections (see Section 5.5 and the SOA).

6.2.11. Visit 12, Week 44 (±7 Days of the Projected Visit Date)

The following procedures will be performed at this visit:

- Vital signs and temperature: single sitting blood pressure, pulse rate, respiratory rate (after 5 minute rest), and temperature (oral or tympanic [°C or °F]); weight (lbs or kg) (see Section 7.2.1).

- Review ECHO/Cardiology Consult if applicable (see Section 7.2.4).

- Targeted physical examination: To include confrontational visual fields for neurologic assessment (see Section 7.2.2.2).

- Laboratory testing: blood chemistry to include cTnI and NTproBNP, hematology and urinalysis (see SOA and Section 7.2.5).

  Note: if NTproBNP >300 pg/mL order repeat NTproBNP, ECHO and cardiology consult prior to Visit 13 unless there has already been an ECHO and cardiology consult for NTproBNP >300 pg/mL.

- Urine pregnancy test (see Section 7.2.5 and Table 3).

- Pharmacokinetics: PF-00547659 (see SOA, and Section 7.5).

- Colonoscopy will be performed for subjects undergoing routine cancer surveillance (see Section 7.4.1 and SOA).

- Partial Mayo Score (see Section 7.4, Appendix 1 and SOA).

  - Calculation of total Mayo Score (includes flexible sigmoidoscopy or colonoscopy results, stool frequency, rectal bleeding, and physician's global assessment) (see Section 7.4, Appendix 1, and SOA footnote t). Only for subjects undergoing routine cancer surveillance. Total Mayo Score should be calculated only for the first study visit following the surveillance colonoscopy.

- Complete Stool Diary (see Section 7.4, Appendix 3, and SOA).

- Collect stool sample for enteric pathogens (See Section 7.3.2).

- Dispense labeled stool container and plastic bag to subject to subjects who have had a disease flare **only.**

- Drug dispensing: administer the appropriate dose of SC PF-00547659 to subject as described in the Investigational Product Administration section of this protocol (see Sections 5.2.2 and 5.2.3). **Observe for injection site and allergic reactions for a period of at least 30-60 minutes (but total duration should be determined at the discretion of the investigator).**

- Neurological Assessments: Timed 25-Foot Walk (T25FW), 9-Hole Peg Test (9-HPT), Symbol Digit Modality Test (SDMT), and Multiple Sclerosis Neuropsychological Questionnaire (MSNQ) (see Section 7.3.1 and SOA).

- Monitoring of adverse events: as described in the Adverse Event, Serious Adverse Event Recording and Reporting Sections (see Section 8.14.1 and the SOA).

- Concomitant treatment and/or therapies and medications: as described in the Concomitant Medications Sections (see Section 5.5 and the SOA).

6.2.12. Visit 13, Week 48 (±7 Days of the Projected Visit Date)

At this visit, the serum samples for PK, ADAs and Nabs, and PD biomarkers must be collected prior to investigational product administration. Disease activity should also be documented to establish each subject's relapse status and/or treatment failure.

The following procedures will be performed at this visit:

- Vital signs and temperature: single sitting blood pressure, pulse rate, respiratory rate (after 5 minute rest), and temperature (oral or tympanic [°C or °F]); weight (lbs or kg)) (see Section 7.2.1).

- Review ECHO/Cardiology Consult if applicable (see Section 7.2.4).

- Targeted physical examination: To include confrontational visual fields for neurologic assessment (see Section 7.2.2.2).

- Single, standard 12-lead electrocardiogram (see Section 7.2.3).

- Laboratory testing: blood chemistry to include cTnI and NTproBNP, hematology and urinalysis (see Section 7.2.5 and SOA).

Note: if NTproBNP >300 pg/mL order repeat NTproBNP, ECHO and cardiology consult prior to Visit 14 unless there has already been an ECHO and cardiology consult for NTproBNP >300 pg/mL.

- Urine pregnancy test (see Section 7.2.5 and Table 3).
- Pharmacokinetics: PF-00547659, ADAs and Nabs (see SOA and Section 7).
- Colonoscopy will be performed for subjects undergoing routine cancer surveillance (see Section 7.4.1 and SOA).
- Partial Mayo Score (see Section 7.4, Appendix 1 and SOA).
    - Calculation of total Mayo Score (includes flexible sigmoidoscopy or colonoscopy results, stool frequency, rectal bleeding, and physician's global assessment) (see Section 7.4, Appendix 1, and SOA footnote t). Only for subjects undergoing routine cancer surveillance. Total Mayo Score should be calculated only for the first study visit following the surveillance colonoscopy.
- Complete Stool Diary (see Section 7.4, Appendix 3, and SOA).
- Collect stool sample for enteric pathogens (see Section 7.3.2).
- Dispense labeled stool container and plastic bag to subject to subjects who have had a disease flare **only.**
- Drug dispensing: administer the appropriate dose of SC PF-00547659 to subject as described in the Investigational Product Administration section of this protocol (see Sections 5.2.2 and 5.2.3). **Observe for injection site and allergic reactions for a period of at least 30-60 minutes (but total duration should be determined at the discretion of the investigator).**
- Neurological Assessments: Timed 25-Foot Walk (T25FW), 9-Hole Peg Test (9-HPT), Symbol Digit Modality Test (SDMT), and Multiple Sclerosis Neuropsychological Questionnaire (MSNQ) (see Section 7.3.1 and SOA).
- JC virus DNA sample (see Section 7.3.1.6).
- JC virus Antibody testing (see Section 7.3.1.6).
- Monitoring of adverse events: as described in the Adverse Event, Serious Adverse Event Recording and Reporting Sections (see Section 8.14.1 and the SOA).
- Concomitant treatment and/or therapies and medications: as described in the Concomitant Medications Sections (see Section 5.5 and the SOA).

6.2.13. Visit 14, Week 52 (±7 Days of the Projected Visit Date)

The following procedures will be performed at this visit:

- Vital signs and temperature: single sitting blood pressure, pulse rate, respiratory rate (after 5 minute rest), and temperature (oral or tympanic [°C or °F]); weight (lbs or kg) (see Section 7.2.1).
- Review ECHO/Cardiology Consult if applicable (see Section 7.2.4).
- Targeted physical examination: To include confrontational visual fields for neurologic assessment (see Section 7.2.2.2).
- Laboratory testing: blood chemistry to include cTnI and NTproBNP, hematology and urinalysis (see SOA and Section 7.2.5).

Note: if NTproBNP >300 pg/mL order repeat NTproBNP, ECHO and cardiology consult prior to Visit 15 unless there has already been an ECHO and cardiology consult for NTproBNP >300 pg/mL.

- Urine pregnancy test (see Section 7.2.5 and Table 3).
- Pharmacokinetics: PF-00547659 (see SOA, and Section 7.5).
- Colonoscopy will be performed for subjects undergoing routine cancer surveillance (see Section 7.4.1 and SOA).
- Partial Mayo Score (see Section 7.4, Appendix 1 and SOA).
    - Calculation of total Mayo Score (includes flexible sigmoidoscopy or colonoscopy results, stool frequency, rectal bleeding, and physician's global assessment) (see Section 7.4, Appendix 1, and SOA footnote t). Only for subjects undergoing routine cancer surveillance. Total Mayo Score should be calculated only for the first study visit following the surveillance colonoscopy.
- Complete Stool Diary (see Section 7.4, Appendix 3, and SOA).
- Collect stool sample for enteric pathogens (See Section 7.3.2).
- Dispense labeled stool container and plastic bag to subject to subjects who have had a disease flare **only.**
- Drug dispensing: administer the appropriate dose of SC PF-00547659 to subject as described in the Investigational Product Administration section of this protocol (see Sections 5.2.2 and 5.2.3). **Observe for injection site and allergic reactions for a period of at least 30-60 minutes (but total duration should be determined at the discretion of the investigator).**

- Neurological Assessments: Timed 25-Foot Walk (T25FW), 9-Hole Peg Test (9-HPT), Symbol Digit Modality Test (SDMT), and Multiple Sclerosis Neuropsychological Questionnaire (MSNQ) (see Section 7.3.1 and SOA).

- Monitoring of adverse events: as described in the Adverse Event, Serious Adverse Event Recording and Reporting Sections (see Section 8.14.1 and the SOA).

- Concomitant treatment and/or therapies and medications: as described in the Concomitant Medications Sections (see Section 5.5 and the SOA).

6.2.14. Visit 15, Week 56 (±7 Days of the Projected Visit Date)

At this visit, the serum samples for PK and PD biomarkers must be collected prior to investigational product administration. Disease activity should also be documented to establish each subject's relapse status and/or treatment failure.

The following procedures will be performed at this visit:

- Vital signs and temperature: single sitting blood pressure, pulse rate, respiratory rate (after 5 minute rest), and temperature (oral or tympanic [°C or °F]); weight (lbs or kg) (see Section 7.2.1).

- Review ECHO/Cardiology Consult if applicable (see Section 7.2.4).

- Targeted physical examination: To include confrontational visual fields for neurologic assessment (see Section 7.2.2.2).

    - Single, standard 12-lead electrocardiogram (see Section 7.2.3).

- Laboratory testing: blood chemistry to include cTnI and NTproBNP, hematology and urinalysis (see Section 7.2.5 and SOA).

Note: if NTproBNP >300 pg/mL order repeat NTproBNP, ECHO and cardiology consult prior to Visit 16 unless there has already been an ECHO and cardiology consult for NTproBNP >300 pg/mL.

- Urine pregnancy test (see Section 7.2.5 and Table 3).

- Pharmacokinetics: PF-00547659 (see SOA, and Section 7.5).

- Colonoscopy will be performed for subjects undergoing routine cancer surveillance (see Section 7.4.1 and SOA).

- Partial Mayo Score (see Section 7.4, Appendix 1 and SOA).

    - Calculation of total Mayo Score (includes flexible sigmoidoscopy or colonoscopy results, stool frequency, rectal bleeding, and physician's global assessment) (see

Section 7.4, Appendix 1, and SOA footnote t). Only for subjects undergoing routine cancer surveillance. Total Mayo Score should be calculated only for the first study visit following the surveillance colonoscopy.

- Complete Stool Diary (see Section 7.4, Appendix 3, and SOA).
- Collect stool sample for enteric pathogens (see Section 7.3.2).
- Dispense labeled stool container and plastic bag to subject to subjects who have had a disease flare **only.**
- Drug dispensing: administer the appropriate dose of SC PF-00547659 to subject as described in the Investigational Product Administration section of this protocol (see Sections 5.2.2 and 5.2.3). **Observe for injection site and allergic reactions for a period of at least 30-60 minutes (but total duration should be determined at the discretion of the investigator).**
- Neurological Assessments: Timed 25-Foot Walk (T25FW), 9-Hole Peg Test (9-HPT), Symbol Digit Modality Test (SDMT), and Multiple Sclerosis Neuropsychological Questionnaire (MSNQ) (see Section 7.3.1 and SOA).
- Monitoring of adverse events: as described in the Adverse Event, Serious Adverse Event Recording and Reporting Sections (see Section 8.14.1 and the SOA).
- Concomitant treatment and/or therapies and medications: as described in the Concomitant Medications Sections (see Section 5.5 and the SOA).

6.2.15. Visit 16, Week 60 (±7 Days of the Projected Visit Date)

The following procedures will be performed at this visit:

- Vital signs and temperature: single sitting blood pressure, pulse rate, respiratory rate (after 5 minute rest), and temperature (oral or tympanic [°C or °F]); weight (lbs or kg) (see Section 7.2.1).
- Review ECHO/Cardiology Consult if applicable (see Section 7.2.4).
- Complete physical examination: To include confrontational visual fields for neurologic assessment (see Section 7.2.2.1).
- Laboratory testing: blood chemistry to include cTnI and NTproBNP, hematology and urinalysis (see SOA and Section 7.2.5).

Note: if NTproBNP >300 pg/mL order repeat NTproBNP, ECHO and cardiology consult prior to Visit 17 unless there has already been an ECHO and cardiology consult for NTproBNP >300 pg/mL.

- Urine pregnancy test (see Section 7.2.5 and Table 3).
- Dispense labeled stool container and plastic bag to subject to subjects who have had a disease flare **only.**
- Drug dispensing: administer the appropriate dose of SC PF-00547659 to subject as described in the Investigational Product Administration section of this protocol (see Sections 5.2.2 and 5.2.3). **Observe for injection site and allergic reactions for a period of at least 30-60 minutes (but total duration should be determined at the discretion of the investigator).**
- Pharmacokinetics: PF-00547659 (see SOA, and Section 7.5).
- Colonoscopy will be performed for subjects undergoing routine cancer surveillance (see Section 7.4.1 and SOA).
- Partial Mayo Score (see Section 7.4, Appendix 1 and SOA).
    - Calculation of total Mayo Score (includes flexible sigmoidoscopy or colonoscopy results, stool frequency, rectal bleeding, and physician's global assessment) (see Section 7.4, Appendix 1, and SOA footnote t). Only for subjects undergoing routine cancer surveillance. Total Mayo Score should be calculated only for the first study visit following the surveillance colonoscopy.
- Complete Stool Diary (see Section 7.4, Appendix 3, and SOA).
- Collect stool sample for enteric pathogens (see Section 7.3.2).
- Neurological Assessments: Timed 25-Foot Walk (T25FW), 9-Hole Peg Test (9-HPT), Symbol Digit Modality Test (SDMT), and Multiple Sclerosis Neuropsychological Questionnaire (MSNQ) (see Section 7.3.1 and SOA).
- Monitoring of adverse events: as described in the Adverse Event, Serious Adverse Event Recording and Reporting Sections (see Section 8.14.1 and the SOA).
- Concomitant treatment and/or therapies and medications: as described in the Concomitant Medications Sections (see Section 5.5 and the SOA).

6.2.16. Visit 17, Week 64 (±7 Days of the Projected Visit Date)

At this visit, the serum samples for PK, ADAs and Nabs, and PD biomarkers must be collected prior to investigational product administration. Disease activity should also be documented to establish each subject's relapse status and/or treatment failure.

The following procedures will be performed at this visit:

- Vital signs and temperature: single sitting blood pressure, pulse rate, respiratory rate (after 5 minute rest), and temperature (oral or tympanic [°C or °F]); weight (lbs or kg) (see Section 7.2.1).

- Review ECHO/Cardiology Consult if applicable (see Section 7.2.4).

- Targeted physical examination: To include confrontational visual fields for neurologic assessment (see Section 7.2.2.2).

- Single, standard 12-lead electrocardiogram (see Section 7.2.3).

- Laboratory testing: blood chemistry to include cTnI and NTproBNP, hematology and urinalysis (see Section 7.2.5 and SOA).

Note: if NTproBNP >300 pg/mL order repeat NTproBNP, ECHO and cardiology consult prior to Visit 18 unless there has already been an ECHO and cardiology consult for NTproBNP >300 pg/mL.

- Urine pregnancy test (see Section 7.2.5 and Table 3).

- Pharmacokinetics: PF-00547659, ADAs and Nabs (see SOA and Section 7).

- Colonoscopy will be performed for subjects undergoing routine cancer surveillance (see Section 7.4.1 and SOA).

- Partial Mayo Score (see Section 7.4, Appendix 1 and SOA).

    - Calculation of total Mayo Score (includes flexible sigmoidoscopy or colonoscopy results, stool frequency, rectal bleeding, and physician's global assessment) (see Section 7.4, Appendix 1, and SOA footnote t). Only for subjects undergoing routine cancer surveillance. Total Mayo Score should be calculated only for the first study visit following the surveillance colonoscopy.

- Complete Stool Diary (see Section 7.4, Appendix 3, and SOA).

- Collect stool sample for enteric pathogens (see Section 7.3.2).

- Dispense labeled stool container and plastic bag to subject to subjects who have had a disease flare **only.**

- Drug dispensing: administer the appropriate dose of SC PF-00547659 to subject as described in the Investigational Product Administration section of this protocol (see Sections 5.2.2 and 5.2.3). **Observe for injection site and allergic reactions for a period of at least 30-60 minutes (but total duration should be determined at the discretion of the investigator).**

- Neurological Assessments: Timed 25-Foot Walk (T25FW), 9-Hole Peg Test (9-HPT), Symbol Digit Modality Test (SDMT), and Multiple Sclerosis Neuropsychological Questionnaire (MSNQ) (see Section 7.3.1 and SOA).

- Monitoring of adverse events: as described in the Adverse Event, Serious Adverse Event Recording and Reporting Sections (see Section 8.14.1 and the SOA).

- Concomitant treatment: as described in the Concomitant Treatments Sections (see Section 5.5 and the SOA).

6.2.17. Visit 18, Week 68 (±7 Days of the Projected Visit Date)

The following procedures will be performed at this visit:

- Vital signs and temperature: single sitting blood pressure, pulse rate, respiratory rate (after 5 minute rest), and temperature (oral or tympanic [°C or °F]); weight (lbs or kg) (see Section 7.2.1).

- Review ECHO/Cardiology Consult if applicable (see Section 7.2.4).

- Targeted physical examination: To include confrontational visual fields for neurologic assessment (see Section 7.2.2.2).

- Laboratory testing: blood chemistry to include cTnI and NTproBNP, hematology and urinalysis (see SOA and Section 7.2.5).

Note: if NTproBNP >300 pg/mL order repeat NTproBNP, ECHO and cardiology consult prior to Visit 19 unless there has already been an ECHO and cardiology consult for NTproBNP >300 pg/mL.

- Urine pregnancy test (see Section 7.2.5 and Table 3).

- Pharmacokinetics: PF-00547659 (see SOA, and Section 7.5).

- Colonoscopy will be performed for subjects undergoing routine cancer surveillance (see Section 7.4.1 and SOA).

- Partial Mayo Score (see Section 7.4, Appendix 1 and SOA).

    - Calculation of total Mayo Score (includes flexible sigmoidoscopy or colonoscopy results, stool frequency, rectal bleeding, and physician's global assessment) (see Section 7.4, Appendix 1, and SOA footnote t). Only for subjects undergoing routine cancer surveillance. Total Mayo Score should be calculated only for the first study visit following the surveillance colonoscopy.

- Complete Stool Diary (see Section 7.4, Appendix 3, and SOA).

- Collect stool sample for enteric pathogens (See Section 7.3.2).

- Drug dispensing: administer the appropriate dose of SC PF-00547659 to subject as described in the Investigational Product Administration section of this protocol (see Sections 5.2.2 and 5.2.3). **Observe for injection site and allergic reactions for a period of at least 30-60 minutes (but total duration should be determined at the discretion of the investigator).**

- Dispense labeled stool container and plastic bag to subject to provide a refrigerated or frozen stool specimen at the subsequent visit.

- Neurological Assessments: Timed 25-Foot Walk (T25FW), 9-Hole Peg Test (9-HPT), Symbol Digit Modality Test (SDMT), and Multiple Sclerosis Neuropsychological Questionnaire (MSNQ) (see Section 7.3.1 and SOA).

- Monitoring of adverse events: as described in the Adverse Event, Serious Adverse Event Recording and Reporting Sections (see Section 8.14.1 and the SOA).

- Concomitant treatment: as described in the Concomitant Treatments Sections (see Section 5.5 and the SOA).

6.2.18. Visit 19, Week 72 (±7 Days of the Projected Visit Date)

The following procedures will be performed at this visit:

- Vital signs and temperature: single sitting blood pressure, pulse rate, respiratory rate (after 5 minute rest), and temperature (oral or tympanic [°C or °F]); weight (lbs or kg) (see Section 7.2.1).

- Review ECHO/Cardiology Consult if applicable (see Section 7.2.4).

- Complete physical examination: To include confrontational visual fields for neurologic assessment (see Section 7.2.2.1).

- Single, standard 12-lead electrocardiogram (see Section 7.2.3).

- Laboratory testing: blood chemistry to include cTnI and NTproBNP, hematology and urinalysis. (see Section 7.2.5 and SOA).

- Urine pregnancy test (see Section 7.2.5 and Table 3).

- Laboratory Pharmacodynamics: hsCRP and stool sample for fecal calprotectin (see SOA and Section 7.6).

- Pharmacokinetics: PF-00547659 (see SOA, and Section 7.5).

- Colonoscopy will be performed for subjects undergoing routine cancer surveillance (see Section 7.4.1 and SOA).

- Partial Mayo Score (see Section 7.4, Appendix 1 and SOA).

    - Calculation of total Mayo Score (includes flexible sigmoidoscopy or colonoscopy results, stool frequency, rectal bleeding, and physician's global assessment) (see Section 7.4, Appendix 1, and SOA footnote t). Only for subjects undergoing routine cancer surveillance. Total Mayo Score should be calculated only for the first study visit following the surveillance colonoscopy.

- Collect stool sample for enteric pathogens (See Section 7.3.2).

- Drug dispensing: administer the appropriate dose of SC PF-00547659 to subject as described in the Investigational Product Administration section of this protocol (see Sections 5.2.2 and 5.2.3). **Observe for injection site and allergic reactions for a period of at least 30-60 minutes (but total duration should be determined at the discretion of the investigator).**

- Neurological Assessments: Timed 25-Foot Walk (T25FW), 9-Hole Peg Test (9-HPT), Symbol Digit Modality Test (SDMT), and Multiple Sclerosis Neuropsychological Questionnaire (MSNQ) (see Section 7.3.1 and SOA).

- JC virus DNA sample (see Section 7.3.1.6).

- JC virus Antibody testing (see Section 7.3.1.6).

- Peripheral blood gene expression profiling (mRNA) and proteins associated with UC, inflammation and mechanism of drug activity (see Section 7.4 and SOA).

- Monitoring of adverse events: as described in the Adverse Event, Serious Adverse Event Recording and Reporting Sections (see Section 8.14.1 and the SOA).

- Concomitant treatment: as described in the Concomitant Treatments Sections (see Section 5.5 and the SOA).

6.2.19. Visits 20 - 36, Weeks 76 – 140 (±7 Days of the Projected Visit Date)

- Amended Informed Consent (Visit 20).

- Vital signs: single sitting blood pressure, pulse rate; weight (lbs or kg) (see Section 7.2.1).

- Review ECHO/Cardiology Consult if applicable (see Section 7.2.4).

- Single, standard 12-lead electrocardiogram only at Visits 22, 25, 28, 31 and 34 (see SOA and Section 7.2.3).

- Targeted physical examination: To include confrontational visual fields for neurologic assessment (see Section 7.2.2.2).
- Laboratory testing: blood chemistry to include cTnI and NTproBNP, hematology and urinalysis only at Visits 22, 25, 28, 31 and 34 (see SOA and Section 7.2.5).
- Urine pregnancy test (see Section 7.2.5 and Table 3).
- Partial Mayo Score (see Section 7.4, Appendix 1 and SOA).
- Complete Stool Diary (see Section 7.4, Appendix 3, and SOA).
- Complete SCCAI (see Section 7.4, Appendix 2, and SOA).
- Collect stool sample for enteric pathogens **only if symptomatic** (See Section 7.3.2).
- Neurological Assessments: Timed 25-Foot Walk (T25FW), 9-Hole Peg Test (9-HPT), Symbol Digit Modality Test (SDMT), and Multiple Sclerosis Neuropsychological Questionnaire (MSNQ) (see Section 7.3.1 and SOA).
- JC virus DNA sample only at Visits 26 and 32 (see Section 7.3.1.6).
- JC virus Antibody testing only at Visits 26 and 32 (see Section 7.3.1.6).
- Drug dispensing: complete 75 mg SC PF-00547659 assignment as described in the Study Drug and Administration at Visit 20. Administer the appropriate dose of SC PF-00547659 to subject as described in the Investigational Product Administration section of this protocol (see Sections 5.2.2 and 5.2.3). **Observe for injection site and allergic reactions for a period up to 30-60 minutes (but total duration should be determined at the discretion of the investigator).**
- Monitoring of adverse events: as described in the Adverse Event, Serious Adverse Event Recording and Reporting Sections (see Section 8.14.1 and the SOA).
- Concomitant treatment: as described in the Concomitant Treatments Sections (see Section 5.5 and the SOA).

6.2.20. Visit 37 Week 144 (±7 Days of the Projected Visit Date)

The following procedures will be performed at this visit:

- Vital signs: single sitting blood pressure, pulse rate; weight (lbs or kg) (see Section 7.2.1).
- Review ECHO/Cardiology Consult if applicable (see Section 7.2.4).

- Targeted physical examination: To include confrontational visual fields for neurologic assessment (see Section 7.2.2.2).

- Single, standard 12-lead electrocardiogram (see Section 7.2.3).

- Laboratory testing: blood chemistry to include cTnI and NTproBNP, hematology and urinalysis. (see Section 7.2.5 and SOA).

Note: if NTproBNP >300 pg/mL order repeat NTproBNP, ECHO and cardiology consult prior to Visit 38; if **NTproBNP >124 pg/mL**, and subject has previously had an ECHO, order ECHO and cardiology consult prior to Visit 38.

- Urine pregnancy test (see Section 7.2.5 and Table 3).

- Partial Mayo Score (see Section 7.4, Appendix 1 and SOA).

- Complete Stool Diary (see Section 7.4, Appendix 3, and SOA).

- Complete SCCAI (see Section 7.4, Appendix 2, and SOA).

- Collect stool sample for enteric pathogens **only if symptomatic** (See Section 7.3.2).

- Neurological Assessments: Timed 25-Foot Walk (T25FW), 9-Hole Peg Test (9-HPT), Symbol Digit Modality Test (SDMT), and Multiple Sclerosis Neuropsychological Questionnaire (MSNQ) (see Section 7.3.1 and SOA).

- JC virus DNA sample (see Section 7.3.1.6).

- JC virus Antibody testing (see Section 7.3.1.6).

- Drug dispensing: administer the appropriate dose of SC PF-00547659 to subject as described in the Investigational Product Administration section of this protocol (see Sections 5.2.2 and 5.2.3). **Observe for injection site and allergic reactions for a period of at least 30-60 minutes (but total duration should be determined at the discretion of the investigator).**

- Monitoring of adverse events: as described in the Adverse Event, Serious Adverse Event Recording and Reporting Sections (see Section 8.14.1 and the SOA).

- Concomitant Treatment: as described in the Concomitant Treatments Sections (see Section 5.5 and the SOA).

6.3. Follow-Up

6.3.1. Visit 38, Week 156 (±7 Days of the Projected Visit Date)

The following procedures will be performed at this visit:

- Vital signs: single sitting blood pressure, pulse rate; weight (lbs or kg) (see Section 7.2.1).
- Review ECHO/Cardiology Consult if applicable (see Section 7.2.4).
- Targeted physical examination: To include confrontational visual fields for neurologic assessment (see Section 7.2.2.2).
- Urine pregnancy test (see Section 7.2.5 and Table 3).
- Pharmacokinetics: PF-00547659, ADAs and Nabs (see SOA and Section 7).
- Neurological Assessments: Timed 25-Foot Walk (T25FW), 9-Hole Peg Test (9-HPT), Symbol Digit Modality Test (SDMT), and Multiple Sclerosis Neuropsychological Questionnaire (MSNQ) (see Section 7.3.1 and SOA).
- Collect stool sample for enteric pathogens **only if symptomatic** (See Section 7.3.2).
- Monitoring of adverse events: as described in the Adverse Event, Serious Adverse Event Recording and Reporting Sections (see Section 8.14.1 and the SOA).
- Concomitant treatment: as described in the Concomitant Treatments Sections (see Section 5.5 and the SOA).

6.3.2. Final Onsite StudyVisit: Visit 39, Week 168/End of Study (EOS) (±7 Days of the Projected Visit Date)

The following procedures will be performed at this visit:

- Vital signs: single sitting blood pressure, pulse rate, weight (lbs or kg) (see Section 7.2.1).
- Review ECHO/Cardiology Consult if applicable (see Section 7.2.4).
- Targeted physical examination: To include confrontational visual fields for neurologic assessment (see Section 7.2.2.2).
- Single, standard 12-lead electrocardiogram (see Section 7.2.3).
- Laboratory testing: blood chemistry to include cTnI and NTproBNP, hematology and urinalysis (see SOA and Section 7.2.5).

- Urine pregnancy test (see Section 7.2.5 and Table 3).
- Neurological Assessments: Timed 25-Foot Walk (T25FW), 9-Hole Peg Test (9-HPT), Symbol Digit Modality Test (SDMT), and Multiple Sclerosis Neuropsychological Questionnaire (MSNQ) (see Section 7.3.1 and SOA).
- JC virus DNA testing (see Section 7.3.1.6).
- JC virus Antibody testing (see Section 7.3.1.6).
- Collect stool sample for enteric pathogens **only if symptomatic** (See Section 7.3.2).
- Monitoring of adverse events: as described in the Adverse Event, Serious Adverse Event Recording and Reporting Sections (see Section 8.14.1 and the SOA).
- Concomitant treatment: as described in the Concomitant Treatments Sections (see Section 5.5 and the SOA).
- End of Study CRF is completed when the subject completes participation in the study.

6.4. Early Withdrawal

Subjects may withdraw from this 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, behavioral, or administrative reasons. Subjects must be withdrawn if they develop any opportunistic infection, eg, PML. Subjects are encouraged to stay in the protocol unless disease symptoms become intolerable, as lack of response may be due to the pharmacokinetic/pharmacodynamic characteristics of the study drug.

Subjects who request to discontinue study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a subject specifically withdraws consent for any further contact. Subjects should notify the investigator of the decision to withdraw consent from future follow-up in writing, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is from further treatment with study drug only or also from study procedures and/or post treatment study follow-up.

Additional reasons a subject may be withdrawn from active treatment include but are not limited to, AE, SAE, protocol violations, and failure to return for visits.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. 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. Lost to follow-up is defined by the inability to reach the subject after a minimum of three documented phone calls, faxes, or emails as well as lack of response by subject to one 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 permissible local methods to obtain the date and cause of death.

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. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request the subject to return for a final visit, if applicable, and follow up with the subject regarding any unresolved AE(s).

Subjects who withdraw from this study due to an increase in disease symptoms may see their personal physician for treatment, which may include treatments prohibited during the study. Subjects that do withdraw from active treatment should complete the procedures for the early withdrawal visit listed below, and enter the 6 month follow up period of the protocol.

The following procedures will be performed at the Early Withdrawal Visit prior to Visit 37:

- Vital signs: single sitting blood pressure, pulse rate, weight (lbs or kg) (see Section 7.2.1).
- Review ECHO/Cardiology Consult if applicable (see Section 7.2.4).
- Targeted physical examination: To include confrontational visual fields for neurologic assessment (see Section 7.2.2.2).
- Single, standard 12-lead electrocardiogram (see Section 7.2.3).
- Laboratory testing: blood chemistry to include cTnI and NTproBNP, hematology and urinalysis (see SOA and Section 7.2.5 and).

Note: if NTproBNP >300 pg/mL order repeat NTproBNP, ECHO and cardiology consult prior to Visit 20; if **NTproBNP >124 pg/mL**, and subject has previously had an ECHO, order ECHO and cardiology consult prior to Visit 20

- Urine pregnancy test (see Section 7.2.5 and Table 3).
- Pharmacokinetics: PF-00547659, ADAs and NAbs (see Section 7 and SOA).
- Complete SCCAI (see Section 7.4, Appendix 2, and SOA).
- Collect stool sample for enteric pathogens **only if symptomatic** (See Section 7.3.2).
- Complete Stool Diary (see Section 7.4, Appendix 3, and SOA).
- Neurological Assessments: Timed 25-Foot Walk (T25FW), 9-Hole Peg Test (9-HPT), Symbol Digit Modality Test (SDMT), and Multiple Sclerosis Neuropsychological Questionnaire (MSNQ) (see Section 7.3.1 and SOA).
- JC virus DNA sample (see Section 7.3.1.6).

- JC virus Antibody testing (see Section 7.3.1.6).

- Monitoring of adverse events: as described in the Adverse Event, Serious Adverse Event Recording and Reporting Sections (see Section 8.14.1 and the SOA).

- Concomitant treatment: as described in the Concomitant Treatments Sections (see Section 5.5 and the SOA).

- End of study CRF is completed when subjects withdraw from the study.

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.

6.4.1. Post-Withdrawal Visit

Results from study A7281001 indicated the elimination of PF-00547659 follows IgG2 pharmacokinetics when dosed in the range selected from the current study. It has been determined that at 24 weeks after the last dose the majority of subjects are likely to have concentrations below the limit of quantification. Therefore, it is advised that subjects withdrawing from the study prior to Week 144 enter into the follow-up period with their first follow-up visit occurring 3 months after their last dose.

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 can not be performed the investigator will document the reason for this and any corrective and preventive actions which he/she has taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely fashion.

7.1. Pregnancy Testing

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

In the case of a positive confirmed pregnancy, the subject will be withdrawn from study medication, should complete the procedures for the early withdrawal visit and enter the 6 month follow-up period.

7.2. Safety

Average monthly blood sampling volume for a subject that completes all currently scheduled assessments through Week 168 is approximately 33 mL.

7.2.1. Vital Signs, Height, and Weight

Vital signs (blood pressure, heart rate, respirations and oral or tympanic temperature (°C or °F) will be measured at every study visit up to Visit 19. After Visit 19, vital signs (blood pressure and heart rate) will be measured at every study visit. Additional collection times, or changes to collection times of blood pressure and pulse rate will be permitted, as necessary, to ensure appropriate collection of safety data.

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

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

The same size blood pressure cuff, which has been properly sized and calibrated, will be used to measure blood pressure each time. The use of automated devices for measuring blood pressure (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, all vital signs should be obtained prior to the nominal time of the blood collection.

Height (inches or centimeters) will be recorded at the Baseline visit only.

Weight (lbs or kg) without shoes will be measured at each visit, and at Early Withdrawal (see STUDY PROCEDURES).

7.2.2. Physical Exam

7.2.2.1. Complete Physical Exam

Complete physical examinations will be performed at the Baseline visit, Weeks 20, 40, 60, and 72, if required (see Table 1 and Section 6). Complete physical examinations must be performed by the investigator, sub-investigator, or a qualified health 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; external genitalia (optional); extremities; neurologic function; back and lymph nodes.

7.2.2.2. Targeted Physical Exam

Targeted physical examinations will be performed at Weeks 4, 8, 12, 16, 24, 28, 32, 36, 44, 48, 52, 56, 64, and 68 during Open Label Treatment Period 1. Targeted physical examination will be performed at each visit during Open Label Treatment Period 2 until EOS (Week 168), and at Early Withdrawal. (see Table 1 and Section 6). Targeted physical examinations must be performed by investigator, sub-investigator, or a qualified health professional per local guidelines and should include skin, heart, lung, confrontational visual fields (eyes) and abdomen.

7.2.3. Electrocardiogram

Single 12-lead ECGs should be collected at the Baseline visit, every 8 weeks to Week 72. After Week 72, a single 12-lead ECG should be collected starting at Week 84, every 12 weeks to Week 144 and at Week 168 or Early Withdrawal (if required) (see Table 1 and Section 6).

All scheduled ECGs should be performed after the subject has rested quietly for at least 10 minutes in a sitting position.

The values of the ECG collected at the Baseline visit will serve as each subject's baseline ECG values. When the timing of the measurements coincides with a blood collection, the ECG should be obtained prior to the nominal time of the blood collection, blood pressure 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.

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.

7.2.4. Transthoracic Echocardiogram (ECHO) and Cardiology Consult (if applicable)

ECHO and cardiology consult will be performed locally only under specified conditions. These conditions are:

- At *baseline* visit: if NTproBNP value is >300 pg/mL if no prior ECHO.
- At the *on-treatment visits up to Week 144*: If no prior ECHO, the first time NTproBNP is >300 pg/mL.
- At the *Week 144 or early withdrawal* visit: If there has been any prior ECHO AND the NTproBNP is >124 pg/mL or if there has been no prior ECHO, and the NTproBNP is >300 pg/mL.
- At the *post-week 144* visits: if there has been no prior ECHO and NTproBNP is >300.

At a minimum, the ECHO must assess RV and LV function, determine LVEF and evaluate for diastolic dysfunction.

The cardiology consult should be focused on any evidence of myocarditis or right or left heart failure or any alternative explanations of the subject's elevated NTproBNP. The cardiologist

should review the serial NTproBNP data available up to that point, and the ECHO, and provide a report that evaluates the etiology of the heart failure or myocarditis if present.

7.2.5. Laboratory Tests

As much as possible, only 1 local laboratory should be used by each investigator for all local laboratory tests. Laboratory certification and laboratory normal ranges must be provided to the sponsor for all laboratories used. A central laboratory will be used for the majority of the laboratory tests; however a local laboratory will be allowed for urgent test results if needed.

Laboratory tests are listed in detail in Table 1 and Section 6.

All laboratory tests with values that become abnormal to a clinically significant degree after investigational product administration must be repeated and the investigator must continue to follow up as medically indicated until values have returned to baseline or until the condition stabilizes. If laboratory values do not return to normal or baseline within a reasonable period, the etiology must be identified and the sponsor notified.

Table 3. Laboratory Tests

Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hemoglobin	BUN and Creatinine[e]	pH	hsCRP[f]
Hematocrit	Glucose (fasting if possible)	Glucose (qual)	
RBC count	Calcium	Protein (qual)	Transthoracic echocardiogram (ECHO)[d]
Platelet count	Sodium	Blood (qual)	
WBC count	Potassium	Ketones	
Total neutrophils (Abs)	Chloride	Nitrites	Urine pregnancy test
Eosinophils (Abs)	AST, ALT	Leukocyte esterase	
Monocytes (Abs)	Total Bilirubin	Microscopy[c]	
Basophils (Abs)	Direct Bilirubin[a]		Stool sample for fecal calprotectin[f]
Lymphocytes (Abs)	Alkaline phosphatase		
	Uric acid		
	Albumin		JC virus DNA testing
	Total protein		
	CPK		JC virus Serology (antibody)
	CPK fractionation[b]		
	NT-proBNP[d]		ADAs
	Troponin I[d]		
			Soluble MAdCAM[f]
			mRNA and proteins[f]

a. Only if Total Bilirubin is elevated.
b. Only if CPK is elevated
c. Only if urine dipstick is positive for blood, protein, nitrites or leukocyte esterase.
d. ECHO and cardiology consult will be performed locally only under specified conditions. These conditions are:

- At *baseline* visit if NTproBNP value is >300 pg/mL and no prior ECHO.
- At the *on-treatment visits up to Week 144*: If no prior ECHO, the first time NTproBNP is >300 pg/mL.
- At the *Week 144 or early withdrawal* visit: If there has been any prior ECHO AND the NTproBNP is >124 pg/mL or if there has been no prior ECHO, and the NTproBNP is >300 pg/mL.
- At the *post-week 144* visits: if there has been no prior ECHO and NTproBNP is >300.

e. Creatinine Clearance determination by central lab using Cockcroft&Gault method.
f. After completion of the Week 72 visit, hsCRP, Soluble MAdCAM and stool sample for fecal calprotectin will no longer be collected for the Open Label Treatment Period 2.

7.3. Special Safety Assessments

As noted above (see Section 1.2.4.1) nonselective inhibitors of lymphocyte trafficking into tissue, such as natalizumab, have been associated with rare cases of Progressive Multifocal Leukoencephalopathy (PML). Because PF-00547659 acts only on the MAdCAM receptor, which is the mediator of lymphocyte trafficking into the gut, this agent should be much safer because it does not interact with VCAM, the mediator of lymphocyte trafficking into the CNS. It is hypothesized that natalizumab interferes with immune surveillance of the CNS, thus permitting opportunistic infections. However, the actual mechanism by which natalizumab therapy results in PML is unknown.

Since PF-00547659 is still in early development, in order to maximally protect study subjects from any potential neurologic risk, this study includes frequent neurologic assessments to detect the earliest possible changes in neurologic function. Any change in function detected by this assessment should trigger an immediate neurologic consultation to rule out PML.

The tests selected for assessment were identified by expert consultation as the rarity of PML has prevented the establishment of clear-cut guidelines for its early detection. Since PML and Multiple Sclerosis (MS) are both white matter diseases, similar findings are expected. Therefore, many of the chosen tests are used frequently to assess MS subjects.

Because none of these tests has been validated for this specific purpose, the investigator's clinical judgment will be necessary in the interpretation of changes that will trigger an immediate formal neurological consultation to determine the cause of the change in neurological function and exclude PML. Such a consultation will typically include MRI and lumbar puncture.

The following neurological assessments will be performed monthly throughout the Open Label Treatment Period 1 and Open Label Treatment Period 2:

- Confrontational Visual Fields which will be performed as part of the physical exam.
- Timed 25-Foot Walk.
- 9-Hole Peg Test (9-HPT).
- Symbol Digit Modality Test (SDMT-written).
- Patient-Multiple Sclerosis Neuropsychological Questionnaire (MSNQ) (Does not trigger a neurology consult).

7.3.1. Neurological Assessments

These tests are rapid, simple to perform and may be performed by the study site staff after reading the simple instructions. Additional training in these tests will be provided at the investigator meeting.

7.3.1.1. Confrontational Visual Fields (to be performed as part of the complete and Targeted Physical examinations)

Confrontation Visual Field Test (CVFT): The CVFT is a basic screening tool to measure the overall field of vision. It is also useful for detecting blind spots and eye diseases. Subjects will be asked to cover one eye while fixing their gaze on the examiner's eyes. This test should be administered by a qualified health professional trained in confrontational visual fields. The examiner will make finger movements, bringing his/her fingers into each quadrant of the visual field. Subjects will be asked how many fingers they see without actually looking at them in order to test peripheral vision. (See Appendix 4 for instructions).

Any change in visual fields detected by this examination must trigger a formal visual field examination by an ophthalmologist. If the visual field test is abnormal then a neurologic consultation to rule out PML must be initiated immediately.

Reference: http://vision.about.com/od/eyeexamination1/f/Confrontation_Fields.htm

7.3.1.2. Timed 25-Foot Walk

Timed 25-Foot Walk (T25-FW): The T25-FW is a quantitative mobility and leg function test based on a timed 25 foot walk. The subject is directed to walk to one end of a clearly marked 25-foot straight course. The subject is instructed to walk as quickly as possible, but safely. The examiner uses a stopwatch to time how long it takes the subject to walk to the 25-foot mark. The task is immediately administered again by having the subject walk back to the start of the 25-foot course. Subjects may use assistive devices when doing this task. The average time of the two trials is taken. Total administration time should be approximately 1-5 minutes. (see Appendix 5 for instructions).

Note: This test requires a stopwatch, a measuring tape (at least 25 feet long), and masking tape to mark the floor are needed.

In a study of normal volunteers, the typical time to complete the 25 foot walk was 3-4 seconds, in contrast to patients with Multiple Sclerosis who took about twice as long.[9] Arthritis and other orthopedic problems can also affect the time on the test.

A 20% increase compared with baseline of the previous study is clinically significant and deterioration not explained by another clear reason should prompt a neurological consultation. Note the term baseline is not defined as the "baseline visit". To further clarify "the baseline" value is the WORSE of the values determined at the screening visit and baseline visit of study A7281009.

Reference: http://www.nationalmssociety.org/for-professionals/researchers/clinical-study-measures/t25-fw/index.aspx

7.3.1.3. 9-Hole Peg Test (9-HPT)

9 Hole Peg Test: The 9-HPT is a brief, standardized test of upper limb function. Both the dominant and non-dominant hands are tested (note: dominant hand is usually the hand that the patient uses to write). The subject is seated at a table with a small, shallow container containing 9 pegs and a wooden or plastic block with 9 empty holes. On a start command when a stopwatch is started, the subject picks up the 9 pegs one peg at a time, and as quickly as possible, puts the pegs in the holes. Once all the pegs are in the holes the patient removes them again as quickly as possible, one at a time, replacing them into the shallow container. The total time to complete the task is recorded. Two consecutive trials with the dominant hand are immediately followed by two consecutive trials with the non-dominant hand. The average time for each hand is calculated. Total administration time should be approximately 10 minutes or less.

Note: this test requires a stopwatch.

In a study of healthy volunteers, typical completion time was about 18 seconds, compared with Multiple Sclerosis patients who required 21-25 seconds.[9] Performance of the test can also be affected by injuries and arthritis.

A 20% increase compared with baseline of the previous study is clinically significant along with deterioration in performance that is not readily explained especially if within the MS

range should prompt a neurological consultation. Note the term baseline is not defined as the "baseline visit". To further clarify "the baseline" value is the WORSE of the values determined at the screening visit and baseline visit of study A7281009.

Refer to (Appendix 6) for instructions.

Reference: http://www.nationalmssociety.org/for-professionals/researchers/clinical-study-measures/9-hpt/index.aspx

7.3.1.4. Symbol Digit Modality Test (SDMT)

Symbol Digit Modality Test (SDMT): The SDMT is a simple test used to screen for organic cerebral dysfunction. It evaluates multiple domains, including attention, visual spanning and motor speed. The SDMT is brief, easy to administer, and has demonstrated sensitivity in detecting not only the presence of brain damage but also changes in cognitive functioning over time and in response to treatment. The SDMT involves a simple substitution task such as in deciphering a code. Using a reference key, the subject has 90 seconds to pair specific numbers with given geometric figures. Subjects can give either written or verbal responses. The written version is being used in this study. Time to administer is approximately 5 minutes.

Results of the SDMT are compared against a normative table that indicates values for populations by age and educational level (12 years of school/high school graduate or less vs 13 years of school/any college or more). Scores are ranked in terms of standard deviation, from +3.0 to -3.0 in 0.5 SD increments. When given a single time, a value that is -1 SD is considered low, -1.5 SD moderately low, and -2.0 SD very low. There has been no validation of change over time, but in a study of impaired patients (baseline no more than -1.5 SD) with Multiple Sclerosis with an ineffective treatment both the placebo and treated patients varied by 4.8-5.2 points over 28 days.[10] The minimum change to reflect 1 SD is 8 points.

A deterioration ≥1 standard deviation on two consecutive visits compared to the baseline of the previous study and a drop in performance should be of concern and prompt a neurological consultation. Note the term baseline is not defined as the "baseline visit". To further clarify "the baseline" value is the WORSE of the values determined at the screening visit and baseline visit of study A7281009.

Refer to Appendix 7 for instructions.

Reference: http://www.hogrefe.co.uk/?/test/show/272/ and Parmenter et al, 2007 article.[11]

7.3.1.5. Multiple Sclerosis Neuropsychological Questionnaire (MSNQ)

Multiple Sclerosis Neuropsychological Screening Questionnaire (MSNQ): The MSNQ is a self-administered PRO questionnaire. It is designed as a quick test to identify possible neuropsychological impairment, originally in subjects with Multiple Sclerosis. The MSNQ has 15 questions, and subjects rate the frequency and severity of symptoms associated with neuropsychological impairment. There are 2 MSNQ; one for patients and one for a close family member or friend. Both forms are reliable and valid. However, only the patient form will be used in this study.

The MSNQ is a sensitive test for detection of neurocognitive abnormalities in patients with MS. The test covers several different cognitive domains (attention, memory, language) and integrates them into a single value. Patients with MS scored significantly higher than normal controls on the self-reported values.

	Self-report (mean+/-sd)
MS	27.4+/-11.9
Normal	16.0+/-6.2

For self-reported results, a cut-off of 24 correctly identified cognitive impairment 68% of the time (sensitivity 0.83, specificity 0.6).

Experience with this test is generally limited to subjects with multiple sclerosis. Based on early experience with Crohn's Disease subjects, variability between repeat tests appears excessive and results are being evaluated for information only.

Refer to Appendix 8 for instructions.

7.3.1.6. JC Virus

Samples for JC virus antibody will be taken every 6 months throughout the study until the final onsite visit. At a minimum, the final samples will be tested. The samples may be stored with the central shipper until an appropriate analysis plan is determined.

Samples for JC Virus DNA will be taken every 6 months throughout the study until the final onsite visit. At a minimum, the final samples may be tested. The shipment address and contact information for the lab will be provided to the Investigator as soon as this information will become available. The samples may be stored with the central shipper until an appropriate analysis plan is determined.

7.3.2. *C. Difficile*

Highly sensitive tests, with high negative predictive value, should be employed to exclude *C. difficile* infection in subjects with a flare of UC. 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 is encouraged where permitted by local regulation. Molecular techniques such as PCR for detection of toxin RNA are also acceptable alternatives. This test will be mandatory for subjects who experience a disease flare.

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

7.4. Diagnostic and Efficacy Assessments

7.4.1. Flexible Sigmoidoscopy or Colonoscopy (if preferred)

A flexible sigmoidoscopy or colonoscopy must be performed at study Visit 5 (Week 16). Additionally, between Weeks 52 and 68, if routine colonoscopy for cancer surveillance is performed within the study a Total Mayo score should be obtained. Optional colonoscopies/flexible sigmoidoscopy performed between Weeks 40 and 72 will provide additional Total Mayo Score for exploratory analysis. If it is necessary a bowel prep should be conducted as per local routine. The position of the endoscope at the post-treatment 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 flexible sigmoidoscopy or colonoscopy at baseline. The endoscopy report and any photographs and/or video recordings taken during the procedure per local custom should be filed in the patient's chart. The findings of the endoscopy component should be completed at the end of the procedure to document the endoscopic subscore in the event that the data is entered at a different location.

A copy of the endoscopy report and any photographs and/or video recordings taken during the procedure must be obtained and filed in the subject's chart and must be available to the sponsor upon request. The report and any photographs and/or video recordings taken during the procedure must be sufficient to complete the endoscopy component on the Mayo Scoring System CRF. A request should also be made to obtain any biopsy samples that were taken during the procedure.

To ensure measurement consistency and validity of study efficacy assessments, video recordings of endoscopic procedures will be captured using a study-specific video capture kit and uploaded to a secure website for review by a central reader.

Scoring will be performed by the central reader at Week 16 of the study. Scores will be returned to the investigative sites in a timely manner. Site personnel will be trained on the video capture equipment suppliedby the central reading CRO and instructed on how to upload the video recording data.

Precautions will be taken to ensure confidentiality. The central reader will remain blinded to the study as no information regarding disease history or treatments is to be communicated from the sites.

7.4.2. Optional Endoscopic Biopsy Substudy

Only for subjects who consent during flexible sigmoidoscopy or colonoscopy (*whichever preferred*). The analysis may include the following:

mRNA (all sites):

The largest standard forceps should be used to obtain biopsies. Biopsies should be taken one-at-a-time, and each should be immediately placed into a separate sample collection tube. The biopsy collection tube will contain an RNA stabilizing liquid. For RNA biopsies should be taken from abnormally lesional mucosa, and biopsies from non lesionsal mucosa. The biopsy

must be completely submerged in the liquid. Labels should clearly specify whether the biopsy is from a lesional or non-lesional area. Frankly ulcerated areas should be avoided. Shire and the central laboratory vendor will provide sites with instructions and supplies for the collection, processing, and shipment of biopsy samples.

Assessment of Histology (all sites):

These biopsies are being collected for the purposes of assessing the effectiveness of drug in decreasing inflammatory cell infiltration at the site of disease. Histological and protein assessment may include different subsets of lymphocytes, hematopoietic cells and/or protein biomarkers and will be performed on formalin fixed tissue. The largest standard forceps should be used to obtain biopsies. Biopsies should be taken one-at-a-time. Biopsies from lesional tissue should be placed in the container provided (which contains formalin). Additionally, biopsies from non-lesional mucosa should be placed in the separate contained (also containing formalin. Labels should clearly specify whether the biopsies are from inflamed or normal appearing mucosa. Frankly ulcerated areas should be avoided. Shire and the central laboratory vendor will provide sites with instructions and supplies for the collection, processing, and shipment of biopsy samples.

Mucosal Healing (all sites):

Subjects may undergo endoscopy to evaluate mucosal healing by visualization. Data may be combined with the data from the other MAdCAM IBD studies. Endoscopic scoring will be performed using the Mayo-Score. The procedures may also be recorded on CD-ROMs.

Tissue Biology (SELECTED SITES):

The objective of this study is to explore the effect of PF-00547659 on endoscopic tissue. Approximately 40 subjects are needed for meaningful data. Data may be combined with the data from the other MAdCAM IBD studies.

The analysis may include the following:

- T and B lymphocytes to be isolated from LMPC's (obtained from intestinal biopsies) and subsequently subjected to FACS analysis that may include using antibodies against B7, CD45 RO, CD27, CCR6, CCR9, CD3 and CD19/CD10.

- Histologic disease activity.

- Immunohistochemistry (IHC) that may include different subsets of lymphocytes, hematopoietic cells and/or protein biomarkers.

- mRNA transcripts.

Additional information may be provided in the laboratory manual under separate cover.

Individual subjects may also elect to participate or not in this portion of the study without affecting their overall eligibility for the study.

7.4.3. Subject Stool Diary

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

- 'Normal' number of stools per day (when not having a flare).
- Number of times need 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).

Patients will be required to enter diary data for the 3 days immediately preceding the flexible sigmoidoscopy visit prior to the Week 16 visit. *Note: The term "immediately" indicates a preference and is not considered a requirement. To calculate the Mayo Score data, 3 consecutive days preceding the flexible sigmoidoscopy or colonoscopy may be used.* Should any patient be required to perform bowel preparation prior to the flexible sigmoidoscopy at Week 16, the patient should be instructed to complete the diary one day prior to initiating bowel preparation. *Note: If a bowel preparation is needed data for 3 consecutive days up to one day prior to the bowel preparation may be used to calculate the Mayo Score.* Diaries to be completed by the patients will be distributed during the baseline visit [Week 12 of study A7281009 (for collection at the flexible sigmoidoscopy visit prior to Week 16)] (See Appendix 3).

7.4.4. Mayo Score

The Mayo score is a tool designed to measure disease activity for UC. The Mayo scoring system ranges from 0 to 12 points and consists of 4 subscores, each graded 0 to 3 with the higher score indicating more severe disease activity (see Appendix 1).

- Stool frequency (Subscore 0-3).
- Rectal bleeding (Subscore 0-3).
- Findings on flexible sigmoidoscopy (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 score at baseline and Week 16 visit will be calculated based on the subject's diary data recorded over the 3 prior consecutive days.

The Mayo endoscopic subscore will be assessed by the mucosal appearance during the flexible sigmoidoscopy or colonoscopy based on the scoring system provided in the protocol (Appendix 1). The endoscopic appearance will be read by both the investigator and central

reader. Centrally read endoscopic subscores will be used for both eligibility and efficacy analyses.

The physician's global assessment (PGA) acknowledges the other three criteria, the subject's abdominal discomfort and sense of general well-being. In addition, the investigator should consider other observations (ie, physical findings) and subject's performance status when making the PGA assessment. It is preferred that the same physician performs all such assessments for a given subject throughout the study.

7.4.5. Partial Mayo Score

A partial Mayo score (Mayo score without the endoscopic subscore) will be assessed prior to the administration of the investigational product and at the specified study visits in the SOA.

7.4.6. Simple Clinical Colitis Activity Index (SCCAI)

The SCCAI measures disease activity as defined by both subjects and examiners and includes the following 13 items: general well-being, abdominal pain, bowel frequency, stool consistency, bleeding, anorexia, nausea or vomiting, abdominal tenderness, extra intestinal complications (eye, mouth, joint, skin), temperature, sigmoidoscopic assessment, nocturnal bowel movements, and urgency of defecation.[7] Scores range from 0 to 19 points, and scores <2.5 have been shown to correlate with Patient-Defined Remission, and a decrease of >1.5 points from baseline correlates with Patient-Defined Significant Improvement.[8] SCCAI will be administered by study site personnel and will reflect a subject's self-assessment of the prior 24-hour period. Scores will be obtained prior to the first dose of study treatment at baseline. Subsequent SCCAI assessments will occur throughout the treatment period prior to the performance of any other study procedures (See Appendix 2).

7.5. Pharmacokinetics

7.5.1. Serum Samples for Analysis of PF-00547659

Blood samples for the assessment of PF-00547659 will be collected and analyzed at the specified time points for the duration of the study at protocol-specified times (See Schedule of Activities). Samples will be analyzed for PF-00547659 using a validated assay. Follow Section 7.7 for serum harvest procedure.

Samples will be analyzed using a validated analytical method in compliance with Shire standard operating procedures.

Collection tube labels must include the following preprinted information: protocol number, subject number, treatment period, study day, and nominal time of sample withdrawal as well as the test identification 'PF-00547659/serum'.

7.5.1.1. Shipment of Serum Samples for Analysis of PF-0547659

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

7.6. Pharmacodynamics

7.6.1. hs CRP

Highly sensitive C reactive protein (hs CRP) is a highly sensitive inflammation biomarker. hs CRP will be measured through regularly scheduled safety laboratory serum samples as specified in the Table 1 and Section 6.

7.6.1.1. Shipment of Samples for Analysis of hs CRP

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

7.6.2. Fecal Calprotectin

Fecal calprotectin (a neutrophil degradation product) is a second inflammation biomarker that will be analyzed. Stool samples for fecal calprotectin measurements will be obtained through stool samples collected at baseline through Week 24, Week 32, and Week 72 as specified in Table 1 and Section 6. Stool samples for fecal calprotectin should be collected at the specified study visit. Labeled stool containers and plastic bags will be provided to the subjects at the preceding visit so they can bring the stool specimen with them at that visit. While it is preferred to provide a fresh specimen, it will not interfere with testing if the stool is refrigerated or frozen. If the subject fails to bring in the stool specimen, they should stay at the site and provide it the day of the visit if at all possible or at the earliest possible time.

Note: Fecal calprotectin will be collected from subjects who were previously in study A7281009 only.

7.6.2.1. Shipment of Fecal Samples for Analysis Fecal Calprotectin

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

7.6.3. Exploratory Biomarkers (Blood/Stool):

- **Soluble MAdCAM in blood may be assessed at baseline and Week 16.**
- **Gene expression profiling (mRNA) in blood and protein associated with UC, inflammation and mechanism of drug activity may be assessed at baseline, Week 16 and Week 72.**
- Analyses relevant to the understanding and treatment of UC may be conducted on the portion of stool samples remaining after calprotectin analysis.

7.6.3.1. Shipment of Samples for Analysis of Exploratory Biomarkers

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

7.7. Immunogenicity

7.7.1. Serum Samples for Anti-drug Antibodies

During all trial sessions, blood samples (2 mL) to provide a minimum of 1 mL of serum for the analysis of anti-PF-00547659 antibodies will be collected at the time points specified in the Table 1 and Section 6.

Samples will be analyzed using a validated analytical method in compliance with Shire standard operating procedures. A positive ADA sample will be further tested for neutralizing antibodies.

Collection tube labels must include the following preprinted information: protocol number, subject number, treatment period, study day, and nominal time of sample withdrawal as well as the test identification 'ADA/serum'.

7.7.1.1. Shipment of Serum Samples for Analysis of Anti-drug Antibodies

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

7.8. Procedure for Serum Collection

During all trial periods, blood samples will be collected into appropriately labeled vacuum tubes **containing no additive glass tube (the silicone coated plastic tube is acceptable if non-additive glass red top tube is not available)** at times specified in the protocol. A serum separator tube should not be used.

Blood samples will be allowed to clot at room temperature (18°C-25°C) **for at least 30 minutes for a complete clot**. Place the clotted samples into an ice/bath for approximately 10 minutes prior to the centrifugation. Serum will be separated from the whole blood within approximately 40 minutes of collection. Specimen should be centrifuged at 1000 to 1200 x g for approximately 10 to 15 minutes in an ambient centrifuge (refrigerated centrifuge is acceptable if it's available) to harvest the serum. After centrifugation, the upper serum layer is carefully transferred with a disposable pipette into a labeled screw capped plastic storage tube. Sample should be re centrifuged immediately if red blood cells are inadvertently drawn into the serum. Serum samples will be frozen in an upright position at approximately -20°C or colder within 60 minutes of sample collection.

8. ADVERSE EVENT REPORTING

8.1. Adverse Events

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

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

the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Shire concurs with that assessment.

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

8.2. Reporting Period

For SAEs, the active reporting period to Shire or its designated representative begins from the time that the subject provides informed consent, which is obtained prior to the subject's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including the End of Study visit. SAEs occurring to a subject after the active reporting period has ended should be reported to the Sponsor if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product are to be reported to the Sponsor.

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

8.3. Definition of an Adverse Event

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

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

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

- Drug overdose;
- Drug withdrawal;

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

8.4. Medication Errors

Medication error may result, in this study, from the administration of the wrong product, to the wrong subject, at the wrong time, per the wrong route, wrong administration location, or at the wrong dosage strength, due to human error. Medication errors include overdose (accidental or intentional). Such medication errors occurring to a study participant are to be captured on the medication error case report form (CRF) which is a specific version of the adverse event (AE) page, and on the SAE form when appropriate. In the event of medication dosing error, the sponsor should be notified immediately.

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

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

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

8.5. Abnormal Test Findings

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

- Test result is associated with accompanying symptoms, and/or
- Test result requires additional diagnostic testing or medical/surgical intervention, and/or
- Test result leads to a change in study dosing or discontinuation from this study, significant additional concomitant drug treatment, or other therapy, and/or

- Test result is considered to be an adverse event by the investigator or sponsor.

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

8.6. Serious Adverse Events

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

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity(substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.
- Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other adverse event outcomes, the important medical event should be reported as serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

8.6.1. Protocol-Specified Serious Adverse Events

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

8.6.2. Potential Cases of Drug-Induced Liver Injury

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

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

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

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

    - For subjects with pre-existing AST or ALT baseline values above the normal range: AST or ALT values ≥2 times the baseline values and ≥3 X ULN, or ≥8 X ULN (whichever is smaller).

- **Concurrent with**

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

The subject should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history and physical assessment. In addition to repeating measurements of AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/ international normalized ratio (INR) and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced person , surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (eg, biliary tract) may be warranted.

All cases confirmed on repeat testing as meeting the laboratory criteria, defined above with no other cause for liver function test (LFT) abnormalities identified at the time should be considered potential Hy's Law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's Law cases should be reported as serious adverse events.

8.7. Hospitalization

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

Hospitalization does not include the following:

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

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical adverse event is not in itself a serious adverse event. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new adverse event or with a worsening of the preexisting condition (eg, for work-up of persistent pre-treatment lab abnormality);
- Social admission (eg, subject has no place to sleep);
- Administrative admission (eg, for yearly physical exam);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical adverse event (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Pre-planned 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 non-invasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as an AE, and the resulting appendectomy should be recorded as treatment of the AE.

8.8. Severity Assessment

If required on the adverse event case report forms, the investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the adverse event. 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 adverse event. A severe event is not necessarily a serious event. For example, a headache may be severe (interferes significantly with subject's usual function) but would not be classified as serious unless it met one of the criteria for serious adverse events, listed above.

8.9. Causality Assessment

The investigator's assessment of causality must be provided for all adverse events (serious and non-serious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the serious adverse 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 adverse event; 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 (see the Section on Reporting Requirements). 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 a serious adverse event is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the serious adverse event reporting requirements, if applicable.

8.10. Exposure During Pregnancy

All pregnancies are to be reported from the time informed consent is signed until the defined follow-up period stated in Section 7.1.

Any report of pregnancy for any female study participant or the partner of a male study participant must be reported within 24 hours to Shire Global Drug Safety using the Shire Investigational and Marketed Products Pregnancy Report Form. A copy of the Shire Investigational and Marketed Products Pregnancy Report Form (and any applicable follow-up reports) must also be sent to the CRO/Shire medical monitor using the details specified in the emergency contact information section of the protocol. The pregnant female study participant must be withdrawn from the study.

Every effort should be made to gather information regarding the pregnancy outcome and condition of the infant. It is the responsibility of the investigator to obtain this information within 30 calendar days after the initial notification and approximately 30 calendar days postpartum.

Pregnancy complications such as spontaneous abortion/miscarriage or congenital abnormality are considered SAEs and must be reported using the Shire Clinical Study Adverse Event Form for Serious Adverse Events (SAEs) and Non-serious AEs as Required by Protocol. Note: An elective abortion is not considered an SAE.

In addition to the above, if the investigator determines that the pregnancy meets serious criteria, it must be reported as an SAE using the Shire Clinical Study Serious Adverse Event Form for Serious Adverse Events (SAEs) and Non-serious AEs as Required by Protocol as well as the Shire Investigational and Marketed Products Pregnancy Report Form. The test date of the first positive serum/urine β-hCG test or ultrasound result will determine the pregnancy onset date.

8.11. Occupational Exposure

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

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

8.12. Withdrawal Due to Adverse Events (See also the Section 6.4 on Early Withdrawal)

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

When a subject withdraws because of a serious adverse event, the serious adverse event must be reported in accordance with the reporting requirements defined below.

8.13. Eliciting Adverse Event Information

The investigator is to report all directly observed adverse events and all adverse events spontaneously reported by the study subject. In addition, each study subject will be questioned about adverse events.

8.14. Reporting Requirements

Each adverse event is to be assessed to determine if it meets the criteria for serious adverse events. If a serious adverse event occurs, expedited reporting will follow local and international regulations, as appropriate.

8.14.1. Serious Adverse Event Reporting Requirements

All initial and follow-up SAE reports must be reported by the investigator to Shire Global Drug Safety and the CRO/Shire medical monitor within 24 hours of the first awareness of the event. In addition, any SAE(s) considered "related" to the investigational product and discovered by the investigator at any interval after the study has completed must be reported to Shire Global Drug Safety within 24 hours of the first awareness of the event.

In particular, if the serious adverse event is fatal or life-threatening, notification to Shire must be made immediately, irrespective of the extent of available adverse event information. This timeframe also applies to additional new information (follow-up) on previously forwarded serious adverse event reports as well as to the initial and follow-up reporting of exposure during pregnancy exposure via breastfeeding and occupational exposure cases.

The investigator must complete, sign, and date the Shire Clinical Study Adverse Event Form for Serious Adverse Events (SAEs) and Non-serious AEs as Required by Protocol and verify the accuracy of the information recorded on the form with the corresponding source documents (Note: Source documents are not to be sent unless requested) and fax or e-mail the form to Shire Global Drug Safety. A copy of the Shire Clinical Study Adverse Event Form for Serious Adverse Events (SAEs) and Non-serious AEs as Required by Protocol (and any applicable follow-up reports) must also be sent to the CRO/Shire medical monitor using the details specified in the emergency contact information section of the protocol.

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

For all serious adverse events, the investigator is obligated to pursue and provide information to Shire in accordance with the timeframes for reporting specified above. In addition, an investigator may be requested by Shire to obtain specific additional follow-up information in an expedited fashion. This information collected for serious adverse events is more detailed than that captured on the adverse event case report form. In general, this will include a description of the adverse event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications, vaccines, and/or illnesses must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Shire or its designated representative.

8.14.2. Protocol Specific Medically Important Events

Any unexplained change in neurological status or abnormalities in the neurological assessments should prompt a neurological consult and if appropriate, be reported as an adverse event or medically important event. Events that already meet SAE criteria (eg, seizure, stroke) should be reported immediately (See Section 8.6). If clinically indicated, an MRI scan and possibly a lumbar puncture for JC virus DNA should be performed to rule out PML or other causes of the neurological findings. All cases will be reviewed and adjudicated by the DMC.

In case of unexplained neurological signs or symptoms consistent with PML, treatment with PF-00547659 should be halted and further neurological evaluation is required.

8.14.3. Non-Serious Adverse Event Reporting Requirements

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

8.14.4. Sponsor's Reporting Requirements to Regulatory Authorities

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

9. DATA ANALYSIS/STATISTICAL METHODS

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

9.1. Sample Size Determination

All eligible subjects, based on inclusion/exclusion criteria, from the A7281009 study may be enrolled. It is estimated that approximately 90% of the subjects (about 331 subjects) from study A7281009 are likely to enroll into this open label extension study A7281010. The sample size is chosen based on clinical outcome of study A7281009 rather than statistical consideration.

9.2. Exploratory Efficacy Analysis

Descriptive statistics will be provided for the exploratory efficacy analysis. The binary endpoints such as clinical remission, clinical response will be summarized with frequency and percentage by time point; and the continuous variables will be summarized with n, mean, median, standard deviation etc. These summaries may be provided by the strata of responding status at entry based on the feeder study.

All subjects who have received at least one dose of planned investigational product in the open lable extension study will be included into the exploraty efficacy analysis. Detailed methodologies of these analyses will be described in the SAP.

9.3. Exploratory Pharmacodynamic Analysis

Fecal calprotectin, hsCRP and exploratory biomarkers will be listed and summarized by visit, and change from baseline for these endpoints will also be summarized at specific time points as reported in the SOA.

Appropriate regression models may be used to look at association between these endpoints and any covariates of clinical interests.

Data from the substudy may be combined with biopsy data from other ongoing MAdCAM studies for analysis.

9.4. Pharmacokinetic Analysis

Blood samples will be collected prior to dosing for analysis of plasma trough concentrations of PF-00547659. Serum concentration data obtained from all subjects in this study will be tabulated and plotted to assess average steady state concentrations following repeat SC dosing of PF-00547659. As subjects enrolled in this study will have previously been followed in a separate protocol (the feeder study) where more PK sampling may have been performed, the trough PK data collected from this study may be combined with data from the previous study (the A7281009 study) into a single database.

Presence of anti-PF-00574659 antibodies will be listed and summarized by time post dose for each dose.

In subjects with a positive ADA, presence of neutralizing antibodies may be listed and summarized by time post dose for each dose.

9.5. Safety Analysis

Safety data may be reviewed and summarized on an ongoing basis as needed during the study since this is an open-label study. A set of safety summary tables will be produced to evaluate potential risks associated with the safety and tolerability of administering the study medication. All clinical AEs, SAEs, on-treatment AEs, as well as discontinuations due to AEs will be summarized with frequency and percentage. Continuous outcomes (eg, vitals, safety lab parameters, etc) will be summarized using n, mean, median, standard deviation etc. Change from baseline on selected safety endpoints may be additionally summarized. Subject listings may also be produced for these safety endpoints.

The safety endpoints will be listed and summarized in accordance with Shire Data Standards. Detailed methodologies of these analyses will be described in the SAP.

9.6. Interim Analysis

Two interim analyses (IAs) may be performed for this study when 50% of subjects from the Phase 2 study (A7281009) have been enrolled in this study (A7281010), and the last subject from the Phase 2 study (A7281009) has been enrolled in this study (A7281010). The purpose of the IAs is to provide additional data on the durability of response, remission, and safety from A7281009 to facilitate the decision-making process of initiating future studies. Summary statistics for safety, efficacy as well as subject demographics will be provided at IA. Detailed analysis will be described in the SAP.

Additional interim analyses may also be performed when it is deemed necessary to evaluate safety and efficacy during the trial.

9.7. Data Monitoring Committee

An external Data Monitoring Committee will be in place to review the safety of subjects on an ongoing basis and to adjudicate any subjects with unexplained neurological or cardiac findings. Membership of this committee shall include at least one neurologist with expertise in PML and one cardiologist with expertise in heart failure and/or myocarditis. Work-up of such suspected PML cases will include a neurology consultation as well as an MRI scan, and a lumbar puncture, if clinically indicated. Additional procedures may be deemed necessary. Given the lack of therapeutic options for subjects who have failed at least 1 conventional therapy, PF-00547659 with its distinct mechanism of action and known safety profile appears to have a favorable Risk-Benefit profile. The added precautions regarding PML are probably unnecessary but will serve to increase the confidence in PF-00547659 for future development.

Additional cardiac monitoring will be implemented in this study. Serum samples for CPK (with reflex isoenzymes), troponin I and NT-proBNP will be drawn with the safety labs. Elevation of troponin I >0.05 ng/mL or CPK with MB or should prompt a cardiology consult. Any subject who experiences an initial on-study elevation of NTproBNP to >300 pg/mL shall have an echocardiogram and cardiology consult. All subjects who have had an echocardiogram, in whom the NTproBNP remains >124 pg/mL at the 144 week visit, shall have a repeat echocardiogram and cardiology consultation ordered no later than the following visit. All cases of on-study elevation of NTproBNP to >300 pg/mL, elevation in cardiac troponin I (cTnI) or CK/MB or new ECG changes will be reviewed by the DMC.

The DMC will be responsible for ongoing monitoring of safety of subjects in the study according to the Charter. The recommendations made by the DMC to alter the conduct of the study or amend the protocol will be forwarded to Shire for final decision. Shire 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.

10. QUALITY CONTROL AND QUALITY ASSURANCE

During study conduct, Shire or its agent will conduct periodic monitoring visits to ensure that the protocol and GCPs are being followed. The monitors may review source documents to confirm that the data recorded on CRFs is accurate. The investigator and institution will allow Shire monitors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification.

The study site may be subject to review by the institutional review board (IRB)/independent ethics committee (IEC), and/or to quality assurance audits performed by Shire, or companies working with or on behalf of Shire, and/or to inspection by appropriate regulatory authorities.

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 case report form (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 Shire and should not be made available in any form to third parties, except for authorized representatives of Shire or appropriate regulatory authorities, without written permission from Shire.

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 is true. Any corrections to entries made in the CRFs, source documents must be dated, initialed and explained (if necessary) and should not obscure the original entry.

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

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

11.2. Record Retention

To enable evaluations and/or audits from regulatory authorities or Shire, 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, telephone calls reports). The records should be retained by the investigator according to ICH, local regulations, or as specified in the Clinical Study Agreement, whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Shire should be prospectively notified. The study records must be transferred to a designee acceptable to Shire, such as another investigator, another institution, or to an independent third party arranged by Shire. 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 Shire's written permission before disposing of any records, even if retention requirements have been met.

12. ETHICS

12.1. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

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/IEC. All correspondence with the IRB/IEC should be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to Shire.

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

12.2. Ethical Conduct of this Study

This study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for Good Clinical Practice (International Conference on Harmonization 1996), and the Declaration of Helsinki (World Medical Association 1996 and 2008).

In addition, this study will be conducted in accordance with the protocol, the International Conference on Harmonisation guideline on Good Clinical Practice, and applicable local regulatory requirements and laws.

12.3. Subject Information and Consent

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

Subject names, address, birth date and other identifiable data will be replaced by anumerical code consisting of a numbering system provided by Shire in order to de-identify the trial subject.

In case of data transfer, Shire will maintain high standards of confidentiality and protection of subject personal data.

The informed consent document must be in compliance with ICH GCP, local regulatory requirements, and legal requirements.

The informed consent document(s) used during the informed consent process must be reviewed by the sponsor, approved by the IRB/IEC, and available for inspection.

The investigator must ensure that each study subject, or his/her legally acceptable representative, is fully informed about the nature and objectives of this study and possible risks associated with participation. The investigator, or a person designated by the investigator, will obtain written informed consent from each subject or the subject's legally acceptable representative before any

study-specific activity is performed. The investigator will retain the original of each subject's signed consent document.

12.4. Subject Recruitment

Advertisements approved by ethics committees and investigator databases may be used as recruitment procedures.

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

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable Competent Authority in any area of the World, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of the investigational product, Shire should be informed immediately.

In addition, the investigator will inform Shire 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 sufficient subjects have been recruited and completed this study as stated in the regulatory application (ie, Clinical Study 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 this study in that Member State.

13.2. End of Trial in all Participating Countries

End of Trial in all participating countries is defined as Last Subject Last Visit.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, drug safety problems, or at the discretion of Shire. In addition, Shire retains the right to discontinue development of PF-00547659 at any time.

If a study is prematurely terminated or discontinued, Shire 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 Shire, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

Publication of study results is discussed in the Clinical Study Agreement.

15.1. Communication of Results by Shire

Shire fulfils 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 (EudracCT), and/or www.shire.com and other public registries in accordance with applicable local laws/regulations.

In all cases, study results are reported by Shire 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

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

Primary Completion Date is defined as the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the pre-specified protocol or was terminated.

EudraCT

Shire posts EU Basic Results on EudraCT for all Shire-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

www.shiretrials.com

Shire 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.shire.com for Shire-sponsored interventional studies after primary publication or after 18 months of last subject last visit.

15.2. Publications by Investigators

Shire has no objection to publication by Investigator of any information collected or generated by Investigator, whether or not the results are favorable to the Investigational Drug. However, to ensure against inadvertent disclosure of Confidential Information or unprotected Inventions, Investigator will provide Shire an opportunity to review any proposed publication or other type of disclosure before it is submitted or otherwise disclosed.

The investigator will provide manuscripts, abstracts, or the full text of any other intended disclosure (poster presentation, invited speaker or guest lecturer presentation, etc.) to Shire at

least 30 days before they are submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, 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 (other than the Study results themselves) before disclosure.

If this Study is part of a multi-centre study, the investigator agrees that the first publication is to be a joint publication covering all centers. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of this Study at all participating sites, Investigator is free to publish separately, subject to the other requirements of this Section.

For all publications relating to this Study, 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 Clinical Study Agreement between Shire and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the Clinical Study Agreement.

16. REFERENCES

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Appendix 1. Mayo Scoring System for Assessment of Ulcerative Colitis Activity*

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

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

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

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

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

Appendix 2. Simple Clinical Colitis Activity Index (SCCAI)

SIMPLE CLINICAL COLITIS ACTIVITY INDEX

	Scores				
	0	1	2	3	4
Bowel Frequency (day)	1-3	4-6	7-9	>9	
Bowel Frequency (night)	1-3	4-6			
Urgency of Defecation	--	Hurry	Immediately	Incontinence	
Blood in Stool	--	Trace	Occasionally frank	Usually frank	
General well-being	Very well	Slightly below par	Poor	Very Poor	Terrible
Arthritis, pyoderma gangrenosum, eruthema nodosum, uveitis		1 per manifestation			

Reprinted with permission from: Walmsley R, Ayres R, Pounder R, and Allan R. A simple clinical colitis activity index. Gut 1998;43:29-32.

Appendix 3. Sample Subject Stool Diary

SUBJECT STOOL DIARY

What is your normal number of stools per day (when not having a flare)?	_____

QUESTIONS	ANSWERS
Date (dd/MMM/yyyy) (eg,: 10 Aug 2010)	___ - ____ - _____
How many times did you need to go to the toilet to have a bowel movement?	_____
Was there any blood present in your stool at any of these times?	[ ] Yes [ ] No
How would you describe the blood in your stools? (Please cross one box only)	[ ] No blood seen [ ] Streaks of blood with stool less than half the time [ ] Obvious blood with stool most of the time [ ] Blood alone passes

Appendix 4. Confrontational Visual Fields

To begin the test, you will be asked to cover one eye, fixing your gaze on the examiner's eyes. The examiner will then conduct finger movements, bringing his or her hands into your visual field from the sides. Because your vision is divided into four quadrants in your brain, the examiner will hold up fingers in each quadrant. You will say how many fingers you see without actually looking at them, thus testing your peripheral, or side, vision.

Source: http://vision.about.com/od/eyeexamination1/f/Confrontation_Fields.htm

Appendix 5. Timed Ambulation 25 Foot Test

Subjects will walk a predefined straight 25-foot course as quickly as possible. The location of the course should remain constant. It should be made clear to the subjects that they should walk as quickly as possible and that they will be timed. Stopwatch timing will begin as soon as the subject indicates that they are ready to go and fully cross the start line. Timing will stop once the subject fully steps over the finish line.

Reference: Multiple Sclerosis Functional Composite (MSFC) Administration and Scoring Manual. National Multiple Sclerosis Society, October 2001.

Appendix 6. 9-Hole Peg Test Administration

Pegboard is centered in front of subject with pegs placed in the container next to the board on the same side as the hand being tested. The dominant hand is tested first. The following instructions are given to the subject as the examiner briefly demonstrates the test:

"Pick up the pegs one at a time, using your dominant hand only, and put them into the holes in any order until all of the holes are filled. Then remove pegs one at a time, and return them to the container. Stabilize the board with your other hand. This is a practice test. See how fast you can put all the pegs in and take them out again. Are you ready? Go."

After the subject completes the practice trial, the examiner says, "This will be the actual test. The Instructions are the same. Work as quickly as you can. Are you ready? Go!

[During the test] The examiner says, "faster."

The stopwatch is started by the examiner as soon as the subject touches the first peg, and is stopped when the last peg hits the container. The container is next placed on the opposite side of the pegboard and the other hand is tested.

Other considerations:

1. It is acceptable to switch the position of the box to accommodate the patient.
2. Record time for each trial in total seconds. There are two trials per hand.
3. Maximum time of 5 minutes (300 seconds) to complete one trial.
4. For subjects with upper extremity tremors or truncal ataxias, stabilization of elbows on the table surface may be used.

The Rolyan 9-Hole Peg Test container cover (manufactured by Smith and Nephew, Inc), can be used to store pegs during administration of the test; however, a towel, felt cloth or the Dycem Mat under the container to keep dropped pegs from rolling away on the floor may be helpful. Please calculate the total score in seconds. Test is administered using the dominant and nondominant hands.

Reference: Multiple Sclerosis Functional Composite (MSFC) Administration and Scoring Manual. National Multiple Sclerosis Society, October 2001.

Appendix 7. Symbol Digit Modality Test

Administering the Written Version of the SDMT

This version of the test may be either group or individually administered. The test form is handed to the examinee(s) and the following instructions are read aloud by the examiner (examiner reads only the boldface words):

- Please look at these boxes at the top of the page. You can see that each box in the upper row has a little mark in it. Now look at the boxes under the marks has a number. Each of the marks in the top row is different, and under each mark in the bottom row is a different number.

- Now look at the next line of boxes (examiner points to line of boxes) just under the top two rows. Notice that the boxes on the top have marks, but the boxes underneath are empty. You are to fill each empty box with the number that should go there according to the way they are paired in the key at the top of the page. For example, if you look at the first mark, and then look up at the key, you will see that the number 1 goes in the first empty box. So write the number 1 in the first box. Now, what number should you put in the second box? (Number 5) That's right. So write the number 5 in the second box. What number goes in the third box? (Number 2) Two, right. That is the idea. You are to fill each of the empty boxes with the numbers that should go in them according to the key. Now for practice, fill in the rest of the boxes until you come to the double line. When you come to the double line, stop.

The examiner should check to see that each examinee understands the task. Any errors made in the first 10 practice responses should be immediately pointed out by the examiner and corrected by the examinee. If an examinee has not understood the nature of the task, the instructions are repeated with further examples until the nature of the test is clearly understood. The examiner then continues with the following instructions:

- Now when I say "Go!" write in the numbers just like you have been doing as fast as you can until I say "Stop!" When you come to the end of the first line, go quickly to the next line without stopping, and so on. If you make a mistake, do not erase, just write the correct answer over your mistake. I repeat, DO NOT ERASE as you will waste time. Just write the correct answer over your mistake. Do not skip any boxes and work as quickly as you can. Ready? Go!

Exactly 90 seconds from starting, the examiner says:

- Stop!

Reference: Symbol Digit Modalities Test Manual (Aaron Smith, Ph.D. University of Michigan). Western Psychological Services, March 2010.

Adult Norms for Mean Written SDMT Scores by Age Group and Level of Education[1]

Deviation Units[a]	Age Range 18-24	25-34	35-44	45-54	55-64	65 or more
	12 Years or Less of Education[b]					
-3.0 SD	29	29	27	19	19	6
-2.5 SD	34	33	31	23	23	11
-2.0 SD	38	37	35	28	27	15
-1.5 SD	42	41	39	33	31	20
-1.0 SD	46	45	43	38	35	24
-0.5 SD	50	49	47	42	39	29
0.0 SD	54	53	52	47	43	33
+0.5 SD	59	57	56	52	47	38
+1.0 SD	63	61	60	57	51	42
+1.5 SD	67	65	64	62	55	47
+2.0 SD	71	69	68	66	59	51
+2.5 SD	75	73	72	71	63	56
+3.0 SD	79	77	76	76	67	60

Deviation Units[a]	Age Range 18-24	25-34	35-44	45-54	55-64	65 or more
	13 Years or More of Education[c]					
-3.0 SD	31	30	21	27	23	10
-2.5 SD	37	35	26	31	27	15
-2.0 SD	42	40	32	35	31	21
-1.5 SD	47	44	37	40	35	27
-1.0 SD	52	49	43	44	39	32
-0.5 SD	57	53	49	48	43	38
0.0 SD	62	58	54	52	48	44
+0.5 SD	67	62	60	57	52	49
+1.0 SD	72	67	65	61	56	55
+1.5 SD	77	71	71	65	60	60
+2.0 SD	82	76	77	69	64	66
+2.5 SD	87	80	82	73	68	72
+3.0 SD	92	85	88	78	73	77

a. SD = standard deviation from the mean
b. n = 477
c. n = 830

[1] Smith A. Symbol Digit Modalities Test Manual. Western Psychological Services, Los Angeles. 1982.

Appendix 8. MSNQ - Patient

MSNQ Patient

Name: _____

Date: _____

Circle one: MALE / FEMALE

INSTRUCTIONS:
The following questions ask about problems that you may experience. Rate how often these problems occur **AND** how severe they are. Base your ratings on how you have been over the **last three months**.

Please check the appropriate box.

	Very often, very disruptive (4)	Quite often, interferes w/ life (3)	Occasionally, seldom a problem (2)	Very rarely, no problem (1)	Never, does not occur (0)
1. Are you easily distracted?					
2. Do you lose your thoughts while listening to somebody speak?					
3. Are you slow when trying to solve problems?					
4. Do you forget appointments?					
5. Do you forget what you read?					
6. Do you have trouble describing shows or programs recently watched?					
7. Do you need to have instructions repeated?					
8. Do you have to be reminded to do tasks?					
9. Do you forget errands that were planned?					
10. Do you have difficulty answering questions?					
11. Do you have difficulty keeping track of two things at once?					
12. Do you miss the point of what someone is trying to say?					
13. Do you have difficulty controlling impulses?					
14. Do you laugh or cry with little cause?					
15. Do you talk excessively or focus too much on your own interests?					