STATISTICAL ANALYSIS PLAN

Protocol No.:	A7281010
Protocol Title:	A MULTICENTER OPEN-LABEL EXTENSION STUDY TO ASSESS LONG-TERM SAFETY OF PF-00547659 IN SUBJECTS WITH ULCERATIVE COLITIS (TURANDOT II)
Drug:	SHP647 (MAdCAM) (previously PF-00547659)
Sponsor:	Shire Human Genetic Therapies Inc. 300 Shire Way Lexington, MA 02421 USA
Version No. and Date	Version 3.1, 02 February 2018

Version No:	Document History Description of Update	Author(s)	Effective Date
3.0	Update statistical analysis plan received from Pfizer to Shire standards.	PPD	22 September 2017
3.1	Changed the exposure summaries to include data only from 1010 and added by dose summaries. Added 1009 medications as prior medications Updated PCI criteria for weight Removed Changes from baseline analysis of Geometric mean and added 90% CI for percent change from baseline geometric mean analysis Added clarification on imputation of missing start dates Addition of new outputs and removal of redundant outputs Minor editorial updates throughout	PPD	02 February 2018

TABLE OF CONTENTS

LIST OF TABLES

ABBREVIATIONS

9-HPT	9-Hole Peg Test
ADA	Anti-drug antibody
AE	Adverse event
ALP	Alkaline phosphatase
ALQ	Above the limit of quantification
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic class
BLQ	Below the limit of quantification
BMI	Body mass index
BUN	Blood urea nitrogen
BP	Blood Pressure
CI	Confidence interval
CPK	Creatinine phosphokinase
CRP	C-reactive protein
CTn1	Cardiac troponin I
DMC	Data monitoring committee
DNA	Deoxyribonucleic acid
eCRF	Electronic case report form
ECG	Electrocardiogram
ECHO	Echocardiogram
FAS	Full Analysis Set
FoTA	Final-on-treatment assessment
hsCRP	High-sensitivity C-reactive protein
MedDRA	Medical Dictionary for Regulatory Activities
MSNQ	Multiple Sclerosis Neuropsychological Questionnaire
Nabs	Neutralizing antibodies
NT-proBNP	N-terminal B-type Natriuretic Peptide
PCI	Potentially clinically important
PD	Pharmacodynamic
PK	Pharmacokinetic
PT	Preferred term
QTcB	QT Interval Corrected for Heart Rate using Bazett’s Formula

QTcF	QT Interval Corrected for Heart Rate using Fridericia's Formula
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SCCAI	Simple clinical colitis activity index
SD	Standard deviation
SDMT	Symbol digit modality test
SOC	System organ class
TEAE	Treatment-emergent adverse event
TNF	Tumor necrosis factor
ULN	Upper limit of normal
WHO	World Health Organization

1. Introduction

This statistical analysis plan (SAP) provides a technical and detailed elaboration of the statistical analyses of safety, efficacy, tolerability, pharmacokinetic/pharmacodynamic data as described in the final study protocol version dated 14 November 2016 incorporating most recent amendment 5. Specifications for tables, figures, and listings are contained in a separate document. Statistical analysis plans for pharmacokinetic/pharmacodynamic data are prepared separately and included as appendices to the SAP, as appropriate.

2. STUDY DESIGN

2.1. General Study Design

This is a multi-center Phase 2, open-label, safety extension study for the A7281009 study, which evaluated SHP647 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 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.

Eligible subjects will be asked if they would like to continue participation in an optional endoscopic substudy that will characterize the effect of SHP647 on mucosal healing and tissue biology. Participation in this part of the study will not affect participation in the main study. Approximately 40 subjects are needed for meaningful data. Data may be combined with the data from the other MAdCAM IBD studies. Details of the substudy analysis will not be included in this SAP and will be captured in an independent SAP.

2.2. Randomization

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.

2.3. Blinding

This is an open-label study so blinding is not applicable.

2.4. Schedule of Assessments

Table 1a: 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 of protocol) and Assessments (Section 7 of protocol) 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

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**																	
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
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

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**																	
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
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 of protocol).
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 of protocol). However, mucosal healing may be assessed.

Table 2b: 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

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**																				
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
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).

2.5. Determination of Sample Size

Statistical hypothesis is not applicable to this study and there are no statistical decision rules for this study.

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 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 study A7281009 rather than statistical consideration.

2.6. Multiplicity Adjustments for Type I Error Control

Adjusting for multiplicity is not applicable, there are no statistical hypotheses being tested.

3. OBJECTIVES

3.1. Primary Objective

- The primary objective of this study is to monitor the safety and tolerability of SHP647 during long-term treatment.

3.2. Secondary Objectives

- The secondary objective is to assess pharmacokinetics and immunogenicity of SHP647.

3.3. Exploratory Objectives

- Exploratory objectives include an assessment of the durability of response with long term treatment with SHP647 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 SHP647, PD and clinical endpoints.

4. SUBJECT POPULATION SETS

4.1. Open Label Treatment Period 1 (Week 0-72)

4.1.1. Enrolled Subjects

Enrolled subjects consists of all subjects for whom some study procedures have begun.

4.1.2. Safety Analysis Set

The Safety Set will consist of all enrolled subjects who have taken at least 1 dose of investigational product.

4.1.3. Pharmacokinetic (PK) Set

The PK population is defined as all subjects who received at least 1 dose of investigational product and for whom at least 1 postdose PK sample was collected.

4.1.4. Pharmacodynamic (PD) Set

The PD population is defined as all subjects who received at least 1 dose of investigational product and for whom at least 1 postdose PD sample was collected

5. SUBJECT DISPOSITION

The number of subjects included in each subject set will be summarized by the following treatment groups:

- SH647 75mg no escalation - this comprises all data for patients who receive 75mg throughout the Open Label Treatment Period 1.
- SHP647 75->225 mg – this comprises all data for patients who (prior to protocol amendment 3) up-titrated from 75 mg to 225 mg in Open Label Treatment Period 1.
- SHP647 75 mg overall – this comprises all patients who were randomized to 75 mg in Open Label Treatment Period 1.
- SHP647 225mg – this comprises all patients who were randomized to 225 mg in Open Label Treatment Period 1.
- SHP647 all doses – this comprises all patients.

A subject disposition table will be provided. The subject disposition table will include the number and percentage of subjects included in each subject set. It will also include number and percentage of subjects enrolled, randomized, treated, entering Open Label Treatment Period 1,Open Label Treatment Period 2, follow up period, discontinuing from the study, discontinuing from Open Label Treatment Period 1,Open Label Treatment Period 2, follow up period and discontinuing from the treatment. A detailed summary of the primary reasons for discontinuation from the study and discontinuation from treatment will be presented by treatment group. The percentages will use the number of subjects in the safety analysis set as the denominator and will be presented by the treatment groups defined above. The subject disposition table will be based on the enrolled set.

All subjects who prematurely discontinued during the study will be listed.

The number of subjects enrolled, randomized and completed will be tabulated by site and country. In addition, the duration of enrollment, in days, will be summarized for each site, country, and overall. Duration of enrollment will be calculated as (last date of contact for any subject at that site - the first date of screening or enrollment for any subject at that site + 1).

6. PROTOCOL DEVIATIONS

Different protocol deviations may have a different impact on the analyses. A full list of protocol deviations will be compiled and reviewed by the Clinician and the Statistician to identify key and non-key deviations prior to database release.

Protocol deviations will be listed. In addition, a listing of key deviations will be provided.

7. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

The demographic table will include the summary of age, sex, ethnicity, race, weight, height, body mass index, anti-TNF use (naïve or experienced), smoking history classification and time since diagnosis of Ulcerative Colitis. All information will come from the A7281010 eCRF page with the exception of anti-TNF use and smoking history which will be taken from the A7281009 demographic page, and time since diagnosis of Ulcerative Colitis which will be re-derived as defined below. The demographic table will be presented by the treatment groups defined in Section 5 and also further presented by clinical response status from A7281009.

Time since diagnosis of Ulcerative Colitis = ([Date of Visit 1 {in 1010} - Date of Diagnosis {from 1009}]+1)/365.25.

The baseline characteristics table will include the summary of clinical response, remission and mucosal healing status collected at A7281009 week 12. This table will be presented by the treatment groups defined in Section 5 and will be based on the safety analysis set.

Categorical variables will be summarized by the number of subjects in each category and the percentage of subjects out of the total in the respective analysis set; continuous variables will be described using summary statistics (n, mean, standard deviation, minimum, median, and maximum).

Height and weight at baseline will be used to calculate BMI using the formula below:

$$\text{BMI} = \frac{\text{weight[kg]}}{(\text{height[m]})^2}$$

A listing will be created to show all the demographics and baseline characteristics for each subject in the Safety population.

Medical history, collected at the baseline visit, will be presented by system order class and preferred term using MedDRA version 19.1 and will be listed. In addition, the medical history collected at the screening visit of A7281009 will be presented based on the A7281010 safety analysis set. The data from A7281009 were coded to MedDRA version 18.1 and will be re-coded for this summary. Drug allergies will also be listed.

8. EXTENT OF EXPOSURE AND TREATMENT COMPLIANCE

8.1. Exposure to Investigational Product

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 subcutaneous (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.

- Exposure to the investigational product for the safety analysis set will be summarized in terms of treatment duration, which is calculated as the number of days from the date of first dose of investigational product taken in A7281010 to the date of the last dose investigational product taken in A7281010, inclusively. In addition, the number of injections of investigational product will be summarized both continuously and categorically (6, 12, 18, 24, 30, 36 injections received). Number of injections received for 75mg and 225 mg doses respectively will be presented as well. Descriptive statistics will be presented by treatment group defined in Section 5.

8.2. Measurement of Treatment Compliance

Investigational product dosing compliance for a specified period is defined as the total number of injections actually administered during that period divided by the number of injections planned to be administered during the same period multiplied by 100. Compliance will be summarized by treatment group/Open Label Treatment Period.

Compliance during the treatment period 1 and 2 and overall will be calculated for each subject using the formula:

Compliance = (# injections actually administrated / # injections planned) * 100

The definition of number of injections planned will be the injection schedule following the protocol (baseline to week 72, every 4 weeks for Open Label Treatment Period 1, week 76 to week 144, every 4 weeks for Open Label Treatment Period 2 and baseline to week 144, every 4 weeks for the overall compliance). For early withdrawal, it will be all the scheduled injections before the withdrawn dates.

9. PRIOR AND CONCOMITANT MEDICATION

Version dated 01 December 2016 of the WHO Drug Dictionary will be used to classify prior and concomitant medications by preferred term name.

Prior medication is defined as any medication with the start date prior to the date of the first dose of investigational product within A7281010.

Concomitant medication is defined as any medication with a start date prior to the date of the first dose of investigational product and continuing after the first dose of investigational product or with a start date between the dates of the first and last doses of investigational product, inclusive. Any medication with a start date after the date of the last dose of investigational product will not be considered a concomitant medication.

All the medications from A7281009 study will be imported to A7281010 study. If the medication is discontinued at end of study A7281009 , it will be considered as Prior for study A7281010 whereas if medication is ongoing, then it will be considered as concomitant for study A7281010

Both prior and concomitant medication usage will be summarized by the number and percentage of subjects in each treatment group receiving each medication within each preferred term for the safety analysis set. Medications can be counted both as prior and concomitant medication. Multiple medication usage by a subject in the same category will be counted only once.

All prior and concomitant medication will be listed.

Subjects in the follow up period will be characterized by additional biologic therapy (anti-TNF (Adalimumab, Certolizumab, Certolizumab Pegol, Golimumab, Infliximab), Vedolizumab and Other Biologics (Ustekinumab)) and summarized by treatment group. Additional biological therapies will be listed.

10. EFFICACY ANALYSES

The safety analysis set will be used for all efficacy analyses. No formal statistical analyses will be performed. Descriptive statistics will be provided for the exploratory efficacy analysis. The continuous variables will be summarized with n, mean, standard deviation, minimum, median and maximum by treatment and time point. The categorical endpoints will be summarized with frequency counts and percentages by treatment and time point. All summaries will be presented by A7281010 treatment group as defined in Section 5.

10.1. Primary Efficacy Endpoint(s) and Analysis

Not applicable

10.2. Secondary Efficacy Endpoint(s) and Analysis

The proportion of subjects with mucosal healing (defined as absolute Mayo subscore for endoscopy of 0 or 1), along with their corresponding 90% confidence intervals based on the Wilson score method, at Baseline and Week 16 will be listed and summarized by the treatment groups as defined in Section 5 and their treatment in the A7281009 study (Placebo vs. SHP647) and overall. These three tables will be presented based on centrally read Mayo subscores only. This will initially be based on the non-responder imputation method (please see Section 17.2.1).These summaries will be produced for all subjects, for subjects who were deemed to be clinical responders in A7281009 and for non-responders in A7281009.

These three tables will be repeated based on the observed cases rather than the non-responder imputation method.

Bar graphs with confidence intervals will also be presented for these summaries.

10.3. Exploratory Efficacy Endpoint(s) and Analyses

10.3.1 Total Mayo, Partial Mayo, SCCAI Clinical Response and Clinical Remission

The proportion of subjects with Clinical Response at Baseline and at Week 16 (based on Total Mayo score and defined in Table 2, below and using the A7281009 baseline) will be presented in the same way as mucosal healing (defined in Section 10.2).

The proportion of subjects with Clinical Remission at Baseline and at Week 16 (based on Total Mayo score and defined in Table 2, below) will be presented in the same way as mucosal healing (defined in Section 10.2). In addition, the proportion of patients with Clinical Remission at Baseline and Week 16 will also be presented by remission status in A7281009 and imputation method.

The proportion of subjects with Clinical Response based upon the partial Mayo Score (using the A7281009 baseline) along with the corresponding 90% Wilson confidence intervals will be summarized by the treatment groups defined in Section 5 and their treatment in the

A7281009 study (Placebo vs. SHP647) and overall by monthly visits. This summary table will be produced for both the non-responder imputation method and the observed case.

The proportion of subjects with Clinical Remission based upon the partial Mayo Score will be presented in the same way as the Clinical Response based on the partial Mayo score.

The proportion of subjects with Clinical Response based upon SCCAI (using the A7281009 baseline) along with the corresponding 90% Wilson confidence intervals will be summarized by the treatment groups defined in Section 5 and their treatment in the A7281009 study (Placebo vs. SHP647) and overall by monthly visits. This summary table will be produced for both the non-responder imputation method and the observed case.

The proportion of subjects with Clinical Remission based upon the SCCAI will be presented in the same way as the Clinical Response based on the SCCAI.

Definitions of remission, response and relapse for the Total Mayo, Partial Mayo, and SCCAI are given in Table 2, Table 3 and Table 4.

In addition, the Total Mayo Score, Partial Mayo Score, individual Mayo Subscores, and SCCAI data at baseline from both A7281009 and A7281010 study and the change from baseline of A7281009 over time will be presented by their treatment groups in study A7281010 and A7281009 and overall. Total Mayo Score and endoscopic subscore will be summarized by source of sigmoidoscopy (Centrally or locally read) separately. In addition, categorical summary will also be provided for the subscores in Mayo scores.

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 of at least 3 points in total Mayo score with at least a 30% change, accompanied by at least one point decrease or absolute score of 0 or 1 in rectal bleeding subscore

Table 3: Partial Mayo Score

Clinical Remission	Partial 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 of at least 2 points in partial Mayo score with at least a 30% change, accompanied by at least one point decrease or absolute score of 0 or 1 in rectal bleeding subscore

Table 4: Simple Clinical Colitis Activity Index	
Clinical Remission	Total SCCAI score of <2 points
Clinical Response	Decrease in SCCAI score of ≥3 points

10.3.2 Dose Escalation

For the table for dose escalation only subjects with starting dose of 75mg will be included. Time to dose escalation in subjects for loss of response will be summarized using Kaplan estimates at 0-8, >8-12, >12-16 in 4 week intervals up to >72, together with their SE will be provided. The number and percentage of subjects who experienced dose escalation and censored (subjects who discontinued during the time period or don't have further dosing data after the time period) at each 4 week interval will be presented. The associated Kaplan-Meier plot will be produced.

11. SAFETY ANALYSES

The safety analysis will be performed using the safety analysis set. Safety variables include AEs, clinical laboratory variables, vital signs, and ECG variables, antibody testing, and neurologic assessments. For each safety variable, the last available value on or before first study dosing date (Day 1) is defined as the baseline. A Final on-Treatment Assessment (FoTA) will be defined as the last observation recorded within the period in which the treatment is administered.

11.1. Adverse Events

Adverse events will be coded using Version 19.1 or newer of MedDRA.

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.

An AE (classified by preferred term) that occurs during the study will be considered a treatment-emergent AE (TEAE) if it has a start date and time on or after the first dose of investigational product or if it has a start date and time before the date and time of the first dose of investigational product, but increases in severity on or after the date and time of the first dose of investigational product. If more than 1 AE with the same preferred term is reported before the date and time of the first dose of investigational product, then the AE with the greatest severity will be used as the benchmark for comparison to the AEs occurring after dose of investigational product under the preferred term. For the purposes of summarizing by treatment period, an AE will be considered to be treatment emergent in Treatment Period 1 if it has a start date or increases in severity during open label Treatment Period 1; an AE will be considered to be treatment emergent in Treatment Period 2 if it has a start date or increases in severity during open label Treatment Period 2; an AE will be considered to be treatment emergent in the Follow-up Period if it has a start date or increases in severity during the Follow-up Period.

An overall summary of the number of subjects with TEAEs will be presented by treatment group, overall and for each of the periods that includes the number and percentage of subjects with:

- Any TEAEs,
- Any serious TEAEs,
- Any TEAEs related to investigational product,
- Any serious TEAEs related to investigational product,
- Any TEAEs leading to discontinuation of investigational product,
- Any severe TEAEs,
- Any TEAE leading to death

The number and percentage of subjects reporting TEAEs in each treatment group, overall and for each of the periods, will be tabulated in the following ways:

- By system organ class (SOC) and preferred term (PT),
- Common TEAEs (≥ 5% of subjects in all doses group) by PT
- By SOC, PT, and maximum severity,
- TEAEs considered related to investigational product by SOC and PT.
- Serious TEAEs by SOC and PT,
- TEAEs leading to withdrawal of investigational product by SOC and PT

If more than 1 AE occurs with the same preferred term for the same subject, then the subject will be counted only once for that preferred term using the most severe and most related occurrence for the summarization by severity and by relationship to investigational product.

All information about AEs collected on the eCRF will be listed alongside the treatment, preferred term, and SOC. For injection site AEs, serious AEs, deaths, AEs related to investigational product, and TEAEs leading to study discontinuation, a separate listing will also be provided.

An additional summary of AE's and SAE's by SOC and PT occurring after initiation of additional biologic therapy will be performed by additional biologic (anti-TNF (Infliximab, Adalimumab, Certolizumab, Certolizumab Pegol, Golimumab)vs. Vedolizumab vs. Other Biologics (Ustekinumab)) received in the follow-up period. For this analysis subjects who have adverse events after the first dose of additional biologic therapy will be considered treatment emergent.

Furthermore the following listings will be provided: listing of TEAEs of Myalgia, listing of Clostridium difficile infection adverse events, listing of Gastroenteritis adverse events, listing of injection site reactions and listing of Nasophrayngitis adverse events.

11.2. Clinical Laboratory Variables

Descriptive statistics for clinical laboratory values (in SI units) and changes from baseline at each assessment time point as well as shift tables from baseline to each visit for quantitative variables will be presented by treatment group for the following clinical laboratory variables:

Hematology Hemoglobin, hematocrit, red blood cell (RBC) count, white blood cell (WBC) count, platelet count, total neutrophils (Abs), eosinophils(Abs), monocytes (Abs), basophils (Abs), lymphocytes (Abs)

Biochemistry Blood urea nitrogen (BUN), creatinine, glucose, sodium, potassium, chloride, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), creatine phosphokinase (CPK and CPK fractionation), bilirubin (total and direct), calcium, total protein, albumin, uric acid, NT-proBNP and Troponin I.

Urinalysis Dipstick (pH, protein, glucose, ketones, blood, leukocyte esterase, and nitrites). **NOTE:** microscopic evaluation (RBCs, WBCs, crystals, casts, and bacteria) will be performed when indicated by the dipstick results.

Other JC virus DNA testing, JC virus Serology (antibody).

Clinical laboratory test values are potentially clinically important (PCI) if they meet either the low or high PCI criteria listed in Table 5: Criteria for Potentially Clinically Important Laboratory Tests. The number and percentage of subjects with post-baseline PCI values will be tabulated by treatment group, overall and by Open Label Treatment Period. The percentages will be calculated relative to the number of subjects with available baseline values and at least 1 post-baseline assessment. The numerator is the total number of subjects with at least 1 post-baseline PCI value. A supportive listing of subjects with post-baseline PCI values will be provided including the subject number, site, baseline, and post-baseline values.

Table 5: Criteria for Potentially Clinically Important Laboratory Tests

Parameter	Age Range	Gender	Outlier Criteria [1]	
			Low	**High**
Hematology				
Eosinophils (%)	All	Male, Female	NA	>0.6x10^3 /uL
Hemoglobin	All	Male, Female	<9g/dL	NA
Neutrophils (%)	All	Male, Female	<1.5x10^3/uL	>8.0x10^3/uL
Platelets	All	Male, Female	<75.0x10^3/uL	>500.0x10^3/uL
Leukocytes (WBC)	All	Male, Female	<3.0x10^3/uL	>16.0x10^3/uL
Lymphocytes	All	Male, Female	<0.8xLLN	>1.2xULN
Monocytes	All	Male, Female	<0.1x10^3/uL	>1.1x10^3/uL
Chemistry				
Albumin	All	Male, Female	<3g/dL	NA
Alkaline Phosphatase	All	Male, Female	NA	>2.5 x ULN
Alanine Aminotransferase (ALT)	All	Male, Female	NA	>2.5 x ULN
Aspartate Aminotransferase (AST)	All	Male, Female	NA	>2.5 x ULN
DILI Screen (ongoing safety monitoring)	All	Male, Female		AST or ALT >3 x ULN and TBL >2 x ULN

Table 5: Criteria for Potentially Clinically Important Laboratory Tests

Parameter	Age Range	Gender	Outlier Criteria [1]	
			Low	High
Total Bilirubin	All	Male, Female	NA	>1.5 x ULN
Direct Bilirubin	All	Male, Female	NA	>1.5 x ULN
Blood Urea Nitrogen (BUN)	All	Male, Female	NA	>2.5 x ULN
Calcium	All	Male, Female	< 8mg/dL	>11.5mg/dL
Chloride	All	Male, Female	< 90mEq/L	>115mEq/L
Creatinine	All	Male, Female	NA	>1.5 x ULN
Potassium	All	Male, Female	< 3.5mEq/L	>5.5mEq/L
Total Protein	All	Male, Female	< 5g/dL	>9g/dL
Glucose	All	Male, Female	< 55mg/dL	>160mg/dL
Sodium	All	Male, Female	< 130mEq/L	>150mEq/L
NT-proBNP	All	Male, Female		>300 pg/mL
Troponin I	All	Male, Female		>0.03ug/L
CK-MB	All	Male, Female		≥25 U/L
Uric acid, Serum	All	Males		>10mg/dL
Uric acid, Serum	All	Females		>9mg/dL
Creatinine phosphokinase (CPK)	All	Male, Female		>2.5 x ULN
Urinalysis				
Leukocyte esterase	All	Male, Female	Present	Present
Protein	All	Male, Female	NA	> 2+
Glucose	All	Male, Female	NA	>1+
Blood	All	Male, Female	NA	>2+

NA=Not Applicable; LLN=Lower Limit of Normal; ULN=Upper Limit of Normal; Intl.=International.

1 If criteria in both directions are shown for a single parameter, then abnormalities in each direction are summarized separately.

A separate listing of CPK data, of subjects with AE of Myalgia, defined as subjects with preferred term of Myalgia, will be presented.

Hy's law

Abnormal values in aspartate transaminase (AST) and/or alanine transaminase (ALT) concurrent with abnormal elevations in total bilirubin 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).

The threshold of laboratory abnormalities for a potential case of drug-induced liver injury depends on the subject's individual baseline values and underlying conditions:

- Subjects with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT >=3 times the upper limit of normal (X ULN) concurrent with a total bilirubin >=2 X ULN with no evidence of hemolysis and an alkaline phosphatase <=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 >=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 by one time the upper limit of normal or >=3 times the upper limit of normal (whichever is smaller).

Subjects potentially meeting Hy's law will be listed.

JC Virus

JC virus antibody will be summarized at baseline of 1009 by treatment group. A shift table from baseline of 1009 to the end of study at each visit will be presented by treatment group in study A7281010.

Any subjects that have a seroconversion (change from negative to positive) or a seroconversion from the baseline of 1009 at any point in either the 1009 or 1010 study will be listed.

JC virus antibody will be listed. JC virus DNA will not be analyzed.

11.3. Vital Signs

Descriptive statistics for vital signs (e.g., systolic and diastolic blood pressure, pulse rate, temperature and body weight) and their changes from baseline at each post-baseline visit and at the end of study will be presented by treatment group.

Vital sign values will be considered PCI if they meet both the observed value criteria and the change from baseline criteria listed in Table 6: Criteria for Potentially Clinically Significant Vital Signs. The number and percentage of subjects with PCI post-baseline values will be tabulated by treatment group and overall,. The percentages will be calculated relative to the number of subjects with baseline and at least 1 post-baseline assessment. The numerator is the total number of subjects with at least 1 PCI post-baseline vital sign value. A supportive listing of subjects with post-baseline PCI values will be provided including the subject number, baseline, and post-baseline PCI values.

Table 6: Criteria for Potentially Clinically Significant Vital Signs

Vital Sign Parameter	Flag	Criteria[a]	
		Observed Value	Change from Baseline
Systolic blood pressure (mmHg)	High	≥180	Increase of ≥20
	Low	≤90	Decrease of ≥20
Diastolic blood pressure (mmHg)	High	≥105	Increase of ≥15
	Low	≤50	Decrease of ≥15
Pulse rate (beats per minute)	High	≥120	Increase of ≥15
	Low	≤50	Decrease of ≥15
Weight (kg)	High	-	Increase of ≥10%
	Low	-	Decrease of ≥10%
BMI (kg/m^2)	High	-	Increase of ≥10%
	Low	<18	Decrease of ≥10%

[a] A post-baseline value is considered as a PCI value if its meets both criteria for observed value and change from baseline.

11.4. Electrocardiogram (ECG) and Echocardiogram (ECHO)

Descriptive statistics for ECG variables (e.g., heart rate, PR interval, RR interval, QRS interval, QT interval, and QTc interval (QTcB and QTcF) and their changes from baseline at each assessment time point will be presented by treatment group. ECG interpretation will be summarized by visit. A shift table from baseline to each visit for qualitative ECG results will be presented.

Electrocardiogram variable values will be considered PCI if they meet or exceed the upper limit values listed in Table 7: Criteria for Potentially Clinically Important ECG Values. The number and percentage of subjects with post-baseline PCI values will be tabulated by treatment group and overall,. The percentages will be calculated relative to the number of subjects with available baseline and at least 1 post-baseline assessment. The numerator is the total number of subjects with at least 1 PCI post-baseline ECG value. A listing of all subjects with post-baseline PCI value will be provided including the subject number, site, baseline, and post-baseline PCI values.

Echocardiogram data will be listed.

Table 7: Criteria for Potentially Clinically Important ECG Values		
ECG Parameter	**Unit**	**Higher Limit**
QRS Interval	msec	≥150
PR Interval	msec	≥250
QTcB Interval	msec	≥500
QTcF Interval	msec	≥500

11.5. Immunogenicity

Presence of anti-PF-00574659 antibodies will be listed and summarized by visit for each treatment group.

In subjects with a positive ADA, presence of neutralizing antibodies will be listed and summarized by visit for each treatment group.

These endpoints will be analyzed for the safety analysis set.

11.6. Physical Examination

Physical examination will be listed.

11.7. Enteric Pathogen

Enteric Pathogen data will be listed.

11.8. Other Safety Variables

11.8.1. Neurological Assessments

As part of the safety evaluation, the following neurological assessments are performed for each subject.

- Confrontational Visual Fields
- Timed 25-Foot Walk
- 9-Hole Peg Test (9-HPT)
- Symbol Digit Modality Test (SDMT)
- Patient-Multiple Sclerosis Neuropsychological Questionnaire (MSNQ)

To provide more precise results about the measurement, programming derived scores will be used in the listing and summary instead of the CRF recorded scores for SDMT. The derived standard deviation (SD) will be based on the age (derived based on test date and date of birth), education level (from the 1009 Social Status CRF page) and test score reported and the norm table provided in the protocol Appendix 7. When the test score is not equal to any of the norm scores, the closet norm score will be used to define the SD. When two norm scores have equal distance to the test score, the lower one will be used.

The neurological assessments will be summarized for the safety population by treatment group. In addition, a summary of clinically significant on-treatment changes in neurological assessments will be presented by treatment group, overall, and period. Clinically significant worsening changes are defined as the following:

- Symbol Digit Modality Test - 1 S.D. decrease or more on two consecutive visits, from the worst (smallest) case before first dosing;
- 9-hole Peg Test - 20% increase or more compared with the worst (greatest) case before first dosing;
- Confrontational Visual Fields Test - change from NORMAL to ABNORMAL when compared to the worst case before first dosing;
- 25-Foot Walk Test - 20% increase or more compared with the worst (greatest) case before first dosing.
- Patient-Multiple Sclerosis Neuropsychological Questionnaire - a 5-point increase or more compared with the worst (greatest) case before first dosing.

Neurological assessments will be listed. Separate listings for subjects with clinically significant on-treatment changes in neurological assessments will also be presented.

12. CLINICAL PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

12.1. Pharmacokinetics Population and Pharmacodynamic Population,

Please see Section 4.

12.2. Pharmacokinetic Methods

All of the pharmacokinetic analyses will be performed using the Pharmacokinetic Analysis Set.

12.2.1. Concentration Data

Blood samples will be collected prior to dosing for analysis of plasma trough concentrations of PF-00547659. Plasma concentrations at each nominal time post dose will be presented by treatment group and summarized using descriptive statistics which include n, mean, median, SD, coefficient of variation (CV), minimum and maximum. A listing of all concentrations will be provided along with scheduled and actual sampling times. A spaghetti plot of individual subject plasma-concentration against actual time post dose (separate plot for each treatment group). Mean concentrations against nominal time will be plotted for each treatment group. This plot will be presented on linear-linear and log-linear scales. These data will be analyzed for the PK population.

Further details of the Population PK methodology will be described in the separate Population Modeling and Analysis Report.

12.2.2. Handling BLQ Values

For PK concentrations, in the listings, Concentrations below the limit of quantification (BLQ) values will be reported as "<LLQ", where LLQ will be replaced with the value for the lower limit of quantification.

For PD and biomarkers with concentrations outside the limit of quantification, in all data presentations (except listings), assayed values below the limit of quantification (BLQ) will be set to 10% less than the given assay lower limit for the specific biomarker. In addition, assayed values above the limit of quantification (ALQ) will be set to 10% more than the assay upper limit if applicable. In listings BLQ values will be reported as "<LLQ" and ULQ values will be reported as ">ULQ" where LLQ and ULQ will be replaced with the values for the lower and upper limits for qualification respectively.

No missing values will be imputed.

12.2.3. Pharmacokinetic Parameters

Please see the separate Population Modeling and Analysis Report.

12.3. Statistical Analysis of Pharmacokinetic Data

Please see the separate Population Modeling and Analysis Report.

12.4. Pharmacodynamic Methods

All of the Pharmacodynamic analyses will be performed using the Pharmacodynamic Analysis Set.

Pharmacodynamic parameters: Fecal calprotectin, hsCRP and Soluble MAdCAM will be summarized as specified below.

12.5. Statistical Analysis of Pharmacodynamic Data

Descriptive statistics (n, mean, SD, coefficient of variation, median, maximum, minimum, geometric mean, and coefficient of variation of geometric mean) for fecal calprotectin, hsCRP and soluble MAdCAM will be presented by timepoint as indicated below,treatment groupand and their treatment in the A7281009 study and overall. Geometric mean percent change from baseline and 90% CIs for these endpoints will also be summarized.

- hsCRP from blood samples will be summarized for the following timepoints: prior to dosing at baseline and every 4 weeks to Week 24, Week 32 and Week 72.
- Fecal calprotectin from stool samples will be summarized at the same time points as for hsCRP.
- Soluble MAdCAM in blood will be summarized for baseline and Week 16.

The following figures will also be provided for the following endpoints:

- hsCRP geometric mean over time with geometric mean SD.
- hsCRP geometric mean percent change from baseline with geometric mean SD.
- Fecal calprotectin geometric mean over time with geometric mean SD.
- Fecal calprotectin geometric mean percent change from baseline with geometric mean SD.

Fecal calprotectin, hsCRP, and soluble MAdCAM will be listed.

13. OTHER ANALYSES

Not applicable

14. INTERIM ANALYSIS

14.1. Interim Analyses

Two interim analyses (IAs) were planned to be performed for this study when 50% of subjects from the Phase 2 study (A7281009) had been enrolled in this study (A7281010), and the last subject from the Phase 2 study (A7281009) had been enrolled in this study (A7281010). In practice, two IAs occurred, one at the time of the topline report for the A7281009 study and one for an end of phase 2 meeting. The purpose of the IAs was to provide additional data on the durability of response, remission, and safety from A7281009, to facilitate the decision-making process of future studies.

14.2. Data Monitoring Committee

An external Data Monitoring Committee was placed 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 included a neurologist with expertise in PML and a cardiologist with expertise in heart failure and/or myocarditis. Work-up of suspected PML cases included a neurology consultation as well as an MRI scan, and a lumbar puncture, if clinically indicated. Given the lack of therapeutic options for subjects who have failed at least 1 conventional therapy, SHP647 with its distinct mechanism of action and known safety profile appears to have a favorable Risk-Benefit profile. The added precautions regarding PML served to increase the confidence in SHP647 for future development.

Additional cardiac monitoring was implemented in this study. Serum samples for CPK (with reflex isoenzymes), troponin I and NT-proBNP were drawn with the safety labs. Elevation of troponin I >0.05 ng/mL or CPK with MB prompted a cardiology consult. Any subject who experienced an initial on-study elevation of NTproBNP to >300 pg/mL had an echocardiogram and cardiology consult. All subjects who had an echocardiogram, in whom the NTproBNP remains >124 pg/mL at the 144 week visit, had 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 was reviewed by the DMC.

The DMC is 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 was 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.

15. COMPUTER METHODS

Statistical analyses will be performed using Version 9.4 (or newer) of SAS® on a suitably qualified environment.

16. CHANGES TO ANALYSES SPECIFIED IN PROTOCOL

Dose escalation was removed in protocol amendment 3, SAP accommodates for subjects enrolled under prior to protocol amendment.

Gene expression profiling (mRNA) and proteins will not be analyzed. JC Virus DNA will not be analyzed.

17. DATA HANDLING CONVENTIONS

17.1. General Data Reporting Conventions

Continuous variables will be summarized using the following descriptive statistics: n, mean, median, standard deviation, minimum, maximum. Categorical and count variables will be summarized by the number of subjects (n) and the percent of subjects in each category. Percentages will be presented to a single decimal place.

17.2. Derived Efficacy Endpoints

17.2.1. Imputation Method

For analyses of binary endpoints in exploratory efficacy endpoints, the non-responder imputation method will be used for missing value imputation from drop out subjects. Subjects that have missing data which means it is not possible to determine their remission/clinical response/mucosal healing will be assigned as having no remission/no clinical response/no mucosal healing to the missing visits.

17.2.2. Total Mayo Score

Responder/Non-responder status will be determined at the final visit (Week 12) of study A7281009 and recorded at the baseline visit of A7281010, however, the responder/non-responder status from the Week 12 visit of study A7281009 in the A7281009 analysis datasets will be used for this study.

The determination of clinical response and clinical remission will be based on the total Mayo score.
The calculation of total Mayo Score includes flexible sigmoidoscopy or colonoscopy results, stool frequency, rectal bleeding, and physician's global assessment. See Appendix 19.1.2 Mayo Scoring System for Assessment of Ulcerative Colitis Activity for how the stool frequency and rectal bleeding subscores are calculated Definitions of clinical response and remission by the Total Mayo score are located in Section 10.3.

17.2.3. Partial Mayo Score

Partial Mayo score is Mayo score without the endoscopic subscore. Therefore the calculation of the partial Mayo score includes stool frequency, rectal bleeding, and physician's global assessment. Definitions of clinical response and remission by the Partial Mayo score are located in Section 10.3.

17.2.4. Simple Clinical Colitis Activity Index

The SCCAI measure disease activity 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. The total

SCCAI score is the sum of the all points collected in the eCRF. Definitions of clinical response and remission by the SCCAI score are located in Section 10.3.

17.3. Repeated or Unscheduled Assessments of Safety Parameters

If a subject has repeated assessments before the start of investigational product, then the results from the final assessment made prior to the start of investigational product will be used as baseline. If end of study assessments are repeated or unscheduled, the last post-baseline assessment will be used as the end of study assessment for generating descriptive statistics. However, all post-baseline assessments will be used for PCI value determination and all assessments will be presented in the data listings.

17.4. Missing Date of Investigational Product

When the date of the last dose of investigational product is missing for a subject, all efforts should be made to obtain the date from the site.

17.5. Missing Date Information for Prior or Concomitant Medications

For prior or concomitant medications, including rescue medications, incomplete (ie, partially missing) start date and/or stop date will be imputed. When the start date and the stop date are both incomplete for a subject, impute the start date first.

17.5.1. Incomplete Start Date

The following rules will be applied to impute the missing numerical fields. If the stop date is complete and the imputed start date is after the stop date, then the start date will be imputed using the stop date.

17.5.1.1. Missing day and month

- If the year of the incomplete start date is the same as the year of the date of the first dose of investigational product, then the day and month of the date of the first dose of investigational product will be assigned to the missing fields
- If the year of the incomplete start date is before the year of the date of the first dose of investigational product, then December 31 will be assigned to the missing fields
- If the year of the incomplete start date is after the year of the date of the first dose of investigational product, then 01 January will be assigned to the missing fields.

17.5.1.2. Missing month only

- The day will be treated as missing and both month and day will be replaced according to the above procedure.

17.5.1.3. Missing day only

- If the month and year of the incomplete start date are the same as the month and year of the date of the first dose of investigational product, then the day of the date of the first dose of investigational product will be assigned to the missing day
- If either the year is before the year of the date of the first dose of investigational product or if both years are the same but the month is before the month of the date of the first dose of investigational product, then the last day of the month will be assigned to the missing day
- If either the year is after the year of the date of the first dose of investigational product or if both years are the same but the month is after the month of the date of the first dose of investigational product, then the first day of the month will be assigned to the missing day.

17.5.2. Incomplete Stop Date

The following rules will be applied to impute the missing numerical fields. If the date of the last dose of investigational product is missing, then replace it with the last visit date. If the imputed stop date is before the start date (imputed or non-imputed start date), then the imputed stop date will be equal to the start date.

17.5.2.1. Missing day and month

- If the year of the incomplete stop date is the same as the year as of the date of the last dose of investigational product, then the day and month of the date of the last dose of investigational product will be assigned to the missing fields
- If the year of the incomplete stop date is before the year of the date of the last dose of investigational product, then 31 December will be assigned to the missing fields
- If the year of the incomplete stop date is after the year of the date of the last dose of investigational product, then 01 January will be assigned to the missing fields.

17.5.2.2. Missing month only

- The day will be treated as missing and both month and day will be replaced according to the above procedure.

17.5.2.3. Missing day only

- If the month and year of the incomplete stop date are the same as the month and year of the date of the last dose of investigational product, then the day of the date of the last dose of investigational product will be assigned to the missing day
- If either the year is before the year of the date of the last dose of investigational product or if both years are the same but the month is before the month of the date of the last dose of investigational product, then the last day of the month will be assigned to the missing day

- If either the year is after the year of the last dose of investigational product or if both years are the same but the month is after the month of the date of the last dose of investigational product, then the first day of the month will be assigned to the missing day.

17.6. Missing Date Information for Adverse Events

AEs with completely missing start dates will be considered Treatment emergent for period 1 and start date will be imputed as the first dose date. . Incomplete stop dates may also be imputed when calculation of the duration of an AE is required per the protocol. If imputation of an incomplete stop date is required, and both the start date and the stop date are incomplete for a subject, impute the start date first.

17.6.1. Incomplete Start Date

Follow same rules as in Section 17.5.1.

17.6.2. Incomplete Stop Date

When required per the protocol, follow the same rules as in Section 17.5.2.

17.7. Missing Severity Assessment for Adverse Events

If severity is missing for an AE starting prior to the date of the first dose of investigational product, then a severity of "Mild" will be assigned. If the severity is missing for an AE starting on or after the date of the first dose of investigational product, then a severity of "Severe" will be assigned. The imputed values for severity assessment will be used for incidence summaries, while the actual values will be used in data listings.

17.8. Missing Relationship to Investigation Product for Adverse Events

If the relationship to investigational product is missing for an AE starting on or after the date of the first dose of investigational product, a causality of "Related" will be assigned. The imputed values for relationship to double-blind investigational product will be used for incidence summaries, while the actual values will be presented in data listings.

17.9. Character Values of Clinical Laboratory Variables

If the reported value of a clinical laboratory variable cannot be used in a statistical analysis due to, for example, that a character string is reported for a numerical variable. The appropriately determined coded value will be used in the statistical analysis. However, the actual values as reported in the database will be presented in data listings.

18. References

No references to note

19. Appendices

19.1. Data Derivation Details

19.1.1. Definitions and Use of Visit Windows in Reporting

Periods	Visit	Study Week	Target Day	Window
Open-Label Treatment Period 1	1	Baseline	1	Rel_day<=1
	2	Week 4	29	1<rel_day<=43
	3	Week 8	57	43<rel_day<=71
	4	Week 12	85	71<rel_day<=99
	5	Week 16	113	99<rel_day<=127
	6	Week 20	141	127<rel_day<=155
	7	Week 24	169	155<rel_day<=183
	8	Week 28	197	183<rel_day<=211
	9	Week 32	225	211<rel_day<=239
	10	Week 36	253	239<rel_day<=267
	11	Week 40	281	267<rel_day<=295
	12	Week 44	309	295<rel_day<=323
	13	Week 48	337	323<rel_day<=351
	14	Week 52	365	351<rel_day<=379
	15	Week 56	393	379<rel_day<=407
	16	Week 60	421	407<rel_day<=435
	17	Week 64	449	435<rel_day<=463
	18	Week 68	477	463<rel_day<=491
	19	Week 72	505	491<rel_day<=519
Open-Label	20	Week 76	533	519<rel_day<=547

Treatment Period 2	21	Week 80	561	547<rel_day<=575
	22	Week 84	589	575<rel_day<=603
	23	Week 88	617	603<rel_day<=631
	24	Week 92	645	631<rel_day<=659
	25	Week 96	673	659<rel_day<=687
	26	Week 100	701	687<rel_day<=715
	27	Week 104	729	715<rel_day<=743
	28	Week 108	757	743<rel_day<=771
	29	Week 112	785	771<rel_day<=799
	30	Week 116	813	799<rel_day<=827
	31	Week 120	841	827<rel_day<=855
	32	Week 124	869	855<rel_day<=883
	33	Week 128	897	883<rel_day<=911
	34	Week 132	925	911<rel_day<=939
	35	Week 136	953	939<rel_day<=967
	36	Week 140	981	967<rel_day<=995
	37	Week 144	1009	995<rel_day<=1023
3 Month Follow-up	38	Week of last dose + 12 Weeks	((Week of last dose + 12 Weeks) x 7) + 1	((Week of last dose + 12 Weeks) x 7) - 13 <rel_day<=((Week of last dose + 12 Weeks) x 7) + 15
6 Month Follow-up	39	Week of last dose + 24 Weeks	((Week of last dose + 24 Weeks) x 7) + 1	((Week of last dose + 24 Weeks) x 7) - 13 <rel_day<=((Week of last dose + 24 Weeks) x 7) + 15

Day 1= First study dosing date.

Baseline is defined as the last available value on or before first study dosing date. If two or more visits fall into the same window, keep the one closest to the Target Day. If two visits are equal distant from the Target Day in absolute value, the visit with correct nominal label should be used. For example, if two visits fall in the window for Week 4 visit with days 24 and 32, the visit that was recorded as Week 4 visit should be used.

19.1.2. Mayo Scoring System for Assessment of Ulcerative Colitis Activity

The Mayo Score ranges from 0 to 12, with higher scores indicating more severe disease. It consists of 4 subscores. Each sub-score ranges from 0 to 3. The 4 components of the Mayo Score are:

Stool Frequency†:

0 = Normal no. of stools for this patient.

1 = 1 to 2 stools more than normal.

2 = 3 to 4 stools more than normal.

3 = 5 or more stools more than normal.

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.

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).

Physician's Global Assessment§:

0 = Normal.

1 = Mild disease.

2 = Moderate disease.

3 = Severe disease.

** The Mayo score ranges from 0 to 12, with higher scores indicating more severe disease. Each subscore ranges from 0 to 3.*

† Each patient 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 patient's daily recollection of abdominal discomfort and general sense of wellbeing, and other observations, such as physical findings and the patient's performance status.

If there are missing diary data, the average will be taken from the 3 most recently available days reported within 5 days prior to the study visit. If there are less than 3 available days reported within 5 days prior to the study visit, the average will be taken from the limited available data unless there is no diary data reported within 5 days. In this case, stool frequency and rectal bleeding subscores will be considered as missing. If at least one of the 4 Mayo subscores is missing, the total Mayo score will be considered as missing.

20. TABLE OF CONTENTS FOR FIGURES, TABLES, AND LISTINGS

Table	Title	Shire Std
14.2.2.2.1.3	Proportion of Subjects with Clinical Response by Timepoint for Non-responders in Study A7281009 using Non-responder Imputation Method [Safety Analysis Set]	N
14.2.2.2.2.1	Proportion of Subjects with by Timepoint using Observed Case [Safety Analysis Set]	N
14.2.2.2.2.2	Proportion of Subjects with Clinical Response by Timepoint for Responders using Observed Case[Safety Analysis Set]	N
14.2.2.2.2.3	Proportion of Subjects with Clinical Response by Timepoint for Non-responders using Observed Case[Safety Analysis Set]	N
14.2.2.2.3.1	Proportion of Subjects in Clinical Remission by Timepoint using Non-responder Imputation Method[Safety Analysis Set]	N
14.2.2.2.3.2	Proportion of Subjects in Clinical Remission by Timepoint for Responders in Study A7281009 using Non-responder Imputation Method [Safety Analysis Set]	N
14.2.2.2.3.3	Proportion of Subjects in Clinical Remission by Timepoint for Non-responders in Study A7281009 using Non-responder Imputation Method[Safety Analysis Set]	N
14.2.2.2.4.1	Proportion of Subjects in Clinical Remission by Timepoint using Observed Case[Safety Analysis Set]	N
14.2.2.2.4.2	Proportion of Subjects in Clinical by Timepoint for Responders using Observed Case[Safety Analysis Set]	N
14.2.2.2.4.3	Proportion of Subjects in Clinical Remission by Timepoint for Non-responders using Observed Case [Safety Analysis Set]	N
14.2.2.2.5.1	Proportion of Subjects in Clinical Remission by Timepoint for those with Remission using Non-responder Imputation Method [Safety Analysis Set]	N
14.2.2.2.5.2	Proportion of Subjects in Clinical Remission by Timepoint for those with No Remission using Non-responder Imputation Method[Safety Analysis Set]	N
14.2.2.2.6.1	Proportion of Subjects in Clinical Remission by Timepoint for those with Remission using Observed Case [Safety Analysis Set]	N
14.2.2.2.6.2	Proportion of Subjects in Clinical Remission by Timepoint for those with No Remission using Observed Case[Safety Analysis Set]	N

Table	Title	Shire Std
14.2.2.3.1	Proportion of Subjects with Clinical Response based on the Partial Mayo Score using Non-Responder Imputation Method[Safety Analysis Set]	N
14.2.2.3.2	Proportion of Subjects with Clinical Response based on the Partial Mayo Score using Observed Case[Safety Analysis Set]	N
14.2.2.3.3	Proportion of Subjects in Clinical Remission based on the Partial Mayo Score by Week using Non-Responder Imputation Method[Safety Analysis Set]	N
14.2.2.3.4	Proportion of Subjects in Clinical Remission based on the Partial Mayo Score using Observed Case[Safety Analysis Set]	N
14.2.2.3.5	Summary of Total Mayo Score, Partial Mayo Score and Subscores by Week [Safety Analysis Set]	Y
14.2.2.4.1	Proportion of Subjects with Clinical Response based on Simple Clinical Colitis Activity Index (SCCAI) Score by Monthly Visits using Non-Responder Imputation Method[Safety Analysis Set]	N
14.2.2.4.2	Proportion of Subjects with Clinical Response based on Simple Clinical Colitis Activity Index (SCCAI)Score by Monthly Visits using Observed Case[Safety Analysis Set]	N
14.2.2.4.3	Proportion of Subjects in Clinical Remission based on Simple Clinical Colitis Activity Index (SCCAI) Score by Monthly Visits using Non-Responder Imputation Method[Safety Analysis Set]	N
14.2.2.4.4	Proportion of Subjects in Clinical Remission based on the Simple Clinical Colitis Activity Index (SCCAI) Score by Monthly Visits using Observed Case [Safety Analysis Set]	N
14.2.2.4.5	Summary of Simple Clinical Colitis Activity Index (SCCAI) at Monthly Visits [Safety Analysis Set]	Y
14.2.2.5.1	Categorical summary of Mayo Subscore- Stool Frequency by Week [Safety Analysis Set]	N
14.2.2.5.2	Categorical summary of Mayo Subscore- Rectal Bleeding by Week [Safety Analysis Set]	N
14.2.2.5.3	Categorical summary of Mayo Subscore- Findings of Sigmoidoscopy by Week [Safety Analysis Set]	N
14.2.2.5.4	Categorical summary of Mayo Subscore- Physician's Global Assessment by Week [Safety Analysis Set]	N
14.2.2.6	Summary of Time to Dose Escalation [Safety Analysis Set]	N
14.2.3.1	Summary of Plasma Concentration (ng/mL) by Nominal Time and Treatment Group[Pharmacokinetic Set]	Y
14.2.3.2.1	Summary of hsCRP (mg/dL) and Change from Baseline of hsCRP (mg/dL) by Week and Treatment Group [Pharmacodynamic Set]	Y
14.2.3.2.2	Summary of Fecal Calprotectin and Change from Baseline of Fecal Calprotectin (ug/g) by Week and Treatment Group [Pharmacodynamic Set]	Y

Table	Title	Shire Std
14.2.3.2.3	Summary of Soluble MAdCAM and Change from Baseline of Soluble MAdCAM (pmol/L) by Week and Treatment Group [Pharmacodynamic Set]	Y
14.3.1.1.1	Overall Treatment-emergent Adverse Events (TEAEs) by Treatment Group [Safety Analysis Set]	Y
14.3.1.1.2	Overall Treatment-emergent Adverse Events (TEAEs) by Treatment Group in Treatment Period 1 [Safety Analysis Set]	Y
14.3.1.1.3	Overall Treatment-emergent Adverse Events (TEAEs) by Treatment Group in Treatment Period 2 [Safety Analysis Set]	Y
14.3.1.1.4	Overall Treatment-emergent Adverse Events (TEAEs) by Treatment Group in Follow-up Period [Safety Analysis Set]	Y
14.3.1.2.1	Treatment-emergent Adverse Events by System Organ Class, Preferred Term and Treatment Group [Safety Analysis Set]	Y
14.3.1.2.2	Treatment-emergent Adverse Events by System Organ Class, Preferred Term and Treatment Group in Treatment Period 1 [Safety Analysis Set]	Y
14.3.1.2.3	Treatment-emergent Adverse Events by System Organ Class, Preferred Term and Treatment Group in Treatment Period 2 [Safety Analysis Set]	Y
14.3.1.2.4	Treatment-emergent Adverse Events by System Organ Class, Preferred Term and Treatment Group in Follow-up Period [Safety Analysis Set]	Y
14.3.1.2.5	Treatment-emergent Adverse Events after Initiation of Additional Anti-TNF Biologic Therapy in the Follow-up period by System Organ Class, Preferred Term and Treatment Group [Safety Analysis Set]	Y
14.3.1.2.6	Treatment-emergent Adverse Events after Initiation of Additional Vedolizumab Biologic Therapy in the Follow-up period by System Organ Class, Preferred Term and Treatment Group [Safety Analysis Set]	Y
14.3.1.2.7	Treatment-emergent Adverse Events after Initiation of Additional Other Biologic Therapy in the Follow-up period by, System Organ Class, Preferred Term and Treatment Group [Safety Analysis Set]	Y
14.3.1.3.1	Frequently Occurring (≥5%) Treatment-emergent Adverse Events by Preferred Term and Treatment Group [Safety Analysis Set]	Y
14.3.1.3.2	Frequently Occurring (≥5%) Treatment-emergent Adverse Events by Preferred Term and Treatment Group in Treatment Period 1 [Safety Analysis Set]	Y
14.3.1.3.3	Frequently Occurring (≥5%) Treatment-emergent Adverse Events by Preferred Term and Treatment Group in Treatment Period 2 [Safety Analysis Set]	Y

Table	Title	Shire Std
14.3.1.3.4	Frequently Occurring (≥5%) Treatment-emergent Adverse Events by Preferred Term and Treatment Group in Follow-up Period [Safety Analysis Set]	Y
14.3.2.1.1	Treatment-emergent Adverse Events by Maximum Severity, System Organ Class, Preferred Term and Treatment Group [Safety Analysis Set]	Y
14.3.2.1.2	Treatment-emergent Adverse Events by Maximum Severity, System Organ Class, Preferred Term and Treatment Group in Treatment Period 1 [Safety Analysis Set]	Y
14.3.2.1.3	Treatment-emergent Adverse Events by Maximum Severity, System Organ Class, Preferred Term and Treatment Group in Treatment Period 2 [Safety Analysis Set]	Y
14.3.2.1.4	Treatment-emergent Adverse Events by Maximum Severity, System Organ Class, Preferred Term and Treatment Group in Follow-up Period [Safety Analysis Set]	
14.3.2.2.1	Treatment-emergent Adverse Events Considered Related to Investigational Product by System Organ Class, Preferred Term and Treatment Group [Safety Analysis Set]	Y
14.3.2.2.2	Treatment-emergent Adverse Events Considered Related to Investigational Product by System Organ Class, Preferred Term and in Treatment Period 1 [Safety Analysis Set]	Y
14.3.2.2.3	Treatment-emergent Adverse Events Considered Related to Investigational Product by System Organ Class, Preferred Term and in Treatment Period 2 [Safety Analysis Set]	Y
14.3.2.2.4	Treatment-emergent Adverse Events Considered Related to Investigational Product by System Organ Class, Preferred Term and in Follow-up Period [Safety Analysis Set]	
14.3.3.2.1	Treatment-emergent Adverse Events leading to Withdrawal of Investigation Product by System Organ Class, Preferred Term and Treatment Group [Safety Analysis Set]	Y
14.3.3.2.2	Treatment-emergent Adverse Events leading to Withdrawal of Investigational Product by System Organ Class, Preferred Term and Treatment Group in Treatment Period 1 [Safety Analysis Set]	Y
14.3.3.2.3	Treatment-emergent Adverse Events leading to Withdrawal of Investigational Product by System Organ Class, Preferred Term and Treatment Group in Treatment Period 2 [Safety Analysis Set	Y
14.3.3.4.1	Serious Treatment-emergent Adverse Events by System Organ Class, Preferred Term and Treatment Group [Safety Analysis Set]	Y
14.3.3.4.2	Serious Treatment-emergent Adverse Events by System Organ Class, Preferred Term and Treatment Group in Treatment Period 1 [Safety Analysis Set]	Y

Table	Title	Shire Std
14.3.3.4.3	Serious Treatment-emergent Adverse Events by System Organ Class, Preferred Term and Treatment Group in Treatment Period 2 [Safety Analysis Set]	Y
14.3.3.4.4	Serious Treatment-emergent Adverse Events by System Organ Class, Preferred Term and Treatment Group in Follow-up Period [Safety Analysis Set]	Y
14.3.3.4.5	Serious Treatment-emergent Adverse Events after Initiation of Additional Anti-TNF Biologic Therapy in the Follow-up period by, System Organ Class, Preferred Term and Treatment Group [Safety Analysis Set]	Y
14.3.3.4.6	Serious Treatment-emergent Adverse Events after Initiation of Additional Vedolizumab Biologic Therapy in the Follow-up period by, System Organ Class, Preferred Term and Treatment Group [Safety Analysis Set]	Y
14.3.3.4.7	Serious Treatment-emergent Adverse Events after Initiation of Additional Other Biologic Therapy in the Follow-up period by, System Organ Class, Preferred Term and Treatment Group [Safety Analysis Set]	Y
14.3.4.1	Quantitative Clinical Laboratory Results by Treatment Group: Hematology [Safety Analysis Set]	Y
14.3.4.2	Quantitative Clinical Laboratory Results by Treatment Group: Biochemistry [Safety Analysis Set]	Y
14.3.4.3	Quantitative Clinical Laboratory Results by Treatment Group: Urinalysis [Safety Analysis Set]	Y
14.3.4.4	Qualitative Clinical Laboratory Results Treatment Group: Urinalysis [Safety Analysis Set]	Y
14.3.4.5	Shift from Baseline in Clinical Laboratory Results by Treatment Group: Hematology [Safety Analysis Set]	Y
14.3.4.6	Shift from Baseline in Clinical Laboratory Results by Treatment Group: Biochemistry [Safety Analysis Set]	Y
14.3.4.7	Shift from Baseline in Clinical Laboratory Results by Treatment Group: Urinalysis [Safety Analysis Set]	Y
14.3.4.8	Potentially Clinically Important (PCI) Laboratory Results by Treatment Group: Hematology [Safety Analysis Set]	Y
14.3.4.9	Potentially Clinically Important (PCI) Laboratory Results by Treatment Group in Treatment Period 1: Hematology [Safety Analysis Set	Y
14.3.4.10	Potentially Clinically Important (PCI) Laboratory Results by Treatment Group in Treatment Period 2: Hematology [Safety Analysis Set]	Y

Table	Title	Shire Std
14.3.4.11	Potentially Clinically Important (PCI) Laboratory Results by Treatment Group: Biochemistry [Safety Analysis Set]	Y
14.3.4.12	Potentially Clinically Important (PCI) Laboratory Results by Treatment Group in Treatment Period 1: Biochemistry [Safety Analysis Set]	Y
14.3.4.13	Potentially Clinically Important (PCI) Laboratory Results by Treatment Group in Treatment Period 2: Biochemistry [Safety Analysis Set]	Y
14.3.4.14	Potentially Clinically Important (PCI) Laboratory Results by Treatment Group: Urinalysis [Safety Analysis Set]	Y
14.3.4.15	Potentially Clinically Important (PCI) Laboratory Results by Treatment Group in Treatment Period 1: Urinalysis [Safety Analysis Set]	Y
14.3.4.16	Potentially Clinically Important (PCI) Laboratory Results by Treatment Group in Treatment Period 2: Urinalysis [Safety Analysis Set]	Y
14.3.4.17	Normal Ranges and Potentially Clinically Important (PCI) Criteria: Hematology	Y
14.3.4.18	Normal Ranges and Potentially Clinically Important (PCI) Criteria: Biochemistry	Y
14.3.4.19	Normal Ranges and Potentially Clinically Important (PCI) Criteria: Urinalysis	Y
14.3.4.20	Categorical Summary of Baseline JC Virus Antibody[Safety Analysis Set]	N
14.3.4.21	Shift from Baseline in JC Virus Antibody to End of Study[Safety Analysis Set]	Y
14.3.5.1	Actual Values and Change from Baseline in Vital Signs by Treatment Group [Safety Analysis Set]	Y
14.3.5.2	Potentially Clinically Important (PCI) Vital Signs Results by Timepoint and Treatment Group [Safety Analysis Set]	Y
14.3.6.1	Actual Values and Change from Baseline in ECG by Treatment Group [Safety Analysis Set]	Y
14.3.6.2	ECG Interpretation by Timepoint and Treatment Group [Safety Analysis Set]	Y
14.3.6.3	Potentially Clinically Important (PCI) ECG Results by Timepoint and Treatment Group [Safety Analysis Set]	Y
14.3.6.6	Shift from Baseline to Post-Baseline Timepoint in Qualitative ECG Results by Treatment Group [Safety Analysis Set]	Y
14.3.6.7	Presence of Anti-drug Antibodies (ADA) by Timepoint[Safety Analysis Set]	N

Table	Title	Shire Std
14.3.6.8	Neutralising Antibodies Development in Subjects with Positive Anti-drug-Antibodies by Timepoint[Safety Analysis Set]	N
14.3.6.9	Categorical summary of Confrontational Visual Fields by Timepoint[Safety Analysis Set]	N
14.3.6.10	Summary of Timed 25-Foot Walk (sec) by Timepoint [Safety Analysis Set]	Y
14.3.6.11	Summary of 9-Hole Peg Test by Timepoint [Safety Analysis Set]	Y
14.3.6.12	Summary of Symbol Digit Modalities Test (SDMT) Scores by Timepoint[Safety Analysis Set]	Y
14.3.6.13	Summary of Patient-Multiple Sclerosis Neuropsychological Questionnaire (MSNQ) Total Score by Timepoint[Safety Analysis Set]	Y
14.3.6.14	Summary of Clinically Significant On-Treatment Changes in Neurological Assessments[Safety Analysis Set]	N
14.3.8.1	Investigational Product Exposure by Treatment Group [Safety Analysis Set]	Y

Figure	Title
14.2.2.1.1.1	Proportion of Subjects with Mucosal Healing at Baseline and Week 16(Centrally read) using Non-responder Imputation Method [Safety Analysis Set]
14.2.2.1.1.2	Proportion of Subjects with Mucosal Healing at Baseline and Week 16(Centrally read) for Responders in Study A7281009 using Non-responder Imputation Method [Safety Analysis Set]
14.2.2.1.1.3	Proportion of Subjects with Mucosal Healing at Baseline and Week 16(Centrally read) for Non-responders in Study A7281009 using Non-responder Imputation Method [Safety Analysis Set]
14.2.2.1.2.1	Proportion of Subjects with Mucosal Healing at Baseline and Week 16(Centrally read) using Observed Case[Safety Analysis Set]
14.2.2.1.2.2	Proportion of Subjects with Mucosal Healing at Baseline and Week 16(Centrally read) for Responders using Observed Case [Safety Analysis Set]

Figure	Title
14.2.2.1.2.3	Proportion of Subjects with Mucosal Healing at Baseline and Week 16(Centrally read) for Non-responders using Observed Case [Safety Analysis Set]
14.2.2.2.1.1	Proportion of Subjects with Clinical Response at Baseline and Week 16 based on Total Mayo Score (Centrally read) using Non-responder Imputation Method [Safety Analysis Set]
14.2.2.2.1.2	Proportion of Subjects with Clinical Response at Baseline and Week 16 based on Total Mayo Score (Centrally read) for Responders in Study A7281009 using Non-responder Imputation Method [Safety Analysis Set]
14.2.2.2.1.3	Proportion of Subjects with Clinical Response at Baseline and Week 16 based on Total Mayo Score (Centrally read) for Non-responders in Study A7281009 using Non-responder Imputation Method [Safety Analysis Set]
14.2.2.2.2.1	Proportion of Subjects with Clinical Response at Week 16 based on the Total Mayo Score (Centrally read) using Observed Case [Safety Analysis Set]
14.2.2.2.2.2	Proportion of Subjects with Clinical Response at Week 16 based on the Total Mayo Score (Centrally read) for Responders using Observed Case [Safety Analysis Set]
14.2.2.2.2.3	Proportion of Subjects with Clinical Response at Week 16 based on the Total Mayo Score (Centrally read) for Non-responders using Observed Case [Safety Analysis Set]
14.2.2.2.3.1	Proportion of Subjects in Clinical Remission at Baseline and Week 16 based on Total Mayo Score (Centrally read) using Non-responder Imputation Method [Safety Analysis Set]
14.2.2.2.3.2	Proportion of Subjects in Clinical Remission at Baseline and Week 16 based on the Total Mayo Score (Centrally read) for Responders in Study A7281009 [Safety Analysis Set]
14.2.2.2.3.3	Proportion of Subjects in Clinical Remission at Baseline and Week 16 based on the Total Mayo Score (Centrally read) for Non-responders in Study A7281009 using Non-responder Imputation Method [Safety Analysis Set]
14.2.2.2.4.1	Proportion of Subjects in Clinical Remission at Baseline and Week 16 based on the Total Mayo Score (Centrally read) using Observed Case [Safety Analysis Set]

Figure	Title
14.2.2.2.4.2	Proportion of Subjects in Clinical Remission at Baseline and Week 16 based on the Total Mayo Score (Centrally read) for Responders using Observed Case [Safety Analysis Set]
14.2.2.2.4.3	Proportion of Subjects in Clinical Remission at Baseline and Week 16 based on the Total Mayo Score (Centrally read) for Non-responders using Observed Case [Safety Analysis Set]
14.2.2.2.5.1	Proportion of Subjects in Clinical Remission at Baseline and Week 16 based on the Total Mayo Score (Centrally read) for those with Remission using Non-responder Imputation Method [Safety Analysis Set]
14.2.2.2.5.2	Proportion of Subjects in Clinical Remission at Baseline and Week 16 based on the Total Mayo Score (Centrally read) for those with No Remission using Non-responder Imputation Method [Safety Analysis Set]
14.2.2.2.6.1	Proportion of Subjects in Clinical Remission at Baseline and Week 16 based on the Total Mayo Score (Centrally read) for those with Remission using Observed Case [Safety Analysis Set]
14.2.2.2.6.2	Proportion of Subjects in Clinical Remission at Baseline and Week 16 based on the Total Mayo Score (Centrally read) for those with No Remission using Observed Case [Safety Analysis Set]
14.2.2.3.1	Proportion of Subjects with Clinical Response based on the Partial Mayo Score using Non-responder Imputation Method [Safety Analysis Set]
14.2.2.3.2	Proportion of Subjects with Clinical Response based on the Partial Mayo Score Observed Case [Safety Analysis Set]
14.2.2.3.3	Proportion of Subjects in Clinical Remission based on the Partial Mayo Score using Non-Responder Imputation Method [Safety Analysis Set]
14.2.2.3.4	Proportion of Subjects in Clinical Remission based on the Partial Mayo Score using Observed Case [Safety Analysis Set]
14.2.2.4.1	Proportion of Subjects in Clinical Response based on SCCAI Score by Monthly Visits using Non-responder Imputation Method [Safety Analysis Set]

Figure	Title
14.2.2.4.2	Proportion of Subjects in Clinical Response based on SCCAI Score by Monthly Visits using Observed Case [Safety Analysis Set]
14.2.2.4.3	Proportion of Subjects in Clinical Remission based on SCCAI Score by Monthly Visits using Non-Responder Imputation Method [Safety Analysis Set]
14.2.2.4.4	Proportion of Subjects in Clinical Remission based on SCCAI Score by Monthly Visits using Observed Case [Safety Analysis Set]
14.2.2.5	Kaplan-Meier curve for Time to Dose Escalation for Subjects Assigned to SHP647 75mg [Safety Analysis Set]
14.2.3.1.1.1	Individual Serum Concentration-Time Profile for SHP647(Linear Scale) [Pharmacokinetic Set]
14.2.3.1.1.2	Individual Serum Concentration-Time profile for SHP647 by ADA status(linear Scale) [Safety Analysis Set]
14.2.3.1.1.3	Individual Serum Concentration-Time profile for SHP647 by NAb status(Linear Scale) [Safety Analysis Set]
14.2.3.1.2	Individual Serum Concentration-Time Profile for SHP647(Log Scale) [Pharmacokinetic Set]
14.2.3.1.3	Mean Serum Concentration-Time Profile for SHP647 (Linear Scale)[Pharmacokinetic Set]
14.2.3.1.4	Mean Serum Concentration-Time Profile for SHP647 (Log Scale)[Pharmacokinetic Set]
14.2.3.2.1	hsCRP (mg/dL) Geometric Mean over Time [Pharmacodynamic Set]
14.2.3.2.2	hsCRP (mg/dL) Geometric Mean Percent Change From Baseline over Time [Pharmacodynamic Set]
14.2.3.2.3	Fecal Calprotectin (mg/dL) Geometric Mean over Time[Pharmacodynamic Set]
14.2.3.2.4	Fecal Calprotectin (mg/dL) Geometric Mean Percent Change from Baseline over Time[Pharmacodynamic Set]

Listing	Title	Shire Std

Listing	Title	Shire Std
16.1.7	Randomization Assignments [All Randomized Subjects]	Y
16.2.1.1	Subject Disposition [All Enrolled Subjects]	Y
16.2.1.2	Subjects Who Terminated from the Study [All Enrolled Subjects]	Y
16.2.1.3	Subject Analysis Set Classification [All Enrolled Subjects]	N
16.2.2.1	Deviations from Inclusion/Exclusion Criteria [All Enrolled Subjects]	N
16.2.2.2	Listing of Protocol Deviations [All Enrolled Subjects]	N
16.2.4.1	Subject Demographics [Safety Analysis Set]	Y
16.2.4.2	Subject Baseline Characteristics [Safety Analysis Set]	N
16.2.4.3	Medical History in Studies A7281009 and A7281010 [Safety Analysis Set]	Y
16.2.4.4	Prior and Concomitant Medications [Safety Analysis Set]	Y
16.2.4.5	Drug allergies [Safety Analysis Set]	N
16.2.4.6	Additional Biological Therapy taken during Follow-up Period [Safety Analysis Set]	N
16.2.5.1	Investigational Product Exposure [Safety Analysis Set]	Y
16.2.5.2	Pharmacokinetic Blood Serum Draw Times and Concentration Data [Pharmacokinetic Set]	N
16.2.5.3	Pharmacodynamics Fecal Calprotectin Collection data [Pharmacodynamic Set]	N
16.2.5.4	Pharmacodynamics Serum hsCRP Collection data [Pharmacokinetic Set]	N
16.2.5.5	Pharmacodynamics Soluble MAdCAM data [Pharmacodynamic Set]	N
16.2.6.1	Listing of Total Mayo Score, Mayo Subscores, Clinical Remission and Clinical Response-Centrally Read [Safety Analysis Set]	N
16.2.6.2	Listing of Partial Mayo Score [Safety Analysis Set]	N
16.2.6.3	Listing of Mayo Score –Endoscopy Subscore [Safety Analysis Set]	N
16.2.6.4	Listing of Simple Clinical Colitis Activity Index (SCCAI) [Safety Analysis Set]	N

Listing	Title	Shire Std
16.2.7.1.1	Adverse Events-Including Injection Site AEs [Safety Analysis Set]	Y
16.2.7.1.2	Adverse Events-Excluding Injection Site AEs [Safety Analysis Set]	Y
16.2.7.2.1	Subjects Reporting Serious Treatment-Emergent Adverse Events [Safety Analysis Set]	Y
16.2.7.2.2	Subjects Reporting Serious Treatment-Emergent Adverse Events Leading to Death [Safety Analysis Set]	Y
16.2.7.3	Subjects Reporting TEAEs Leading to Withdrawal of Investigational Product [Safety Analysis Set]	Y
16.2.7.4	Subjects Reporting Treatment-Emergent Adverse Events [Safety Analysis Set]	Y
16.2.7.5	Subjects Reporting TEAEs Related to Investigational Product [Safety Analysis Set]	Y
16.2.7.6	Subjects Reporting TEAEs of Myalgia [Safety Analysis Set]	Y
16.2.7.7	Subjects Reporting TEAEs of Clostridium Difficile Infection [Safety Analysis Set]	Y
16.2.7.8	Subjects Reporting TEAEs of Gastroenteritis [Safety Analysis Set]	Y
16.2.7.9	Subjects Reporting TEAEs of Nasophrayngitis [Safety Analysis Set]	Y
16.2.7.10	Medication Error [Safety Analysis Set]	Y
16.2.7.11	Subjects Reporting TEAEs of Injection site reactions [Safety Analysis Set]	Y
16.2.8.1.1.1	Clinical Laboratory Sample Collection and Results for Pregnancy Screen [Safety Analysis Set]	Y
16.2.8.1.1.2	Clinical Laboratory Sample Collection [Safety Analysis Set]	Y
16.2.8.1.2	Clinical Laboratory Test Results [Safety Analysis Set]	Y
16.2.8.1.3	Subjects with Potentially Clinically Important Laboratory Test Results [Safety Analysis Set]	Y
16.2.8.1.4	Subjects That Meet the Hy's Law Criteria [Safety Analysis Set]	N
16.2.8.1.5	CK data for Subjects with Adverse Event of Myalgia [Safety Analysis Set]	Y
16.2.8.1.6	JC Virus Antibody[Safety Analysis Set]	N

Listing	Title	Shire Std
16.2.8.1.7	Subjects with Seroconversion at any point during Studies A7281009 and A7281010 [Safety Analysis Set]	N
16.2.8.1.8	Enteric Pathogens [Safety Analysis Set]	N
16.2.8.2.1	Vital Signs [Safety Analysis Set]	Y
16.2.8.2.2	Subjects with Potentially Clinically Important Vital Signs [Safety Analysis Set]	Y
16.2.8.3.1	12-lead ECG Results and Interpretation by Central Reader [Safety Analysis Set]	Y
16.2.8.3.2	Subjects with Potentially Clinically Important ECG Results [Safety Analysis Set]	Y
16.2.8.3.3	Cardiac Function Evaluation-Echocardiogram [Safety Analysis Set]	N
16.2.8.4.1	Anti-drug Antibodies Results [Safety Analysis Set]	N
16.2.8.4.2	Presence of Neutralizing Antibody Development in Subjects with positive Anti-drug Antibodies [Safety Analysis Set]	N
16.2.8.5	Physical Examination [Safety Analysis Set]	N
16.2.8.6.1	Listing of Confrontational Visual Fields [Safety Analysis Set]	N
16.2.8.6.2	Listing of Timed 25-foot Walk [Safety Analysis Set]	N
16.2.8.6.3	Listing of 9-Hole Peg Test [Safety Analysis Set]	N
16.2.8.6.4	Symbol Digit Modalities Test [Safety Analysis Set]	N
16.2.8.6.5	Multiple Sclerosis Neuropsychological Questionnaire Results [Safety Analysis Set]	N
16.2.8.6.6	Listing of Subjects with Clinically Significant On-Treatment Changes in Confrontational Visual Fields Test [Safety Analysis Set]	N
16.2.8.6.7	Listing of Subjects with Clinically Significant On-Treatment Changes in 25-Foot Walk Test [Safety Analysis Set]	N
16.2.8.6.8	Listing of Subjects with Clinically Significant On-Treatment Changes in 9-Hole Peg Test [Safety Analysis Set]	N
16.2.8.6.9	Listing of Subjects with Clinically Significant On-Treatment Changes in Symbol Digit Modality Test (SDMT) [Safety Analysis Set]	N

Listing	Title	Shire Std
16.2.8.6.10	Listing of Subjects with Clinically Significant On-Treatment Changes in Multiple Sclerosis Neuropsychological Questionnaire (MSNQ) [Safety Analysis Set]	N
16.2.8.7	Biopsy Sample [Safety Analysis Set]	N
16.2.8.8	Colonoscopy Report [Safety Analysis Set]	N