Clinical trial results:
A Multicenter Open-Label Extension Study To Assess Long-Term Safety Of PF-00547659 In Subjects With Ulcerative Colitis (TURANDOT II)

Summary

EudraCT number	2012-002031-28
Trial protocol	BE SK NL PL HU CZ DE SE AT ES IT BG
Global end of trial date	13 December 2017

Results information

Result version number	v1 (current)
This version publication date	27 December 2018
First version publication date	27 December 2018

Trial information

Trial identification

Sponsor protocol code	A7281010

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01771809
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Shire
Sponsor organisation address	300 Shire Way, Lexington, United States, MA 02421
Public contact	Study Director, Shire, ClinicalTransparency@shire.com
Scientific contact	Study Director, Shire, ClinicalTransparency@shire.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	13 December 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 December 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 March 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 17
Country: Number of subjects enrolled	Austria: 2
Country: Number of subjects enrolled	Belgium: 17
Country: Number of subjects enrolled	Bulgaria: 1
Country: Number of subjects enrolled	Canada: 16
Country: Number of subjects enrolled	Czech Republic: 14
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	Spain: 8
Country: Number of subjects enrolled	France: 30
Country: Number of subjects enrolled	Hungary: 1
Country: Number of subjects enrolled	Israel: 6
Country: Number of subjects enrolled	Italy: 18
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 21
Country: Number of subjects enrolled	Netherlands: 9
Country: Number of subjects enrolled	New Zealand: 1
Country: Number of subjects enrolled	Poland: 46
Country: Number of subjects enrolled	Russian Federation: 1
Country: Number of subjects enrolled	Serbia: 15
Country: Number of subjects enrolled	Slovakia: 13

Country: Number of subjects enrolled	United States: 90
Country: Number of subjects enrolled	South Africa: 3
Worldwide total number of subjects	331
EEA total number of subjects	161

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	325
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 101 centers in 21 countries between 18 Mar 2013 (first subject first visit) and 13 Dec 2017 (last subject last visit).

Pre-assignment

Screening details:

A total of 331 subjects were randomized and 330 subjects received treatment in the study. One subject discontinued due to adverse event prior to receiving treatment.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	SHP647 75 mg

Arm description:

Subjects received 75 milligrams (mg) of SHP647 subcutaneous (SC) injection every 4 weeks for 72 weeks in the anterolateral right/left thigh or the deltoid area or the abdomen. During the first 72 weeks, a one time dose escalation to 225 mg of SHP647 SC injection every 4 weeks was allowed after 8 weeks of the study for subjects who experienced clinical deterioration or unacceptably low level of response to the investigational product. The decision to escalate was guided by the response and relapse criteria tempered by clinical judgment. Following the first 72 weeks, subjects received 75 mg of SHP647 SC injection every 4 weeks for an additional 72 weeks in the anterolateral right/left thigh or the deltoid area or the abdomen.

Arm type	Experimental
Investigational medicinal product name	SHP647
Investigational medicinal product code	PF-00547659
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received SC injection of SHP647 every 4 weeks in the anterolateral right/left thigh or the deltoid area or the abdomen.

Arm title	SHP647 225 mg

Arm description:

Subjects received 225 mg of SHP647 SC injection every 4 weeks for 72 weeks followed by 75 mg of SHP647 SC injection every 4 weeks for an additional 72 weeks in the anterolateral right/left thigh or the deltoid area or the abdomen.

Arm type	Experimental
Investigational medicinal product name	SHP647
Investigational medicinal product code	PF-00547659
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received SC injection of SHP647 every 4 weeks in the anterolateral right/left thigh or the deltoid area or the abdomen.

Number of subjects in period 1[1]	SHP647 75 mg	SHP647 225 mg
Started	164	166
Completed	93	83
Not completed	71	83
Adverse event, serious fatal	1	-
Other (other)	9	5
Consent withdrawn by subject	34	42
Adverse event, non-fatal	4	12
Other (Insufficient clinical response)	22	20
Lost to follow-up	1	3
Protocol deviation	-	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: All enrolled subjects were not treated with investigational product in this study. Since baseline included treated subjects only, the worldwide number enrolled in the trial differs with the number of subjects reported in the baseline period.

Baseline characteristics

Reporting groups	
Reporting group title	SHP647 75 mg
Reporting group description:	
Subjects received 75 milligrams (mg) of SHP647 subcutaneous (SC) injection every 4 weeks for 72 weeks in the anterolateral right/left thigh or the deltoid area or the abdomen. During the first 72 weeks, a one time dose escalation to 225 mg of SHP647 SC injection every 4 weeks was allowed after 8 weeks of the study for subjects who experienced clinical deterioration or unacceptably low level of response to the investigational product. The decision to escalate was guided by the response and relapse criteria tempered by clinical judgment. Following the first 72 weeks, subjects received 75 mg of SHP647 SC injection every 4 weeks for an additional 72 weeks in the anterolateral right/left thigh or the deltoid area or the abdomen.	
Reporting group title	SHP647 225 mg
Reporting group description:	
Subjects received 225 mg of SHP647 SC injection every 4 weeks for 72 weeks followed by 75 mg of SHP647 SC injection every 4 weeks for an additional 72 weeks in the anterolateral right/left thigh or the deltoid area or the abdomen.	

Reporting group values	SHP647 75 mg	SHP647 225 mg	Total
Number of subjects	164	166	330
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	40.5	41.1	
standard deviation	± 12.75	± 13.68	-
Gender categorical Units: Subjects			
Female	62	70	132
Male	102	96	198
Ethnicity Units: Subjects			
Hispanic or Latino	4	6	10
Not Hispanic or Latino	160	160	320
Unknown or Not Reported	0	0	0
Race Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	11	15	26
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	3	2	5
White	148	143	291
More than one race	0	0	0
Other	2	6	8

End points

End points reporting groups

Reporting group title	SHP647 75 mg

Reporting group description:

Subjects received 75 milligrams (mg) of SHP647 subcutaneous (SC) injection every 4 weeks for 72 weeks in the anterolateral right/left thigh or the deltoid area or the abdomen. During the first 72 weeks, a one time dose escalation to 225 mg of SHP647 SC injection every 4 weeks was allowed after 8 weeks of the study for subjects who experienced clinical deterioration or unacceptably low level of response to the investigational product. The decision to escalate was guided by the response and relapse criteria tempered by clinical judgment. Following the first 72 weeks, subjects received 75 mg of SHP647 SC injection every 4 weeks for an additional 72 weeks in the anterolateral right/left thigh or the deltoid area or the abdomen.

Reporting group title	SHP647 225 mg

Reporting group description:

Subjects received 225 mg of SHP647 SC injection every 4 weeks for 72 weeks followed by 75 mg of SHP647 SC injection every 4 weeks for an additional 72 weeks in the anterolateral right/left thigh or the deltoid area or the abdomen.

Primary: Number of Subjects With Treatment-Emergent Adverse Events (TEAEs), Treatment-Emergent Serious Adverse Events (TESAEs), and who Withdrew From Treatment due to Treatment-Emergent Adverse Events (TEAEs)

End point title	Number of Subjects With Treatment-Emergent Adverse Events (TEAEs), Treatment-Emergent Serious Adverse Events (TESAEs), and who Withdrew From Treatment due to Treatment-Emergent Adverse Events (TEAEs)[1]

End point description:

An adverse event (AE) was defined as any untoward medical occurrence in a clinical investigation subject who was administered a product or medical device; the event did not need to necessarily have a causal relationship with the treatment or usage. A serious adverse event (SAE) was any untoward medical occurrence at any dose that resulted in death, was life threatening (immediate risk of death), required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity, resulted in congenital anomaly/birth defect. Number of subjects with TEAEs, STEAEs, and those withdrew from treatment due to TEAEs were reported. Safety analysis set (SAS) consisted of all enrolled subjects who had received at least 1 dose of SHP647.

End point type	Primary

End point timeframe:

From start of study drug administration up to 168 weeks

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics were done, no inferential statistics performed.

End point values	SHP647 75 mg	SHP647 225 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	164	166		
Units: Subjects				
Subjects with any TEAE	146	147		
Subjects with any TESAE	34	40		
Subjects who withdrew treatment due to TEAE	12	23		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Mucosal Healing at Week 16

End point title	Percentage of Subjects With Mucosal Healing at Week 16

End point description:

Mucosal healing was defined as an absolute Mayo subscore for endoscopy of 0 or 1 (based on centrally read score) as assessed by flexible sigmoidoscopy or colonoscopy. The Mayo score is a tool designed to measure disease activity for ulcerative colitis (UC). The Mayo scoring system ranges from 0 to 12 points and consists of 4 subscores (stool frequency, rectal bleeding, findings on flexible sigmoidoscopy, and physician's global assessment [PGA]) each graded 0 to 3 with the higher score indicating more severe disease activity. The percentage of subjects with mucosal healing at week 16 was reported. The SAS consisted of all enrolled subjects who had received at least 1 dose of SHP647.

End point type	Secondary

End point timeframe:

Week 16

End point values	SHP647 75 mg	SHP647 225 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	164	166		
Units: Percentage of subjects				
number (not applicable)				
Percentage of subjects	27.4	29.5		

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Trough Concentrations of SHP647 Versus Time

End point title	Serum Trough Concentrations of SHP647 Versus Time

End point description:

Serum trough concentrations of SHP647 versus time was reported. The pharmacokinetic (PK) set consisted of all subjects who received at least 1 dose of SHP647 and for whom at least 1 post dose PK sample was collected. Here "n" refers to the number of subjects evaluable for each reporting group respectively at the specified time points.

End point type	Secondary

End point timeframe:

Baseline, Week 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, 72 and 156

End point values	SHP647 75 mg	SHP647 225 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	163	164		
Units: Micrograms/liter (ug/L)				
arithmetic mean (standard deviation)				
Baseline (n=113,117)	6398.62 (± 8584.412)	8064.41 (± 10629.768)		
Week 4 (n=156,160)	5496.56 (± 4026.759)	16787.31 (± 7807.292)		
Week 8 (n=155,157)	6245.79 (± 3371.708)	20345.29 (± 9286.956)		
Week 12 (n=157,155)	9038.72 (± 5540.836)	23915.87 (± 10434.073)		
Week 16 (n=141,149)	10445.24 (± 6387.004)	24772.35 (± 11970.153)		
Week 20 (n=124,124)	10928.76 (± 7900.859)	25582.98 (± 11767.775)		
Week 24 (n=115,123)	11145.54 (± 8019.864)	27832.20 (± 12469.086)		
Week 28 (n=111,121)	12978.11 (± 8772.285)	27797.77 (± 13070.361)		
Week 32 (n=110,119)	12926.04 (± 8798.671)	28381.93 (± 11748.573)		
Week 36 (n=110,110)	12785.55 (± 9182.501)	29666.64 (± 13997.231)		
Week 40 (n=102,109)	13004.90 (± 9544.675)	28947.34 (± 12151.971)		
Week 44 (n=100,102)	13337.50 (± 8620.549)	29855.69 (± 13605.897)		
Week 48 (n=104,99)	14061.44 (± 9257.991)	30010.61 (± 14014.183)		
Week 52 (n=99,98)	14192.83 (± 9326.176)	28917.76 (± 14545.617)		
Week 56 (n=98,97)	15179.77 (± 10405.996)	29985.88 (± 14122.172)		
Week 60 (n=96,90)	15133.54 (± 9673.602)	29086.78 (± 12606.888)		
Week 64 (n=91,91)	15354.29 (± 10112.098)	31613.08 (± 13712.478)		
Week 68 (n=89,96)	15584.38 (± 10407.781)	30609.08 (± 14331.857)		
Week 72 (n=88,90)	15006.48 (± 9390.020)	31342.89 (± 14012.311)		
Week 156 (n=79,81)	983.49 (± 1485.708)	1893.88 (± 4530.680)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Positive Anti-drug (SHP647) Antibodies (ADA)

End point title	Number of Subjects With Positive Anti-drug (SHP647) Antibodies (ADA)

End point description:

The anti-drug antibodies (ADA) positive was defined as ADA log base 2 titer greater than or equal to (>=) 4.64. The number of subjects with positive ADA was reported. The SAS consisted of all enrolled subjects who had received at least 1 dose of SHP647. Here "n" refers to the number of subjects evaluable for each reporting group respectively at the specified time points.

End point type	Secondary

End point timeframe:

Baseline, Week 8, 16, 24, 40, 48, 64 and 156

End point values	SHP647 75 mg	SHP647 225 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	164	166		
Units: Subjects				
Baseline (n=148,153)	9	10		
Week 8 (n=143,151)	3	1		
Week 16 (n=140,144)	1	1		
Week 24 (n=106,119)	1	1		
Week 40 (n=94,104)	1	2		
Week 48 (n=97,92)	1	0		
Week 64 (n=83,86)	1	0		
Week 156 (n=73,81)	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Positive Neutralizing Antibodies (NAb)

End point title	Number of Subjects With Positive Neutralizing Antibodies (NAb)

End point description:

The positive Neutralizing Antibodies (NAb) was defined as NAb titer greater than or equal to (>=) 0.903. The number of subjects with NAb was reported. The SAS consisted of all enrolled subjects who had received at least 1 dose of SHP647. Here "n" refers to the number of subjects evaluable for each reporting group respectively at the specified time points.

End point type	Secondary

End point timeframe:

Baseline, Week 8, 16, 24, 40, 48, 64 and 156

End point values	SHP647 75 mg	SHP647 225 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	164	166		
Units: Subjects				
Baseline (n=8,10)	0	4		
Week 8 (n=3,1)	1	1		
Week 16 (n=1,1)	0	1		
Week 24 (n=1,1)	0	1		
Week 40 (n=1,2)	1	2		
Week 48 (n=1,0)	1	0		
Week 64 (n=1,0)	0	0		
Week 156 (n=0,1)	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From start of study drug administration up to 168 weeks

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	SHP647 225 mg

Reporting group description:

Subjects received 225 mg of SHP647 SC injection every 4 weeks for 72 weeks followed by 75 mg of SHP647 SC injection every 4 weeks for an additional 72 weeks in the anterolateral right/left thigh or the deltoid area or the abdomen.

Reporting group title	SHP647 75 mg

Reporting group description:

Subjects received 75 mg of SHP647 SC injection every 4 weeks for 72 weeks in the anterolateral right/left thigh or the deltoid area or the abdomen. During the first 72 weeks, a one time dose escalation to 225 mg of SHP647 SC injection every 4 weeks was allowed after 8 weeks of the study for subjects who experienced clinical deterioration or unacceptably low level of response to the investigational product. The decision to escalate was guided by the response and relapse criteria tempered by clinical judgment. Following the first 72 weeks, subjects received 75 mg of SHP647 SC injection every 4 weeks for an additional 72 weeks in the anterolateral right/left thigh or the deltoid area or the abdomen.

Serious adverse events	SHP647 225 mg	SHP647 75 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	40 / 166 (24.10%)	34 / 164 (20.73%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung neoplasm malignant			
subjects affected / exposed	1 / 166 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Serous cystadenocarcinoma ovary			
subjects affected / exposed	0 / 166 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Pregnancy			

subjects affected / exposed	1 / 166 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Non-Cardiac chest pain			
subjects affected / exposed	1 / 166 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 166 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 166 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Serum sickness			
subjects affected / exposed	0 / 166 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Gynaecomastia			
subjects affected / exposed	0 / 166 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 166 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			

subjects affected / exposed	0 / 166 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 166 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	0 / 166 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 166 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood iron decreased			
subjects affected / exposed	1 / 166 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Anastomotic fistula			
subjects affected / exposed	1 / 166 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anastomotic stenosis			
subjects affected / exposed	1 / 166 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clavicle fracture			

subjects affected / exposed	1 / 166 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	1 / 166 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	1 / 166 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	1 / 166 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stoma complication			
subjects affected / exposed	1 / 166 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Arrhythmogenic right ventricular dysplasia			
subjects affected / exposed	0 / 166 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 166 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	1 / 166 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Atrial fibrillation			
subjects affected / exposed	1 / 166 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	1 / 166 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 166 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	0 / 166 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Basilar migraine			
subjects affected / exposed	1 / 166 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	1 / 166 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	2 / 166 (1.20%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 166 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Typical aura without headache			

subjects affected / exposed	1 / 166 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 166 (0.60%)	2 / 164 (1.22%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Retinal detachment			
subjects affected / exposed	0 / 166 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 166 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fissure			
subjects affected / exposed	1 / 166 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ulcerative			
subjects affected / exposed	18 / 166 (10.84%)	15 / 164 (9.15%)	
occurrences causally related to treatment / all	1 / 19	0 / 19	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 166 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
subjects affected / exposed	0 / 166 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Enteritis			
subjects affected / exposed	0 / 166 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal stenosis			
subjects affected / exposed	0 / 166 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 166 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 166 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 166 (0.60%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Calculus urinary			
subjects affected / exposed	1 / 166 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	0 / 166 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	1 / 166 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue			

disorders			
Arthralgia			
subjects affected / exposed	1 / 166 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck pain			
subjects affected / exposed	1 / 166 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	1 / 166 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Anal abscess			
subjects affected / exposed	1 / 166 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 166 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 166 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic sinusitis			
subjects affected / exposed	0 / 166 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	0 / 166 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastroenteritis			
subjects affected / exposed	1 / 166 (0.60%)	2 / 164 (1.22%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	1 / 166 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis listeria			
subjects affected / exposed	1 / 166 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis viral			
subjects affected / exposed	0 / 166 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic abscess			
subjects affected / exposed	1 / 166 (0.60%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	1 / 166 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 166 (0.60%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 166 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			

subjects affected / exposed	0 / 166 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 166 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	2 / 166 (1.20%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	SHP647 225 mg	SHP647 75 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	119 / 166 (71.69%)	116 / 164 (70.73%)	
Nervous system disorders			
Headache			
subjects affected / exposed	21 / 166 (12.65%)	17 / 164 (10.37%)	
occurrences (all)	56	23	
General disorders and administration site conditions			
Influenza like illness			
subjects affected / exposed	9 / 166 (5.42%)	8 / 164 (4.88%)	
occurrences (all)	10	11	
Pyrexia			
subjects affected / exposed	7 / 166 (4.22%)	14 / 164 (8.54%)	
occurrences (all)	10	20	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	20 / 166 (12.05%)	9 / 164 (5.49%)	
occurrences (all)	33	14	
Colitis ulcerative			

subjects affected / exposed	36 / 166 (21.69%)	41 / 164 (25.00%)	
occurrences (all)	50	52	
Diarrhoea			
subjects affected / exposed	7 / 166 (4.22%)	11 / 164 (6.71%)	
occurrences (all)	11	13	
Nausea			
subjects affected / exposed	19 / 166 (11.45%)	8 / 164 (4.88%)	
occurrences (all)	20	10	
Vomiting			
subjects affected / exposed	7 / 166 (4.22%)	10 / 164 (6.10%)	
occurrences (all)	7	10	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	11 / 166 (6.63%)	20 / 164 (12.20%)	
occurrences (all)	12	20	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	13 / 166 (7.83%)	8 / 164 (4.88%)	
occurrences (all)	13	9	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	29 / 166 (17.47%)	27 / 164 (16.46%)	
occurrences (all)	42	41	
Back pain			
subjects affected / exposed	18 / 166 (10.84%)	12 / 164 (7.32%)	
occurrences (all)	20	15	
Infections and infestations			
Bronchitis			
subjects affected / exposed	8 / 166 (4.82%)	10 / 164 (6.10%)	
occurrences (all)	12	12	
Clostridium difficile infection			
subjects affected / exposed	4 / 166 (2.41%)	11 / 164 (6.71%)	
occurrences (all)	4	12	
Gastroenteritis			
subjects affected / exposed	13 / 166 (7.83%)	18 / 164 (10.98%)	
occurrences (all)	17	25	

Influenza			
subjects affected / exposed	15 / 166 (9.04%)	8 / 164 (4.88%)	
occurrences (all)	19	9	
Nasopharyngitis			
subjects affected / exposed	28 / 166 (16.87%)	20 / 164 (12.20%)	
occurrences (all)	44	27	
Pharyngitis			
subjects affected / exposed	17 / 166 (10.24%)	2 / 164 (1.22%)	
occurrences (all)	20	2	
Sinusitis			
subjects affected / exposed	10 / 166 (6.02%)	7 / 164 (4.27%)	
occurrences (all)	14	11	
Upper respiratory tract infection			
subjects affected / exposed	20 / 166 (12.05%)	23 / 164 (14.02%)	
occurrences (all)	35	34	
Urinary tract infection			
subjects affected / exposed	10 / 166 (6.02%)	11 / 164 (6.71%)	
occurrences (all)	12	15	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 March 2013	- The withdrawal criteria for Week 16 was updated. - The language for early withdrawal was revised.
21 March 2013	- The rationale for discontinuing immunosuppressive therapy was updated. - The approximate number of subjects was updated. - The optional endoscopic biopsy substudy was updated. - Updates made to clarify halting treatment with study medication for unexplained neurological signs or symptoms and undergoing further neurological evaluation.
24 February 2015	- An Open-label Treatment Period 2 in which subjects received 75 mg SHP647 for an additional 18 months was added. - All language pertaining to dose escalation was removed as a result of Study A7281009 study that did not show additional benefit with the 225-mg dose. - Additional language was added regarding guidance on dose interruption. - Complete Physical Examination was updated to clarify that the external genitalia examination was optional.
04 December 2015	- The Risk Benefit Section was revised to reflect the available biologic treatment for subjects with inflammatory bowel disease. - The 24-month follow-up period was changed to a 6-month follow-up period.
14 November 2016	- The language in the Risk Benefit Section was updated to cite the investigator's brochure as the most current source of overall risk/benefit assessment of SHP647. - The text related to Drug storage and temperature monitoring of storage facility, Reporting and follow-up of pregnancies of female study subjects or partners of male study subjects; and Reporting and follow-up of serious adverse events, were updated.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported