Clinical trial results:
A Randomised Active-Controlled Double-Blind and Open Label Extension Study to Evaluate the Efficacy, Long-term Safety and Tolerability of TP05 3.2 g/day for the Treatment of Active Ulcerative Colitis (UC)

Summary

EudraCT number	2013-000366-11
Trial protocol	SE IE CZ FI GB DK BE ES PL HU LT LV BG SK RO
Global end of trial date	17 May 2016

Results information

Result version number	v1 (current)
This version publication date	04 November 2017
First version publication date	04 November 2017

Trial information

Trial identification

Sponsor protocol code	TP0503

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01903252
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Tillotts Pharma AG
Sponsor organisation address	Baslerstrasse 15, Rheinfelden, Switzerland, 4310
Public contact	Dr. Robert Hofmann, Thillotts Pharma AG, +41 61 935 27 14, rhofmann@tillotts.com
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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	17 May 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 May 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Induction:
The primary objective of the Induction phase is to determine if 8 weeks of treatment with 3.2 g/day of TP05 is not inferior to 3.2 g/day of Asacol™ in inducing clinical and endoscopic remission (a score ≤ 2 points on the Mayo scoring scale with no individual sub-score > 1 point) in subjects with active mild to moderate Ulcerative Colitis (UC).

Open Label Extension (OLE):
The primary objective of the OLE is to assess the safety and tolerability of TP05 over a 26-week period in subjects achieving endoscopic and clinical remission or exhibiting a response during the initial phase of TP0503. Maintenance of clinical remission by TP05 will also be assessed by determining the proportion of patients in clinical remission at the final visit.

Protection of trial subjects:

No special protection of trial subjects

Background therapy:

None

Evidence for comparator:

Tillotts Pharma AG (Rheinfelden, Switzerland) manufactures and markets 400 mg mesalazine tablets (Asacol™) in over 30 countries in Europe and Asia.

Actual start date of recruitment	01 July 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Russian Federation: 101
Country: Number of subjects enrolled	Belarus: 96
Country: Number of subjects enrolled	Canada: 32
Country: Number of subjects enrolled	Ukraine: 130
Country: Number of subjects enrolled	Serbia: 36
Country: Number of subjects enrolled	Norway: 9
Country: Number of subjects enrolled	Poland: 92
Country: Number of subjects enrolled	Romania: 3
Country: Number of subjects enrolled	Slovakia: 5
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	Sweden: 3
Country: Number of subjects enrolled	United Kingdom: 18

Country: Number of subjects enrolled	Belgium: 17
Country: Number of subjects enrolled	Bulgaria: 30
Country: Number of subjects enrolled	Czech Republic: 38
Country: Number of subjects enrolled	Denmark: 36
Country: Number of subjects enrolled	Finland: 3
Country: Number of subjects enrolled	France: 39
Country: Number of subjects enrolled	Hungary: 28
Country: Number of subjects enrolled	Ireland: 1
Country: Number of subjects enrolled	Latvia: 44
Country: Number of subjects enrolled	Lithuania: 54
Worldwide total number of subjects	817
EEA total number of subjects	422

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)	755
From 65 to 84 years	62
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Up to 14 days screening period
179 study centres were activated, 49 centres did not screen or enrol any study subjects, 15 centres screened subjects, but did not enroll any subjects and 115 centres enrolled subjects into the study.

Pre-assignment

Screening details:

INCLUSION CRITERIA
Subjects were required to meet the following criteria for enrollment into the study:
1. Male or non-pregnant, non-lactating females, 18 years of age or older. Females of child bearing potential must have a negative serum pregnancy test prior to randomisation, and must use a hormonal (oral, implantable or injectable) or ba

Pre-assignment period milestones

Number of subjects started	1141[1]
Number of subjects completed	817

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Consent withdrawn by subject: 10
Reason: Number of subjects	Protocol deviation: 314

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The number of subjects that have started the pre-assignment period is the number of subjects screened, i.e 1141. The number of subjects enrolled is 817 which excludes 324 screen failures.

Period 1

Period 1 title	Double-blind induction phase
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	TP05

Arm description:

TP05 (Mesalamine) 1600 mg tablet, 3.2g/day once daily for 12 weeks

Arm type	Experimental
Investigational medicinal product name	TP05
Investigational medicinal product code	
Other name	Mesalamine
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

3.2g/day once daily, with or without food

Arm title	Asacol 400mg

Arm description:

Asacol 400mg, 3.2g/ day (1.6g in the morning and 1.6g in the evening)

Arm type	Active comparator

Investigational medicinal product name	Asacol 400 mg
Investigational medicinal product code	
Other name	Mesalamine, 5-ASA
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

3.2g/day, twice daily for 12 weeks

Number of subjects in period 1	TP05	Asacol 400mg
Started	409	408
Completed	370	367
Not completed	39	41
Consent withdrawn by subject	10	13
Physician decision	2	3
Adverse event, non-fatal	20	18
non-compliance	7	7

Period 2

Period 2 title	Extended Induction Open Label (OLE)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Patients who failed to show a response in either arm at week 8 were withdrawn from the double-blind induction phase and put on an increased daily dose of 4.8g TP05.

Arms

Arm title	TP05

Arm description:

All patients received TP05, 4.8g/day once daily

Arm type	Experimental
Investigational medicinal product name	TP05
Investigational medicinal product code	
Other name	Mesalamine, 5-ASA
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

4.8g/day, three tablets once daily

Number of subjects in period 2[2]	TP05
Started	243
Completed	220
Not completed	23
Consent withdrawn by subject	5
Physician decision	1
Adverse event, non-fatal	17

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Subjects who did not respond to the treatment after 8 weeks of the double-blind induction phase were withdrawn and started another 8 weeks on an increased daily dose of 4.8g (open-label extended induction)

Period 3

Period 3 title	Maintenance Open Label (OLE)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Patients who completed either 12 weeks of the double-blind induction phase or the extended induction phase (OLE) enterd the maintenance Open Label phase

Arms

Are arms mutually exclusive?	No
Arm title	TP05 1.6g/day

Arm description:

Patients who were in remission at week 12 of the double-blind induction phase, entered the maintenance OLE phase on a reduced daily dose of 1.6g (1 tablet a day)

Arm type	Experimental
Investigational medicinal product name	TP05
Investigational medicinal product code	
Other name	Mesalamine, 5-ASA
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

TP05 1.6g/ day, 1 tablet a day with or without food

Arm title	TP05 3.2g/day

Arm description:

Patients who showed a response but not remission in the double-blind induction phase entered the maintenance OLE phase on the same dose as in the double-blind induction (3.2g/d, 2 tablets a day, OD).

Arm type	Experimental
Investigational medicinal product name	TP05
Investigational medicinal product code	
Other name	Mesalamine, 5-ASA
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

3.2g/d (2 tablets) once daily with or without food.

Arm title	TP05 4.8g/day

Arm description:

Patients who lost response between week 8 and 12 of the double-blind induction phase and patients who showed no response at week 8 of the double-blind induction but responded after the extended induction phase (OLE), entered the maintenance OLE phase at a daily dose of 4.8g (3 tablets a day OD).

Arm type	Experimental
Investigational medicinal product name	TP05
Investigational medicinal product code	
Other name	Mesalamine, 5-ASA
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

4.8g/day, 3 tablets once daily with or without food

Number of subjects in period 3	TP05 1.6g/day	TP05 3.2g/day	TP05 4.8g/day
Started	202	274	199
Completed	196	253	181
Not completed	6	21	18
Consent withdrawn by subject	1	6	2
unknown	2	6	-
Adverse event, non-fatal	3	9	14
Lack of efficacy	-	-	2

Baseline characteristics

Reporting groups	
Reporting group title	TP05
Reporting group description:	
TP05 (Mesalamine) 1600 mg tablet, 3.2g/day once daily for 12 weeks	
Reporting group title	Asacol 400mg
Reporting group description:	
Asacol 400mg, 3.2g/ day (1.6g in the morning and 1.6g in the evening)	

Reporting group values	TP05	Asacol 400mg	Total
Number of subjects	409	408	817
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	378	377	755
From 65-84 years	31	31	62
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	43.97	43.3	
standard deviation	± 14.54	± 14.11	-
Gender categorical			
Units: Subjects			
Female	171	178	349
Male	238	230	468
Demographics			
Region of Enrolment			
Units: Subjects			
Belarus	47	49	96
Belgium	9	8	17
Bulgaria	15	15	30
Canada	15	17	32
Czech Republic	20	18	38
Denmark	20	16	36
Finland	2	1	3
Hungary	17	11	28
Ireland	1	0	1
Latvia	22	22	44
Lithuania	26	28	54
Norway	4	5	9
Poland	44	48	92

Romania	2	1	3
Russian Federation	51	50	101
Serbia	18	18	36
Slovakia	2	3	5
France	23	16	39
Ukraine	59	71	130
Spain	0	2	2
Sweden	1	2	3
United Kingdem	11	7	18
Mayo Score			
Mayo Clinic Score			
Units: Score			
arithmetic mean	7.7	7.6	
standard deviation	± 1.3	± 1.3	-
Partial Mayo Score			
Partial Mayo Clinic Score			
Units: Score			
arithmetic mean	5.5	5.3	
standard deviation	± 1.1	± 1.1	-

Subject analysis sets

Subject analysis set title	Baseline
Subject analysis set type	Full analysis

Subject analysis set description:

The 817 randomised subjects

Reporting group values	Baseline		
Number of subjects	817		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	755		
From 65-84 years	62		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean	43.5		
standard deviation	± 14.3		
Gender categorical			
Units: Subjects			
Female	349		
Male	468		

Demographics			
Region of Enrolment			
Units: Subjects			
Belarus	96		
Belgium	17		
Bulgaria	30		
Canada	32		
Czech Republic	38		
Denmark	36		
Finland	3		
Hungary	28		
Ireland	1		
Latvia	44		
Lithuania	45		
Norway	9		
Poland	92		
Romania	3		
Russian Federation	101		
Serbia	36		
Slovakia	5		
France	39		
Ukraine	130		
Spain	2		
Sweden	3		
United Kingdem	18		
Mayo Score			
Mayo Clinic Score			
Units: Score			
arithmetic mean	7.7		
standard deviation	± 1.3		
Partial Mayo Score			
Partial Mayo Clinic Score			
Units: Score			
arithmetic mean	5.4		
standard deviation	± 1.1		

End points

End points reporting groups

Reporting group title	TP05
Reporting group description:	
TP05 (Mesalamine) 1600 mg tablet, 3.2g/day once daily for 12 weeks	
Reporting group title	Asacol 400mg
Reporting group description:	
Asacol 400mg, 3.2g/ day (1.6g in the morning and 1.6g in the evening)	
Reporting group title	TP05
Reporting group description:	
All patients received TP05, 4.8g/day once daily	
Reporting group title	TP05 1.6g/day
Reporting group description:	
Patients who were in remission at week 12 of the double-blind induction phase, entered the maintenance OLE phase on a reduced daily dose of 1.6g (1 tablet a day)	
Reporting group title	TP05 3.2g/day
Reporting group description:	
Patients who showed a response but not remission in the double-blind induction phase entered the maintenance OLE phase on the same dose as in the double-blind induction (3.2g/d, 2 tablets a day, OD).	
Reporting group title	TP05 4.8g/day
Reporting group description:	
Patients who lost response between week 8 and 12 of the double-blind induction phase and patients who showed no response at week 8 of the double-blind induction but responded after the extended induction phase (OLE), entered the maintenance OLE phase at a daily dose of 4.8g (3 tablets a day OD).	
Subject analysis set title	Baseline
Subject analysis set type	Full analysis
Subject analysis set description:	
The 817 randomised subjects	

Primary: Period 1: Clinical and Endoscopic Remission

End point title	Period 1: Clinical and Endoscopic Remission
End point description:	
Mayo Score of <= 2 points with no individual sub-score > 1	
End point type	Primary
End point timeframe:	
8 weeks	

End point values	TP05	Asacol 400mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	388	386		
Units: Number of Subject	87	95		

Statistical analyses

Statistical analysis title	Non-Inferiority

Statistical analysis description:

Non-inferiority, pre-defined non-inferiority margin 10%, a two-sided 95% confidence interval about the difference in proportion was contructed. If the lower limit of the confidence interval was no less than -10 it would be concluded that the test product is non-inferior to the comparator

Comparison groups	Asacol 400mg v TP05
Number of subjects included in analysis	774
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.005
Method	Newcombe
Parameter estimate	Risk difference (RD)
Point estimate	-2.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.1
upper limit	3.8

Statistical analysis title	Clinical and Endoscopic Remission
Comparison groups	TP05 v Asacol 400mg
Number of subjects included in analysis	774
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.005
Method	Newcombe
Parameter estimate	Risk difference (RD)
Point estimate	-2.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.1
upper limit	3.8

Primary: Period 2: Clinical Response

End point title	Period 2: Clinical Response[1]

End point description:

A decrease in the PMCS of >= 2 points and >= 30% from baseline, with a decrease in the rectal bleeding sub.score of >= 1 point or absolute rectal bleeding subscore of 1 or 0.

End point type	Primary

End point timeframe:

week 16

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: This is the open-label extended induction phase with one arm. The endpoint is the proportion of patients achievien clinical response. There was no comparison between arms and no p-value was established.

End point values	TP05			
Subject group type	Reporting group			
Number of subjects analysed	243			
Units: Number of Subject	183			

Statistical analyses

No statistical analyses for this end point

Primary: Period 3: Clinical Remission

End point title	Period 3: Clinical Remission[2]

End point description:

Clinical Remission was defined as a score of 0 points for both stool frequency and rectal bleeding on the Partial Mayo Clinic Score (PMCS)

End point type	Primary

End point timeframe:

week 38

Notes:

[2] - 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: This is the open-label part of the trial. There are three arms in Period 3 which differ from each other in the daily dose of TP05: 1.6g, 3.2g and 4.8g. The endpoint here is the proportion of patients achieving Clinical Remission in each arm separately. There was no comparison between the three arms and no p-value was established.

End point values	TP05 1.6g/day	TP05 3.2g/day	TP05 4.8g/day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	202	274	199	
Units: Number of Subjects	142	93	61	

Statistical analyses

No statistical analyses for this end point

Primary: Period 1: Clinical Remission

End point title	Period 1: Clinical Remission

End point description:

End point type	Primary

End point timeframe:

Both week 8 and week 12

End point values	TP05	Asacol 400mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	388	386		
Units: Number of Subjects	66	80		

Statistical analyses

Statistical analysis title	Clinical Remission
Comparison groups	TP05 v Asacol 400mg
Number of subjects included in analysis	774
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.013
Method	Newcombe
Parameter estimate	Risk difference (RD)
Point estimate	-3.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.2
upper limit	1.8

Secondary: Period 1: Endoscopic Remission

End point title	Period 1: Endoscopic Remission
End point description:	
End point type	Secondary
End point timeframe: week 8	

End point values	TP05	Asacol 400mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	388	386		
Units: Number of Subjects	36	44		

Statistical analyses

Statistical analysis title	Endoscopic Remission
Comparison groups	TP05 v Asacol 400mg

Number of subjects included in analysis	774
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.001
Method	Newcombe
Parameter estimate	Risk difference (RD)
Point estimate	-2.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.5
upper limit	2.2

Secondary: Period 1: Endoscopic Response

End point title	Period 1: Endoscopic Response
End point description:	

End point type	Secondary
End point timeframe:	
Week 8	

End point values	TP05	Asacol 400mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	388	386		
Units: Score				
number (not applicable)	185	196		

Statistical analyses

Statistical analysis title	Endoscopic Response
Comparison groups	TP05 v Asacol 400mg
Number of subjects included in analysis	774
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.026
Method	Newcombe
Parameter estimate	Risk difference (RD)
Point estimate	-3.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.1
upper limit	3.9

Secondary: Period 1: Clinical Remission

End point title	Period 1: Clinical Remission

End point description:

End point type	Secondary

End point timeframe:

Week 8

End point values	TP05	Asacol 400mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	388	386		
Units: Number of Subjects	92	110		

Statistical analyses

Statistical analysis title	Clinical Remission
Comparison groups	Asacol 400mg v TP05
Number of subjects included in analysis	774
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.048
Method	Newcombe
Parameter estimate	Risk difference (RD)
Point estimate	-4.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.9
upper limit	1.4

Secondary: Period 1: Rectal Bleeding Sub-Score of 0

End point title	Period 1: Rectal Bleeding Sub-Score of 0

End point description:

End point type	Secondary

End point timeframe:

Week 8

End point values	TP05	Asacol 400mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	388	386		
Units: Number of Subjects	212	226		

Statistical analyses

Statistical analysis title	Rectal Bleeding = 0
Comparison groups	TP05 v Asacol 400mg
Number of subjects included in analysis	774
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.042
Method	Newcombe
Parameter estimate	Risk difference (RD)
Point estimate	-3.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.8
upper limit	3.1

Secondary: Period 1: Clinical and Endoscopic Response

End point title	Period 1: Clinical and Endoscopic Response

End point description:

End point type	Secondary

End point timeframe:

Week 8

End point values	TP05	Asacol 400mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	388	386		
Units: Number of Subjects	221	236		

Statistical analyses

Statistical analysis title	Clinical and Endoscopic Response
Comparison groups	TP05 v Asacol 400mg
Number of subjects included in analysis	774
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.048
Method	Newcombe
Parameter estimate	Risk difference (RD)
Point estimate	-4.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11
upper limit	2.7

Secondary: Period 1: Clinical Remission

End point title	Period 1: Clinical Remission
End point description:	
End point type	Secondary
End point timeframe:	
Week 12	

End point values	TP05	Asacol 400mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	388	386		
Units: Number of Subjects	93	113		

Statistical analyses

Statistical analysis title	Clinical Remission
Comparison groups	TP05 v Asacol 400mg
Number of subjects included in analysis	774
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.068
Method	Newcombe
Parameter estimate	Risk difference (RD)
Point estimate	-5.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.5
upper limit	0.9

Secondary: Period 1: Clinical Response

End point title	Period 1: Clinical Response
End point description:	

End point type	Secondary
End point timeframe:	
Week 12	

End point values	TP05	Asacol 400mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	388	386		
Units: Number of Subjects	223	233		

Statistical analyses

Statistical analysis title	Clinical Response
Comparison groups	TP05 v Asacol 400mg
Number of subjects included in analysis	774
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.021
Method	Newcombe
Parameter estimate	Risk difference (RD)
Point estimate	-2.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.8
upper limit	4

Secondary: Period 1: Rectal Bleeding Sub-Score of 0

End point title	Period 1: Rectal Bleeding Sub-Score of 0
End point description:	

End point type	Secondary

End point timeframe:
Week 12

End point values	TP05	Asacol 400mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	388	386		
Units: Number of Subjects	193	205		

Statistical analyses

Statistical analysis title	Rectal Bleeding Score = 0
Comparison groups	TP05 v Asacol 400mg
Number of subjects included in analysis	774
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.03
Method	Newcombe
Parameter estimate	Risk difference (RD)
Point estimate	-3.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.3
upper limit	3.7

Secondary: Period 1: Clinical Response

End point title	Period 1: Clinical Response

End point description:

End point type	Secondary

End point timeframe:
Both at week 8 and week 12

End point values	TP05	Asacol 400mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	388	386		
Units: Number of Subjects	216	230		

Statistical analyses

Statistical analysis title	Clinical Response
Comparison groups	Asacol 400mg v TP05
Number of subjects included in analysis	774
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.042
Method	Newcombe
Parameter estimate	Risk difference (RD)
Point estimate	-3.9
Confidence interval	
level	90 %
sides	2-sided
lower limit	-10.8
upper limit	3

Secondary: Period 1: Change in Mayo Score

End point title	Period 1: Change in Mayo Score
End point description:	
End point type	Secondary
End point timeframe:	
Week 8	

End point values	TP05	Asacol 400mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	371	375		
Units: Score				
number (not applicable)	3.1	3.2		

Statistical analyses

Statistical analysis title	Change in Mayo Score
Comparison groups	TP05 v Asacol 400mg
Number of subjects included in analysis	746
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.557
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5
upper limit	0.3
Variability estimate	Standard deviation

Secondary: Period 1: Change in Partial Mayo Score

End point title	Period 1: Change in Partial Mayo Score
End point description:	
End point type	Secondary
End point timeframe:	
Week 8	

End point values	TP05	Asacol 400mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	387	383		
Units: Score				
number (not applicable)	2.5	2.5		

Statistical analyses

Statistical analysis title	Change in Partial Mayo Score
Comparison groups	TP05 v Asacol 400mg
Number of subjects included in analysis	770
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.987
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	0.3

Secondary: Period 1: Change in Stool Frequency

End point title	Period 1: Change in Stool Frequency
End point description:	

End point type	Secondary
End point timeframe:	
Week 8	

End point values	TP05	Asacol 400mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	387	383		
Units: Score				
number (not applicable)	0.9	0.9		

Statistical analyses

Statistical analysis title	Change in Stool Frequency
Comparison groups	TP05 v Asacol 400mg
Number of subjects included in analysis	770
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.455
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	0.2

Secondary: Period 1: Change in Rectal Bleeding

End point title	Period 1: Change in Rectal Bleeding
End point description:	

End point type	Secondary
End point timeframe:	
Week 8	

End point values	TP05	Asacol 400mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	387	383		
Units: Score				
number (not applicable)	0.9	1.0		

Statistical analyses

Statistical analysis title	Change in Rectal Bleeding
Comparison groups	TP05 v Asacol 400mg
Number of subjects included in analysis	770
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.937
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	0.1

Secondary: Period 1: Change in Physician Global Assessment

End point title	Period 1: Change in Physician Global Assessment
End point description:	
End point type	Secondary
End point timeframe:	
Week 8	

End point values	TP05	Asacol 400mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	387	383		
Units: Score				
number (not applicable)	0.6	0.7		

Statistical analyses

Statistical analysis title	Change in Physician Global Assessment
Comparison groups	TP05 v Asacol 400mg

Number of subjects included in analysis	770
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.357
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.1

Secondary: Period 1: Change in Endoscopy Score

End point title	Period 1: Change in Endoscopy Score
End point description:	
End point type	Secondary
End point timeframe:	
Week 8	

End point values	TP05	Asacol 400mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	371	375		
Units: Score				
number (not applicable)	0.5	0.6		

Statistical analyses

Statistical analysis title	Change in Endoscopy Score
Comparison groups	TP05 v Asacol 400mg
Number of subjects included in analysis	746
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.099
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0

Secondary: Period 2: Clinical Remission

End point title	Period 2: Clinical Remission

End point description:

End point type	Secondary

End point timeframe:
Week 16

End point values	TP05			
Subject group type	Reporting group			
Number of subjects analysed	243			
Units: Number of Subjects	53			

Statistical analyses

No statistical analyses for this end point

Secondary: Period 2: Rectal Bleeding Score of 0

End point title	Period 2: Rectal Bleeding Score of 0

End point description:

End point type	Secondary

End point timeframe:
Week 16

End point values	TP05			
Subject group type	Reporting group			
Number of subjects analysed	243			
Units: Number of Subjects	146			

Statistical analyses

No statistical analyses for this end point

Secondary: Period 2: Stool Frequency Score of 0

End point title	Period 2: Stool Frequency Score of 0

End point description:

End point type	Secondary

End point timeframe:
Week 16

End point values	TP05			
Subject group type	Reporting group			
Number of subjects analysed	243			
Units: Number of Subjects	64			

Statistical analyses

No statistical analyses for this end point

Secondary: Period 2: Urgency

End point title	Period 2: Urgency

End point description:

End point type	Secondary

End point timeframe:
Week 16

End point values	TP05			
Subject group type	Reporting group			
Number of subjects analysed	243			
Units: Number of Subjects	109			

Statistical analyses

No statistical analyses for this end point

Secondary: Period 2: UC-Related Complications

End point title	Period 2: UC-Related Complications

End point description:

End point type	Secondary

End point timeframe:
Week 16

End point values	TP05			
Subject group type	Reporting group			
Number of subjects analysed	243			
Units: Number of Subjects	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Period 3: Clinical and Endoscopic Remission

End point title	Period 3: Clinical and Endoscopic Remission

End point description:

End point type	Secondary

End point timeframe:

Week 38

End point values	TP05 1.6g/day	TP05 3.2g/day	TP05 4.8g/day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	202	274	199	
Units: Number of Subjects	133	108	59	

Statistical analyses

No statistical analyses for this end point

Secondary: Period 3: Clinical Response

End point title	Period 3: Clinical Response

End point description:

End point type	Secondary

End point timeframe:

Week 38

End point values	TP05 1.6g/day	TP05 3.2g/day	TP05 4.8g/day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	202	274	199	
Units: Number of Subjects	190	230	156	

Statistical analyses

No statistical analyses for this end point

Secondary: Period 3: Clinical and Endoscopic Response

End point title	Period 3: Clinical and Endoscopic Response

End point description:

End point type	Secondary

End point timeframe:

Week 38

End point values	TP05 1.6g/day	TP05 3.2g/day	TP05 4.8g/day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	202	274	199	
Units: Number of Subjects	181	214	138	

Statistical analyses

No statistical analyses for this end point

Secondary: Period 3: Endoscopic Remission

End point title	Period 3: Endoscopic Remission

End point description:

End point type	Secondary

End point timeframe:

Week 38

End point values	TP05 1.6g/day	TP05 3.2g/day	TP05 4.8g/day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	202	274	199	
Units: Number of Subjects	76	64	27	

Statistical analyses

No statistical analyses for this end point

Secondary: Period 3: Endoscopic Response

End point title	Period 3: Endoscopic Response

End point description:

End point type	Secondary

End point timeframe:

Week 38

End point values	TP05 1.6g/day	TP05 3.2g/day	TP05 4.8g/day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	202	274	199	
Units: Number of Subjects	149	161	106	

Statistical analyses

No statistical analyses for this end point

Secondary: Period 3: Rectal Bleeding Sub-Score of 0

End point title	Period 3: Rectal Bleeding Sub-Score of 0

End point description:

End point type	Secondary

End point timeframe:

Week 38

End point values	TP05 1.6g/day	TP05 3.2g/day	TP05 4.8g/day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	202	274	199	
Units: Number of Subjects	178	209	149	

Statistical analyses

No statistical analyses for this end point

Secondary: Period 3: Stool Frequency Score of 0

End point title	Period 3: Stool Frequency Score of 0

End point description:

End point type	Secondary

End point timeframe:

Week 38

End point values	TP05 1.6g/day	TP05 3.2g/day	TP05 4.8g/day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	202	274	199	
Units: Number of Subjects	148	101	66	

Statistical analyses

No statistical analyses for this end point

Secondary: Period 3: Urgency

End point title	Period 3: Urgency

End point description:

End point type	Secondary

End point timeframe:

Week 38

End point values	TP05 1.6g/day	TP05 3.2g/day	TP05 4.8g/day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	202	274	199	
Units: Number of Subjects	41	101	90	

Statistical analyses

No statistical analyses for this end point

Secondary: Period 3: UC-Related Complications

End point title	Period 3: UC-Related Complications

End point description:

End point type	Secondary

End point timeframe:

Week 38

End point values	TP05 1.6g/day	TP05 3.2g/day	TP05 4.8g/day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	202	274	199	
Units: Number of Subjects	3	2	1	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: July 2013 to May 2016	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.1
Reporting groups	
Reporting group title	TP05/TP05
Reporting group description: Subjects that were in the TP05 arm in the double-blind induction phase and received TP05 in the open-label phase	
Reporting group title	TP05/Asacol
Reporting group description: Subject in the Asacol arm in the double-blind induction phase and on TP05 in the open-label-phase	

Serious adverse events	TP05/TP05	TP05/Asacol	
Total subjects affected by serious adverse events			
subjects affected / exposed	24 / 409 (5.87%)	18 / 408 (4.41%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Cryoglobulinaemia vasculitis			
subjects affected / exposed	1 / 409 (0.24%)	0 / 408 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Fading fetus			
subjects affected / exposed	1 / 409 (0.24%)	0 / 408 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Nasal septum deformation			
subjects affected / exposed	0 / 409 (0.00%)	1 / 408 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pulmonary embolism			
subjects affected / exposed	0 / 409 (0.00%)	1 / 408 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 409 (0.00%)	2 / 408 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ligament rupture			
subjects affected / exposed	1 / 409 (0.24%)	0 / 408 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fruacture			
subjects affected / exposed	1 / 409 (0.24%)	0 / 408 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Artrial fibrilation			
subjects affected / exposed	1 / 409 (0.24%)	0 / 408 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive heart disease			
subjects affected / exposed	1 / 409 (0.24%)	0 / 408 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Unstable agina			
subjects affected / exposed	1 / 409 (0.24%)	0 / 408 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral haematoma			

subjects affected / exposed	0 / 409 (0.00%)	1 / 408 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarctrion			
subjects affected / exposed	0 / 409 (0.00%)	1 / 408 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 409 (0.24%)	0 / 408 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 409 (0.49%)	2 / 408 (0.49%)	
occurrences causally related to treatment / all	1 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Chronic pancreatitis			
subjects affected / exposed	1 / 409 (0.24%)	0 / 408 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deterioration ulcerative colitis			
subjects affected / exposed	9 / 409 (2.20%)	6 / 408 (1.47%)	
occurrences causally related to treatment / all	3 / 10	1 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctitis ulcerative			
subjects affected / exposed	1 / 409 (0.24%)	0 / 408 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute haemorrhagic cystitis			
subjects affected / exposed	0 / 409 (0.00%)	1 / 408 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Musculoskeletal and connective tissue disorders			
Herniated disk			
subjects affected / exposed	0 / 409 (0.00%)	1 / 408 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Chronic tonsillitis			
subjects affected / exposed	1 / 409 (0.24%)	0 / 408 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium dificile			
subjects affected / exposed	1 / 409 (0.24%)	0 / 408 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flue			
subjects affected / exposed	1 / 409 (0.24%)	0 / 408 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perichonditis			
subjects affected / exposed	0 / 409 (0.00%)	1 / 408 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 409 (0.24%)	1 / 408 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetes melitus			
subjects affected / exposed	0 / 409 (0.00%)	1 / 408 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	TP05/TP05	TP05/Asacol	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	131 / 409 (32.03%)	108 / 408 (26.47%)	
Gastrointestinal disorders			
Ulcerative colitis deterioration			
subjects affected / exposed	58 / 409 (14.18%)	75 / 408 (18.38%)	
occurrences (all)	58	75	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/28568974