Clinical trial results:
A Phase 2a, Randomised, Double-Blind, Placebo-Controlled Study to Evaluate the Safety/Tolerability and Efficacy of TOP1288 200 mg Rectal Solution Once Daily for 4 Weeks in Symptomatic Ulcerative Colitis Patients with Moderate to Severe Disease Activity

Summary

EudraCT number	2016-000390-20
Trial protocol	GB HU LV PL LT BG CZ
Global end of trial date	31 October 2017

Results information

Result version number	v1 (current)
This version publication date	10 August 2018
First version publication date	10 August 2018

Trial information

Trial identification

Sponsor protocol code	TOP1288-TV-02

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02888379
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Topivert Pharma Limited
Sponsor organisation address	52 Princes Gate, London, United Kingdom, SW7 2PG
Public contact	Head of Clinical Development , TOPIVERT Pharma Limited, +44 203763 9469, Mike.Taylor@topivert.com
Scientific contact	Head of Clinical Development , TOPIVERT Pharma Limited, +44 203763 9469, Mike.Taylor@topivert.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	31 October 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 October 2017
Global end of trial reached?	Yes
Global end of trial date	31 October 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to assess the effect of TOP1288 200 mg Rectal Solution on endoscopic remission, as indicated by the Mayo Clinic modified endoscopic subscore, after 4 consecutive weeks of once daily bedtime treatment

Protection of trial subjects:

Safety assessments were performed during the screening period (after informed consent was obtained) and the double-blind treatment period (at Day 1 [prior to and following dosing], Day 7 [±2 days], and Week 4 [±2 days]). Following Week 4, there was a 1-week follow-up period for collection of AE information, including outcome of previously reported unresolved AEs.
The safety of the IMP was assessed via collection of AEs (including any clinically significant untoward histological findings), vital signs measurements, and clinical laboratory test results (hematology, clinical chemistry, and urinalysis). The investigator was to elicit information regarding the occurrence of AEs through open-ended questioning of the subject, a physical examination, and by review of laboratory test results. Any clinically significant untoward histological finding from a colon biopsy (compared to the baseline findings) was to be recorded as an AE. Progression of disease was recorded as an AE. Significant medication errors/misuse was captured as an AE. Each reported AE was evaluated for seriousness, severity, causal relationship to the IMP, duration, action taken, and outcome, all of which were recorded in the eCRF.

Background therapy:

The majority of subjects (and all subjects in the Czech Republic) received standard of care background treatment with a stable dose of oral 5-ASA (at doses ≤4.8 g/day). Oral corticosteroids were also permitted (prednisolone, at doses ≤30 mg/day or budesonide ≤9 mg/day).

Evidence for comparator: -

Actual start date of recruitment	08 September 2016
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	Poland: 14
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	Czech Republic: 4
Country: Number of subjects enrolled	Hungary: 8
Country: Number of subjects enrolled	Latvia: 12
Country: Number of subjects enrolled	Lithuania: 4
Country: Number of subjects enrolled	Ukraine: 32
Worldwide total number of subjects	77
EEA total number of subjects	45

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)	71
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study Period was 08 September 2016 (first subject screened) – 28 June 2017 (last subject completed). A total of 31 sites in 7 countries (Czech Republic, Hungary, Latvia, Lithuania, Poland, Ukraine and United Kingdom) screened at least 1 subject in the study.

Pre-assignment

Screening details:

A total of 60 to 80 subjects were planned to be enrolled/randomized to TOP1288 200 mg Rectal Solution or matching Placebo Rectal Solution in a 2:1 ratio: 138 subjects were screened, and 77 subjects were randomized.

Period 1

Period 1 title	Intent-to-treat (ITT)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

The bottles containing TOP1288 200 mg Rectal Solution and matching Placebo Rectal Solution were yellow and identical in appearance, with the IMP masked. Both treatments were identical with respect to packaging, volume administered, viscosity, and the applicator used. The process for breaking the blind was handled through the IWRS. Investigators were not to break the blind unless there was a subject safety issue that required immediate unblinding for proper management of the subject.

Arms

Are arms mutually exclusive?	Yes
Arm title	ITT Experimental

Arm description:

TOP1288 200 mg Rectal Solution Once Daily for 4 Weeks

Arm type	Experimental
Investigational medicinal product name	TOP1288
Investigational medicinal product code	TOP1288
Other name	
Pharmaceutical forms	Rectal solution
Routes of administration	Rectal use

Dosage and administration details:

A dose of 200 mg TOP1288 was given once daily in 100ml of the Rectal Solution.

Arm title	ITT Placebo

Arm description:

Placebo Rectal Solution Once Daily for 4 Weeks

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	Placebo
Other name	
Pharmaceutical forms	Rectal solution
Routes of administration	Rectal use

Dosage and administration details:

A 100 ml dose of the rectal solution was given once daily.

Number of subjects in period 1	ITT Experimental	ITT Placebo
Started	51	26
Completed	45	21
Not completed	6	5
Consent withdrawn by subject	3	-
Adverse event, non-fatal	3	2
Lack of efficacy	-	3

Period 2

Period 2 title	modified intent-to-treat (mITT)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

The bottles containing TOP1288 200 mg Rectal Solution and matching Placebo Rectal Solution were yellow and identical in appearance, with the IMP masked. Both treatments were identical with respect to packaging, volume administered, viscosity, and the applicator used. The process for breaking the blind was handled through the IWRS. Investigators were not to break the blind unless there was a subject safety issue that required immediate unblinding for proper management of the subject.

Arms

Are arms mutually exclusive?	Yes
Arm title	mITT Experimental

Arm description:

TOP1288 200 mg Rectal Solution Once Daily for 4 Weeks

Arm type	Experimental
Investigational medicinal product name	TOP1288
Investigational medicinal product code	TOP1288
Other name	
Pharmaceutical forms	Rectal solution
Routes of administration	Rectal use

Dosage and administration details:

A dose of 200 mg TOP1288 was given once daily in 100ml of the Rectal Solution.

Arm title	mITT Placebo

Arm description:

Placebo Rectal Solution Once Daily for 4 Weeks

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	Placebo
Other name	
Pharmaceutical forms	Rectal solution
Routes of administration	Rectal use

Dosage and administration details:

A 100 ml dose of the rectal solution was given once daily.

Number of subjects in period 2	mITT Experimental	mITT Placebo
Started	45	21
Completed	41	20
Not completed	4	1
No Week 4 Endoscopy	4	1

Period 3

Period 3 title	Per Protocol (PP)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

The bottles containing TOP1288 200 mg Rectal Solution and matching Placebo Rectal Solution were yellow and identical in appearance, with the IMP masked. Both treatments were identical with respect to packaging, volume administered, viscosity, and the applicator used. The process for breaking the blind was handled through the IWRS. Investigators were not to break the blind unless there was a subject safety issue that required immediate unblinding for proper management of the subject.

Arms

Are arms mutually exclusive?	Yes
Arm title	PP Experimental

Arm description:

TOP1288 200 mg Rectal Solution Once Daily for 4 Weeks

Arm type	Experimental
Investigational medicinal product name	TOP1288
Investigational medicinal product code	TOP1288
Other name	
Pharmaceutical forms	Rectal solution
Routes of administration	Rectal use

Dosage and administration details:

A dose of 200 mg TOP1288 was given once daily in 100ml of the Rectal Solution.

Arm title	PP Placebo

Arm description:

Placebo Rectal Solution Once Daily for 4 Weeks

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	Placebo
Other name	
Pharmaceutical forms	Rectal solution
Routes of administration	Rectal use

Dosage and administration details:

A 100 ml dose of the rectal solution was given once daily.

Number of subjects in period 3	PP Experimental	PP Placebo
Started	41	20
Completed	37	17
Not completed	4	3
Protocol deviation	4	3

Baseline characteristics

Reporting groups	
Reporting group title	ITT Experimental
Reporting group description: TOP1288 200 mg Rectal Solution Once Daily for 4 Weeks	
Reporting group title	ITT Placebo
Reporting group description: Placebo Rectal Solution Once Daily for 4 Weeks	

Reporting group values	ITT Experimental	ITT Placebo	Total
Number of subjects	51	26	77
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)	48	23	71
From 65-84 years	3	3	6
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	42.6	42.3	
standard deviation	± 13.12	± 14.16	-
Gender categorical Units: Subjects			
Female	22	12	34
Male	29	14	43
Concomitant Steroid use			
'Concomitant' medications are medications which start at any time prior to randomization, and ongoing at the time of randomization, or which start at any time after randomization up until the subject's post treatment follow up visit.			
Units: Subjects			
Yes	13	6	19
No	38	20	58
Concomitant immunomodulator use			
'Concomitant' medications are medications which start at any time prior to randomization, and ongoing at the time of randomization, or which start at any time after randomization up until the subject's post treatment follow up visit.			
Units: Subjects			
Yes	6	3	9
No	45	23	68
Concomitant 5-ASA use			
'Concomitant' medications are medications which start at any time prior to randomization, and ongoing at the time of randomization, or which start at any time after randomization up until the subject's post treatment follow up visit.			

Units: Subjects			
Yes	51	24	75
No	0	2	2
Prior biologic use			
'Prior' medications are medications which started and stopped prior to randomization.			
Units: Subjects			
Yes	1	1	2
No	50	25	75
Smoking Status Units: Subjects			
Current	3	0	3
Former	7	4	11
Never	41	22	63
MES			
Mayo Clinic modified endoscopic subscore			
Units: arbitrary			
arithmetic mean	2.3	2.4	
standard deviation	± 0.48	± 0.50	-
Partial Mayo Clinic Score			
Partial Mayo Clinic Score is the sum of endoscopic, rectal bleeding, and stool frequency subscores			
Units: arbitrary			
arithmetic mean	6.1	6.3	
standard deviation	± 1.17	± 1.28	-
Duration of UC Units: Years			
arithmetic mean	7.3	5.3	
standard deviation	± 6.80	± 4.55	-

End points

End points reporting groups	
Reporting group title	ITT Experimental
Reporting group description: TOP1288 200 mg Rectal Solution Once Daily for 4 Weeks	
Reporting group title	ITT Placebo
Reporting group description: Placebo Rectal Solution Once Daily for 4 Weeks	
Reporting group title	mITT Experimental
Reporting group description: TOP1288 200 mg Rectal Solution Once Daily for 4 Weeks	
Reporting group title	mITT Placebo
Reporting group description: Placebo Rectal Solution Once Daily for 4 Weeks	
Reporting group title	PP Experimental
Reporting group description: TOP1288 200 mg Rectal Solution Once Daily for 4 Weeks	
Reporting group title	PP Placebo
Reporting group description: Placebo Rectal Solution Once Daily for 4 Weeks	

Primary: Endoscopic remission	
End point title	Endoscopic remission
End point description: Proportion of Subjects Achieving Endoscopic Remission (MES of 0 or 1) at Week 4 (Day 29±2). Endoscopic remission is defined as a Mayo Clinic modified endoscopy subscore of 0 (indicating normal or inactive disease) or 1 (mild disease).	
End point type	Primary
End point timeframe: The primary efficacy endpoint is proportion of subjects achieving endoscopic remission at Visit 3 (Week 4 [Day 29±2])	

End point values	ITT Experimental	ITT Placebo	mITT Experimental	mITT Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	51	26	41	20
Units: Number of subjects achieving remission	14	13	14	13

End point values	PP Experimental	PP Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	17		
Units: Number of subjects achieving	14	11		

remission

Statistical analyses

Statistical analysis title	Percentage difference between TOP1288 and Placebo
Statistical analysis description:	
Difference in percentage responder rate between experimental (TOP1288) and placebo groups.	
Comparison groups	ITT Experimental v ITT Placebo
Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	equivalence[1]
P-value	= 0.986 [2]
Method	Fisher exact
Parameter estimate	Difference of means
Point estimate	-23
Confidence interval	
level	90 %
sides	2-sided
lower limit	-41.68
upper limit	-3.42

Notes:

[1] - Difference in percentage responder rate between experimental and placebo groups.

[2] - 1-sided p-value, testing TOP1288 remission proportion greater than placebo remission proportion, was
calculated from Fisher’s exact test

Statistical analysis title	Percentage difference between TOP1288 and placebo
Statistical analysis description:	
Difference in percentage responder rate between experimental (TOP1288) and placebo groups.	
Comparison groups	mITT Experimental v mITT Placebo
Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	equivalence[3]
P-value	= 0.995 [4]
Method	Fisher exact
Parameter estimate	Difference of means
Point estimate	-31
Confidence interval	
level	90 %
sides	2-sided
lower limit	-52.21
upper limit	-9.49

Notes:

[3] - Difference in percentage responder rate between experimental and placebo groups.

[4] - 1-sided p-value, testing TOP1288 remission proportion greater than placebo remission proportion, was
calculated from Fisher’s exact test

Statistical analysis title	Percentage difference between TOP1288 and placebo

Statistical analysis description:	
Difference in percentage responder rate between experimental (TOP1288) and placebo groups.	
Comparison groups	PP Experimental v PP Placebo
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	equivalence[5]
P-value	= 0.984 [6]
Method	Fisher exact
Parameter estimate	Difference of means
Point estimate	-27
Confidence interval	
level	90 %
sides	2-sided
lower limit	-50.01
upper limit	-3.73

Notes:

[5] - Difference in percentage responder rate between experimental and placebo groups.

[6] - 1-sided p-value, testing TOP1288 remission proportion greater than placebo remission proportion, was
calculated from Fisher's exact test

Secondary: Change from baseline to Week 4 in UCEIS Score

End point title	Change from baseline to Week 4 in UCEIS Score

End point description:

Following sigmoidoscopy, the central reader also graded the endoscopic findings using the Ulcerative Colitis Endoscopic Index of Severity (UCEIS) scale, which provided a composite score for vascular pattern, bleeding, and erosions and ulcers for the most severe lesions observed during endoscopic examination. The assessment was completed at screening visit (baseline) and visit 3 (Week 4).
For quantitative measurements, change from baseline to week 4 was calculated as [Value at Week 4 Visit – Baseline Value].

End point type	Secondary

End point timeframe:

The secondary efficacy objectives assessed the effect of 4 weeks of treatment with TOP1288 200 mg Rectal Solution compared with Placebo Rectal Solution on the change from baseline to Week 4

End point values	ITT Experimental	ITT Placebo	mITT Experimental	mITT Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	51	26	41	20
Units: UCEIS Score				
arithmetic mean (standard deviation)	-0.67 (± 1.681)	-1.35 (± 1.810)	-0.83 (± 1.843)	-1.75 (± 1.888)

End point values	PP Experimental	PP Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	17		
Units: UCEIS Score				
arithmetic mean (standard deviation)	-1.00 (±	-1.82 (±		

1.841)	2.007)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to Week 4 in Partial Mayo Clinic Score

End point title	Change from baseline to Week 4 in Partial Mayo Clinic Score

End point description:

The Partial Mayo Clinic Score is the sum of the endoscopic, rectal bleeding, and stool frequency subscores of the Mayo Clinic Score scale. The Physician's Global Assessment subscale was not included in the Partial Mayo Clinic Score. Scoring ranged between 0 and 3 for each of the parameters. The assessment was completed at screening visit (baseline) and visit 3 (Week 4). For quantitative measurements, change from baseline to week 4 was calculated as [Value at Week 4 visit – Baseline Value].

End point type	Secondary

End point timeframe:

The secondary efficacy objectives assessed the effect of 4 weeks of treatment with TOP1288 200 mg Rectal Solution compared with Placebo Rectal Solution on the change from baseline to Week 4

End point values	ITT Experimental	ITT Placebo	mITT Experimental	mITT Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	51	26	41	20
Units: Change Partial Mayo Clinic Score				
arithmetic mean (standard deviation)	-1.78 (± 2.194)	-2.54 (± 2.284)	-2.22 (± 2.242)	-3.30 (± 2.055)

End point values	PP Experimental	PP Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	17		
Units: Change Partial Mayo Clinic Score				
arithmetic mean (standard deviation)	-2.43 (± 2.167)	-3.35 (± 2.149)		

Statistical analyses

No statistical analyses for this end point

Secondary: Endoscopic healing

End point title	Endoscopic healing

End point description:

Endoscopic healing is defined as Mayo Clinic modified endoscopic (MES) subscore of 0. Mayo Clinic modified endoscopic subscore were assessed at visit 3 (Week 4).

End point type	Secondary

End point timeframe:

Number of subjects achieving endoscopic remission at Visit 3 (Week 4 [Day 29±2])

End point values	ITT Experimental	ITT Placebo	mITT Experimental	mITT Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	51	26	41	20
Units: Number of subjects	7	6	7	6

End point values	PP Experimental	PP Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	17		
Units: Number of subjects	7	6		

Statistical analyses

Statistical analysis title	Percentage difference between TOP1288 and placebo
Statistical analysis description:	
Difference in percentage responder rate between experimental (TOP1288) and placebo groups.	
Comparison groups	ITT Experimental v ITT Placebo
Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.344
Method	Fisher exact
Parameter estimate	Mean difference (final values)
Point estimate	-9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-28.06
upper limit	9.36

Statistical analysis title	Percentage difference between TOP1288 and placebo
Statistical analysis description:	
Difference in percentage responder rate between experimental (TOP1288) and placebo groups.	
Comparison groups	mITT Experimental v mITT Placebo

Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.321
Method	Fisher exact
Parameter estimate	Mean difference (final values)
Point estimate	-13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-36.03
upper limit	10.18

Statistical analysis title	Percentage difference between TOP1288 and placebo
Statistical analysis description:	
Difference in percentage responder rate between experimental (TOP1288) and placebo groups.	
Comparison groups	PP Experimental v PP Placebo
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.303
Method	Fisher exact
Parameter estimate	Mean difference (final values)
Point estimate	-16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-42.31
upper limit	9.56

Secondary: Rectal Bleeding

End point title	Rectal Bleeding

End point description:

Proportion of subject with an improvement (reduction) in Mayo Clinic rectal bleeding, change from baseline to visit 3 (Week 4) in mayo clinic rectal bleeding subscore was calculated. Subjects observed with ≥1 improvement (reduction) in change from baseline to visit 3 (Week 4) in mayo clinical rectal bleeding was considered as a responder (i.e. proportion of subjects with an improvement in Mayo Clinic rectal bleeding). Screening visit was considered as baseline for this endpoint.

End point type	Secondary

End point timeframe:

Number of subjects achieving improvement in Mayo Clinic Rectal Bleeding Subscore of ≥1 at Visit 3 (Week 4 [Day 29±2])

End point values	ITT Experimental	ITT Placebo	mITT Experimental	mITT Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	51	26	41	20
Units: Number of subjects	31	15	28	15

End point values	PP Experimental	PP Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	17		
Units: Number of subjects	26	13		

Statistical analyses

Statistical analysis title	Percentage difference between TOP1288 and placebo
Statistical analysis description: Difference in percentage responder rate between experimental (TOP1288) and placebo groups.	
Comparison groups	ITT Experimental v ITT Placebo
Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.794
Method	Chi-squared
Parameter estimate	Mean difference (final values)
Point estimate	3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-20.1
upper limit	26.29

Statistical analysis title	Percentage difference between TOP1288 and placebo
Statistical analysis description: Difference in percentage responder rate between experimental (TOP1288) and placebo groups.	
Comparison groups	mITT Experimental v mITT Placebo
Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.59
Method	Chi-squared
Parameter estimate	Mean difference (final values)
Point estimate	-7

Confidence interval	
level	95 %
sides	2-sided
lower limit	-30.39
upper limit	16.97

Statistical analysis title	Percentage difference between TOP1288 and placebo
Statistical analysis description:	
Difference in percentage responder rate between experimental (TOP1288) and placebo groups.	
Comparison groups	PP Experimental v PP Placebo
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.751
Method	Chi-squared
Parameter estimate	Mean difference (final values)
Point estimate	-6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-31.12
upper limit	18.72

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Safety assessments were performed during the screening period and the double-blind treatment period. Following Week 4, there was a 1-week follow-up period for collection of AE information, including outcome of previously reported unresolved AEs.

Adverse event reporting additional description:

Each reported AE was evaluated for seriousness, severity, causal relationship to the IMP, duration, action taken, and outcome, all of which were recorded in the eCRF.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18

Reporting groups

Reporting group title	Safety Experimental

Reporting group description:

TOP1288 200 mg Rectal Solution Once Daily for 4 Weeks

Reporting group title	Safety Placebo

Reporting group description:

Placebo Rectal Solution Once Daily for 4 Weeks

Serious adverse events	Safety Experimental	Safety Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 51 (0.00%)	0 / 26 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Safety Experimental	Safety Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	28 / 51 (54.90%)	12 / 26 (46.15%)	
Investigations			
Haemoglobin decreased			
subjects affected / exposed	2 / 51 (3.92%)	1 / 26 (3.85%)	
occurrences (all)	2	1	
Alanine aminotransferase increased			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	
occurrences (all)	1	0	

Aspartate aminotransferase increased			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Faecal calprotectin increased			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Lymphocyte count decreased			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Lymphocyte count increased			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Monocyte count decreased			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Post procedural haemorrhage			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Procedural pain			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Thermal burn			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 51 (3.92%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
Burning sensation			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Dysgeusia			

subjects affected / exposed	0 / 51 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 51 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Frequent bowel movements			
subjects affected / exposed	7 / 51 (13.73%)	5 / 26 (19.23%)	
occurrences (all)	7	6	
Colitis ulcerative			
subjects affected / exposed	6 / 51 (11.76%)	3 / 26 (11.54%)	
occurrences (all)	6	3	
Abdominal pain			
subjects affected / exposed	3 / 51 (5.88%)	0 / 26 (0.00%)	
occurrences (all)	3	0	
Nausea			
subjects affected / exposed	2 / 51 (3.92%)	1 / 26 (3.85%)	
occurrences (all)	2	1	
Colitis			
subjects affected / exposed	2 / 51 (3.92%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
Flatulence			
subjects affected / exposed	2 / 51 (3.92%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
Gastrointestinal sounds abnormal			
subjects affected / exposed	0 / 51 (0.00%)	2 / 26 (7.69%)	
occurrences (all)	0	2	
Abdominal discomfort			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Abdominal distension			

subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Abdominal pain upper			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Diarrhoea			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Dyspepsia			
subjects affected / exposed	0 / 51 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Gastrointestinal motility disorder			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Mouth ulceration			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Nervousness			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Lower respiratory tract infection			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Nasopharyngitis			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Respiratory tract infection			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			

Hypophosphataemia			
subjects affected / exposed	2 / 51 (3.92%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
Hyperglycaemia			
subjects affected / exposed	0 / 51 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Hyperkalaemia			
subjects affected / exposed	0 / 51 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Hypernatraemia			
subjects affected / exposed	1 / 51 (1.96%)	0 / 26 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 November 2016	- New QuintilesIMS Medical Monitor was assigned to the study, and a second study drug manufacturer and supplier is being used for the study. - Number of subjects to be randomised was increased from 60 to a range of approximately 60 to 80. - Following Sponsor approval, the intensive PK blood sampling at Visit 1 may be an optional assessment if the Investigator considers it to be a significant barrier to an individual subject's participation in the study. - Requirement that all patients in the Czech Republic must be receiving a stable oral dose of 5-aminosalicylic acid therapy (up to 4.8 g/day) for at least 2 weeks before Screening, and they must be willing to continue on the regimen for the duration of the study. - Subjects will be advised to remain supine for approximately (not "at least") 1 hour after receiving their first dose of study medication on Day 1. - Patients who test positive for Blastocystis hominis may be eligible for the study based on the judgement of the Investigator. - Haemoglobin range lowered from <10.5 to <8.5 g/dL. Absolute neutrophil count lowered from <1.5 x 109/L to <1.0 x 109/L. - The phrase "or 5 half-lives, whichever is longer" was added in regard to prohibition of the use of the biologic agents, including vedolizumab, for 3 months prior to Screening. - Rescreening allowed once in subjects with a single isolated test result outside the specific range considered clinically significant. - The instructions to subjects to limit their mobility for at least 1 hour following administration and to remain supine, if possible, was removed. - Week 1 assessment of TOP1288 plasma concentrations was added. - Follow-up on unresolved AEs will continue until resolution or until the end of the study (last patient last visit), whichever occurs first.
27 March 2017	- Correction of the 24-hour medical contact to be consistent with all other clinical trial documentation. - Data obtained from subjects enrolled in this study was classified and analysed using four analysis populations (ITT, mITT, PP and Safety). The primary analysis will be based on the Intent-to-Treat (ITT) population. The analysis will be repeated using the modified Intent-to-Treat (mITT) and Per Protocol (PP) populations. Descriptive statistics will be used to summarise all secondary efficacy endpoints, including individual item scores by visit and treatment group, based on the ITT, mITT and PP populations. Clarification that subject demographic characteristics will be summarised for all of the analysis populations. - Clarification that 'no imputation' refers to the primary efficacy endpoint and that other imputation techniques for missing efficacy data will be described in the Statistical Analysis Plan as several key secondary endpoints are not responder-based.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The high response rate seen for all endpoints in the placebo arm confounds assessment for efficacy and hinders the drawing of any firm conclusions. Statistical analysis was conducted for all endpoints, where the system allows input, data is included.

Notes: