Clinical trial results:
Randomized, multicenter, placebo-controlled, double blind study to assess the efficacy and tolerability of 2% diltiazem hydrochloride in the treatment of chronic anal fissure and a 24 week follow-up period

Summary

EudraCT number	2015-003627-54
Trial protocol	CZ ES
Global end of trial date	21 July 2018

Results information

Result version number	v1 (current)
This version publication date	22 August 2019
First version publication date	22 August 2019

Trial information

Trial identification

Sponsor protocol code	150601

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Tecnimede, Sociedade Técnico-Medicinal, S.A.
Sponsor organisation address	Zona Industrial da Abrunheira, R. da Tapada Grande, nº 2, Sintra, Portugal, 2710-089
Public contact	Medical Department, Tecnimede, Sociedade Técnico-Medicinal, S.A., +351 210 414 100, dmed.ct@tecnimede.pt
Scientific contact	Medical Department, Tecnimede, Sociedade Técnico-Medicinal, S.A., +351 210 414 100, dmed.ct@tecnimede.pt

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	21 July 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	21 July 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this clinical trial was to assess the relative efficacy (cure of chronic anal fissure) of the DTZ 2% cutaneous paste compared to placebo, in the treatment of chronic anal fissure (CAF), for up to 12 weeks (cure defined as complete closing evaluated through physical examination and re-epithelialization of the anal fissure observed in the anoscopy).

Protection of trial subjects:

Paracetamol (acetaminophen) and Clonixin were allowed as rescue medication for the shortest possible time. In case the investigator considered that the patient needed other types of rescue medication for the anal fissure, the patient would be withdrawn from the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 February 2017
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	Portugal: 12
Country: Number of subjects enrolled	Spain: 70
Country: Number of subjects enrolled	Czech Republic: 139
Worldwide total number of subjects	221
EEA total number of subjects	221

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)	195

From 65 to 84 years	24
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

First patient was enrolled on 17-Feb-2017 (FPFV) and last patient on 08-Nov-2017 (LPFV). The total number of patients randomised was 222 patients however 1 patient was randomised by error since he/she was still on a wash-out period and was therefore not eligible to be included and to receive study IMP. No data was collected for this patient.

Pre-assignment

Screening details:

Patients aged >=18 years who were diagnosed with idiopathic CAF that was unresponsive to previous therapy,who were able to comply with the study protocol as per investigator criteria, who did not meet any exclusion criterion and who or his/her representative/witness(as per applicable law) signed and dated the study informed consent were included.

Period 1

Period 1 title	Treatment period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Group I

Arm description:

2% DTZ cutaneous paste

Arm type	Experimental
Investigational medicinal product name	Diltiazem hydrochloride
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Cutaneous paste
Routes of administration	Cutaneous use

Dosage and administration details:

The diltiazem hydrochloride paste was presented as a 30 g tube containing the active substance at a 2% concentration (2% DTZ), for cutaneous use.
The 2% DTZ paste was administered to deliver a total daily dose of 16 mg (approximately 8 mg b.i.d.) divided into two administrations (separated by approximately 12 hours).

Arm title	Group II

Arm description:

2% DTZ cutaneous paste placebo

Arm type	Placebo
Investigational medicinal product name	Diltiazem hydrochloride placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Cutaneous paste
Routes of administration	Cutaneous use

Dosage and administration details:

The diltiazem hydrochloride placebo paste was presented as a 30 g tube for cutaneous use.
The 2% DTZ placebo paste was administered to deliver a total daily dose of 16 mg (approximately 8 mg b.i.d.) divided into two administrations (separated by approximately 12 hours).

Number of subjects in period 1	Group I	Group II
Started	106	115
Completed	81	92
Not completed	25	23
Consent withdrawn by subject	6	7
Adverse event, non-fatal	5	5
Changes in concomitant medication	3	1
Lost to follow-up	5	1
Protocol deviation	6	9

Period 2	
Period 2 title	Follow-up period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms	
Are arms mutually exclusive?	Yes
Arm title	Group I

Arm description:

2% DTZ cutaneous paste

Arm type	Experimental
Investigational medicinal product name	Diltiazem hydrochloride
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Cutaneous paste
Routes of administration	Cutaneous use

Dosage and administration details:

The diltiazem hydrochloride paste was presented as a 30 g tube containing the active substance at a 2% concentration (2% DTZ), for cutaneous use.
The 2% DTZ paste was administered to deliver a total daily dose of 16 mg (approximately 8 mg b.i.d.) divided into two administrations (separated by approximately 12 hours).

Arm title	Group II

Arm description:

2% DTZ cutaneous paste placebo

Arm type	Placebo
Investigational medicinal product name	Diltiazem hydrochloride placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Cutaneous paste
Routes of administration	Cutaneous use

Dosage and administration details:

The diltiazem hydrochloride placebo paste was presented as a 30 g tube for cutaneous use.
The 2% DTZ placebo paste was administered to deliver a total daily dose of 16 mg (approximately 8 mg

b.i.d.) divided into two administrations (separated by approximately 12 hours).

Number of subjects in period 2[1]	Group I	Group II
Started	56	61
Completed	53	57
Not completed	3	4
Lost to follow-up	1	3
Protocol deviation	2	1

Notes:

[1] - 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: Only if a patient reached chronic anal fissure (CAF) cure within the treatment period, the patient was followed
for 24 weeks in order to evaluate CAF relapse. Patients who did not achieve cure during the 12 weeks of treatment period were discontinued from the study. In summary, the subsequent period (Period 2) was carried out exclusively in patients that reached clinical cure.

Baseline characteristics

Reporting groups	
Reporting group title	Group I
Reporting group description:	
2% DTZ cutaneous paste	
Reporting group title	Group II
Reporting group description:	
2% DTZ cutaneous paste placebo	

Reporting group values	Group I	Group II	Total
Number of subjects	106	115	221
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)	90	105	195
From 65-84 years	14	10	24
85 years and over	2	0	2
Age continuous			
Units: years			
arithmetic mean	46.90	46.18	
standard deviation	± 14.82	± 12.52	-
Gender categorical			
Units: Subjects			
Female	44	51	95
Male	62	64	126
Smoking habits			
Units: Subjects			
Yes	8	17	25
No	88	88	176
Ex-smoker	9	9	18
NP	1	1	2
Drinking habits			
Units: Subjects			
Yes	22	27	49
No	83	87	170
NP	1	1	2
Relevant medical history			
Units: Subjects			
Yes	21	14	35
No	85	101	186
Post-menopausal (only females)			

The post-menopausal variable/characteristic is only applicable to females.			
Units: Subjects			
Yes	17	23	40
No	27	28	55
NA	62	64	126
Sexual active (only females)			
The sexual active variable/characteristic is only applicable to females.			
Units: Subjects			
Yes	24	24	48
No	20	25	45
UNK	0	2	2
NA	62	64	126
Weight			
Units: Kg			
arithmetic mean	81.16	79.39	
standard deviation	± 14.36	± 14.86	-
Height			
Units: cm			
arithmetic mean	171.89	171.57	
standard deviation	± 8.21	± 8.92	-

End points

End points reporting groups

Reporting group title	Group I
Reporting group description: 2% DTZ cutaneous paste	
Reporting group title	Group II
Reporting group description: 2% DTZ cutaneous paste placebo	
Reporting group title	Group I
Reporting group description: 2% DTZ cutaneous paste	
Reporting group title	Group II
Reporting group description: 2% DTZ cutaneous paste placebo	

Primary: Chronic anal fissure cure within 12 weeks of treatment (Visit 4) (ITT population)

End point title	Chronic anal fissure cure within 12 weeks of treatment (Visit 4) (ITT population)
End point description:	
End point type	Primary
End point timeframe: Patients for which chronic anal fissure (CAF) cure was observed during the 12 week treatment period (cured on visit 2 or 3 or 4 - V2 or V3 or V4).	

End point values	Group I	Group II		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	103	113		
Units: subjects				
Yes	58	65		
No	45	48		

Statistical analyses

Statistical analysis title	Chronic Anal Fissure Cure
Comparison groups	Group I v Group II

Number of subjects included in analysis	216
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.483
Method	Fisher exact

Primary: Chronic anal fissure cure within 12 weeks of treatment (Visit 4) (PP population)

End point title	Chronic anal fissure cure within 12 weeks of treatment (Visit 4) (PP population)

End point description:

End point type	Primary

End point timeframe:

Patients for which chronic anal fissure (CAF) cure was observed during the 12 week treatment period (cured on visit 2 or 3 or 4 - V2 or V3 or V4).

End point values	Group I	Group II		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	91		
Units: subjects				
Yes	56	60		
No	26	31		

Statistical analyses

Statistical analysis title	Chronic Anal Fissure Cure (PP population)
Comparison groups	Group I v Group II
Number of subjects included in analysis	173
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.434
Method	Fisher exact

Secondary: Chronic anal fissure cure within 8 weeks of treatment (Visit 3) (ITT population)

End point title	Chronic anal fissure cure within 8 weeks of treatment (Visit 3) (ITT population)

End point description:

End point type	Secondary

End point timeframe:

Patients for which cure of the chronic anal fissure (CAF) was observed until the 8th week of treatment (cured on visit 2 or 3 - V2 or V3).

End point values	Group I	Group II		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	103	113		
Units: subjects				
Yes	17	21		
No	86	92		

Statistical analyses

Statistical analysis title	Chronic Anal Fissure Cure
Comparison groups	Group I v Group II
Number of subjects included in analysis	216
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.413
Method	Fisher exact

Secondary: Chronic anal fissure cure within 8 weeks of treatment (Visit 3) (PP population)

End point title	Chronic anal fissure cure within 8 weeks of treatment (Visit 3) (PP population)

End point description:

End point type	Secondary

End point timeframe:

Patients for which cure of the chronic anal fissure (CAF) was observed until the 8th week of treatment (cured on visit 2 or 3 - V2 or V3).

End point values	Group I	Group II		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	91		
Units: subjects				
Yes	16	18		
No	66	73		

Statistical analyses

Statistical analysis title	Chronic Anal Fissure Cure
Comparison groups	Group I v Group II
Number of subjects included in analysis	173
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.559
Method	Fisher exact

Secondary: Chronic anal fissure cure after 4 weeks of treatment (Visit 2) (ITT population)

End point title	Chronic anal fissure cure after 4 weeks of treatment (Visit 2) (ITT population)

End point description:

End point type	Secondary

End point timeframe:

Patients for which cure of the chronic anal fissure (CAF) was observed until the 4th week of treatment (cured on visit 2 - V2).

End point values	Group I	Group II		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	103	113		
Units: subjects				
Yes	6	6		
No	97	107		

Statistical analyses

Statistical analysis title	Chronic Anal Fissure Cure
Comparison groups	Group I v Group II
Number of subjects included in analysis	216
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.551
Method	Fisher exact

Secondary: Chronic anal fissure cure after 4 weeks of treatment (Visit 2) (PP population)

End point title	Chronic anal fissure cure after 4 weeks of treatment (Visit 2) (PP population)

End point description:

End point type	Secondary

End point timeframe:

Patients for which cure of the chronic anal fissure (CAF) was observed until the 4th week of treatment (cured on visit 2 - V2).

End point values	Group I	Group II		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	91		
Units: subjects				
Yes	6	4		
No	76	87		

Statistical analyses

Statistical analysis title	Chronic Anal Fissure Cure
Comparison groups	Group I v Group II
Number of subjects included in analysis	173
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.31
Method	Fisher exact

Secondary: Visual analogue scale for pain variation after 12 weeks of treatment (Visit 4) (ITT population)

End point title	Visual analogue scale for pain variation after 12 weeks of treatment (Visit 4) (ITT population)

End point description:

End point type	Secondary

End point timeframe:

Symptomatic improvement of pain triggered by defecation vs. baseline assessed as variation in millimetres, using a visual analogue scale (VAS) for pain applied on the 12th week of treatment (visit 4 – V4).

End point values	Group I	Group II		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	105		
Units: mm				
arithmetic mean (standard deviation)	43.79 (± 29.60)	44.08 (± 30.25)		

Statistical analyses

Statistical analysis title	Visual analogue scale for pain variation
Comparison groups	Group I v Group II
Number of subjects included in analysis	205
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.527
Method	t-test, 1-sided

Secondary: Visual analogue scale for pain variation after 12 weeks of treatment (Visit 4) (PP population)

End point title	Visual analogue scale for pain variation after 12 weeks of treatment (Visit 4) (PP population)

End point description:

End point type	Secondary

End point timeframe:

Symptomatic improvement of pain triggered by defecation vs. baseline assessed as variation in millimetres, using a visual analogue scale (VAS) for pain applied on the 12th week of treatment (visit 4 – V4).

End point values	Group I	Group II		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	90		
Units: mm				
arithmetic mean (standard deviation)	49.78 (± 26.46)	46.82 (± 28.43)		

Statistical analyses

Statistical analysis title	Visual analogue scale for pain variation
Comparison groups	Group I v Group II

Number of subjects included in analysis	172
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.241
Method	t-test, 1-sided

Secondary: Visual analogue scale for pain variation after 8 weeks of treatment (Visit 3) (ITT population)

End point title	Visual analogue scale for pain variation after 8 weeks of treatment (Visit 3) (ITT population)

End point description:

End point type	Secondary

End point timeframe:

Symptomatic improvement of pain triggered by defecation assessed as variation in millimetres, using a visual analogue scale (VAS) for pain applied on the 8th week of treatment (visit 3 – V3).

End point values	Group I	Group II		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	105		
Units: mm				
arithmetic mean (standard deviation)	38.52 (± 28.48)	38.29 (± 27.48)		

Statistical analyses

Statistical analysis title	Visual analogue scale for pain variation
Comparison groups	Group I v Group II
Number of subjects included in analysis	205
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.476
Method	t-test, 1-sided

Secondary: Visual analogue scale for pain variation after 8 weeks of treatment (Visit 3) (PP population)

End point title	Visual analogue scale for pain variation after 8 weeks of treatment (Visit 3) (PP population)

End point description:

End point type	Secondary

End point timeframe:

Symptomatic improvement of pain triggered by defecation assessed as variation in millimetres, using a visual analogue scale (VAS) for pain applied on the 8th week of treatment (visit 3 – V3).

End point values	Group I	Group II		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	90		
Units: mm				
arithmetic mean (standard deviation)	43.85 (± 26.62)	40.11 (± 25.61)		

Statistical analyses

Statistical analysis title	Visual analogue scale for pain variation
Comparison groups	Group I v Group II
Number of subjects included in analysis	172
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.174
Method	t-test, 1-sided

Secondary: Visual analogue scale for pain variation after 4 weeks of treatment (Visit 2) (ITT population)

End point title	Visual analogue scale for pain variation after 4 weeks of treatment (Visit 2) (ITT population)

End point description:

End point type	Secondary

End point timeframe:

Symptomatic improvement of pain triggered by defecation assessed as variation in millimetres, using a visual analogue scale (VAS) for pain applied on the 4th week of treatment (visit 2 – V2).

End point values	Group I	Group II		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	105		
Units: mm				
arithmetic mean (standard deviation)	27.81 (± 24.40)	25.35 (± 25.98)		

Statistical analyses

Statistical analysis title	Visual analogue scale for pain variation
Comparison groups	Group I v Group II
Number of subjects included in analysis	205
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.243
Method	t-test, 1-sided

Secondary: Visual analogue scale for pain variation after 4 weeks of treatment (Visit 2) (PP population)

End point title	Visual analogue scale for pain variation after 4 weeks of treatment (Visit 2) (PP population)

End point description:

End point type	Secondary

End point timeframe:

Symptomatic improvement of pain triggered by defecation assessed as variation in millimetres, using a visual analogue scale (VAS) for pain applied on the 4th week of treatment (visit 2 – V2).

End point values	Group I	Group II		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	90		
Units: mm				
arithmetic mean (standard deviation)	31.07 (± 23.84)	25.38 (± 25.56)		

Statistical analyses

Statistical analysis title	Visual analogue scale for pain variation
Comparison groups	Group I v Group II
Number of subjects included in analysis	172
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.067
Method	t-test, 1-sided

Secondary: Chronic anal fissure relapse during the 24-week follow-up period (ITT population)

End point title	Chronic anal fissure relapse during the 24-week follow-up period (ITT population)

End point description:

End point type	Secondary

End point timeframe:

Patients with fissure relapse during a 24-week follow-up period after treatment withdrawal (final visit - VF).

End point values	Group I	Group II		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	57		
Units: subjects				
Yes	7	6		
No	48	51		

Statistical analyses

Statistical analysis title	Chronic anal fissure relapse
Comparison groups	Group I v Group II
Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.472
Method	Fisher exact

Secondary: Chronic anal fissure relapse during the 24-week follow-up period (PP population)

End point title	Chronic anal fissure relapse during the 24-week follow-up period (PP population)

End point description:

End point type	Secondary

End point timeframe:

Patients with fissure relapse during a 24-week follow-up period after treatment withdrawal (final visit - VF).

End point values	Group I	Group II		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	55		
Units: subjects				
Yes	7	6		
No	46	49		

Statistical analyses

Statistical analysis title	Chronic anal fissure relapse
Comparison groups	Group I v Group II
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.471
Method	Fisher exact

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The collection of adverse events started at the day of the first administration (V1) of the Investigational Medicinal Product and finished when the clinical trial was concluded (including the follow-up monitoring visits).

Adverse event reporting additional description:

The adverse events information reported is only focused in the treatment period of the study since it is not possible to report the results from both phases separately due to platform restrictions. For any information about the follow-up analysis, the sponsor must be contacted.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	Group I

Reporting group description:

2% DTZ cutaneous paste

Reporting group title	Group II

Reporting group description:

2% DTZ cutaneous paste placebo

Serious adverse events	Group I	Group II	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 105 (4.76%)	2 / 115 (1.74%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon cancer			
subjects affected / exposed	1 / 105 (0.95%)	0 / 115 (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			
Ligament injury			
subjects affected / exposed	1 / 105 (0.95%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Cholecystectomy			

subjects affected / exposed	0 / 105 (0.00%)	1 / 115 (0.87%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgery			
subjects affected / exposed	0 / 105 (0.00%)	1 / 115 (0.87%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle operation			
subjects affected / exposed	1 / 105 (0.95%)	0 / 115 (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			
Pain			
subjects affected / exposed	0 / 105 (0.00%)	1 / 115 (0.87%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Social circumstances			
Social stay hospitalisation			
subjects affected / exposed	0 / 105 (0.00%)	1 / 115 (0.87%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Anal fistula			
subjects affected / exposed	1 / 105 (0.95%)	0 / 115 (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			
Back pain			
subjects affected / exposed	1 / 105 (0.95%)	0 / 115 (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			
Perirectal abscess			

subjects affected / exposed	1 / 105 (0.95%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HIV infection			
subjects affected / exposed	1 / 105 (0.95%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syphilis			
subjects affected / exposed	1 / 105 (0.95%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Group I	Group II	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	32 / 105 (30.48%)	34 / 115 (29.57%)	
Vascular disorders			
Haemorrhage			
subjects affected / exposed	3 / 105 (2.86%)	4 / 115 (3.48%)	
occurrences (all)	3	4	
Nervous system disorders			
Burning sensation			
subjects affected / exposed	0 / 105 (0.00%)	3 / 115 (2.61%)	
occurrences (all)	0	3	
General disorders and administration site conditions			
Condition aggravated			
subjects affected / exposed	3 / 105 (2.86%)	8 / 115 (6.96%)	
occurrences (all)	3	8	
Pain			
subjects affected / exposed	3 / 105 (2.86%)	2 / 115 (1.74%)	
occurrences (all)	3	2	
Gastrointestinal disorders			
Proctalgia			

subjects affected / exposed	5 / 105 (4.76%)	7 / 115 (6.09%)	
occurrences (all)	5	7	
Anal fissure			
subjects affected / exposed	1 / 105 (0.95%)	4 / 115 (3.48%)	
occurrences (all)	1	4	
Haemorrhoids			
subjects affected / exposed	5 / 105 (4.76%)	8 / 115 (6.96%)	
occurrences (all)	6	8	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	3 / 105 (2.86%)	5 / 115 (4.35%)	
occurrences (all)	3	5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 August 2017	1) To ensure that all potential effects in pregnant women, foetus and newborns were captured for evaluation. 2) Addition of another rescue medication in order to relief the chronic anal fissure severe pain, since in some cases acetominophen is not enough.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported