Clinical trial results:
Randomized multicenter, placebo-controlled, single blind study to assess the efficacy and tolerability of a combination of a cream containing ubidecarenone, dexpanthenol and chlorhexidine and a paste containing 2% diltiazem hydrochloride in the treatment of chronic anal fissure.

Summary

EudraCT number	2005-005675-15
Trial protocol	PT CZ ES
Global end of trial date	24 April 2014
Results information	
Result version number	v2 (current)
This version publication date	10 June 2017
First version publication date	22 September 2016
Version creation reason	• Changes to summary attachments wE would like to remove the summary results since is not mandatory.

Trial information

Trial identification	
Sponsor protocol code	DIL-UBI-DEX-CLO II/2003/003/PT
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors	
Sponsor organisation name	Tecnimede, Sociedade Técnico Medicinal
Sponsor organisation address	Ru a da Tapada Grande, nº 2 , Abrunheira, Portugal, 2710-089
Public contact	Rita Neves, Tecnimede, Sociedade Técnico Medicinal, 0351 210 414 187, dmed.ct@tecnimede.pt
Scientific contact	Rita Neves, Tecnimede, Sociedade Técnico Medicinal, 0351 210 414 187, 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	27 August 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 April 2014
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 of the concomitant administration of UDC cream and DTZ 2% paste versus the administration of DTZ 2% paste + placebo of the UDC (PLC) after 8 weeks of CAF treatment.

Protection of trial subjects:

To minimize Chronic Anal Fissure's pain patients were allowed to continue the conservative treatment and had access to rescue medication (paracetamol).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 January 2009
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: 117
Country: Number of subjects enrolled	Spain: 52
Country: Number of subjects enrolled	Czech Republic: 71
Worldwide total number of subjects	240
EEA total number of subjects	240

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)	214
From 65 to 84 years	26

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment lasted 6 months after inclusion of the first patient in each country and per each study part.

Pre-assignment

Screening details:

Patients included signed the ICF, were able to comply with the study protocol, were aged 18 years or above, were diagnosed with idiopathic Chronic anal fissure unresponsive to previous therapy and did not present any exclusion criteria.
From the 244 patients screened only 240 were randomized.

Period 1

Period 1 title	Overall Period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Group I

Arm description:

the DTZ 2% cutaneous paste and the PLC cutaneous cream

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

Dosage and administration details:

Total daily dose of 16 mg was planned for DTZ 2% and 400 mg for placebo.

Arm title	Group II

Arm description:

DTZ 2% cutaneous paste and the UDC cutaneous cream

Arm type	Experimental
Investigational medicinal product name	Diltiazem and UDC
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Cutaneous emulsion, Cutaneous paste
Routes of administration	Rectal use

Dosage and administration details:

Total daily dose of 16 mg was planned for DTZ 2% and 400 mg of UDC

Number of subjects in period 1[1]	Group I	Group II
Started	112	114
Completed	94	93
Not completed	18	21
PP inclusion criteria violation	18	21

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The discrepancies are due to ITT analysis. There were subjects that not applied the medication

Baseline characteristics

Reporting groups	
Reporting group title	Group I
Reporting group description:	
the DTZ 2% cutaneous paste and the PLC cutaneous cream	
Reporting group title	Group II
Reporting group description:	
DTZ 2% cutaneous paste and the UDC cutaneous cream	

Reporting group values	Group I	Group II	Total
Number of subjects	112	114	226
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)	104	98	202
From 65-84 years	8	16	24
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	43.52	47.43	
standard deviation	± 14.79	± 14.89	-
Gender categorical Units: Subjects			
Female	51	65	116
Male	61	49	110

End points

End points reporting groups	
Reporting group title	Group I
Reporting group description: the DTZ 2% cutaneous paste and the PLC cutaneous cream	
Reporting group title	Group II
Reporting group description: DTZ 2% cutaneous paste and the UDC cutaneous cream	

Primary: Chronic anal fissure cure after 8 weeks of treatment (intention to treat population)	
End point title	Chronic anal fissure cure after 8 weeks of treatment (intention to treat population)
End point description:	
End point type	Primary
End point timeframe: After 8 weeks of treatment	

End point values	Group I	Group II		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	114		
Units: Subjects	65	73		

Statistical analyses

Statistical analysis title	Cure Proportion Comparision
Comparison groups	Group I v Group II
Number of subjects included in analysis	226
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.413
Method	Fisher exact

Secondary: Changes in visual analogue scale for pain after 8 weeks of treatment (intention to treat population)	
End point title	Changes in visual analogue scale for pain after 8 weeks of treatment (intention to treat population)
End point description:	

End point type	Secondary
End point timeframe: After 8 weeks of treatment	

End point values	Group I	Group II		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	114		
Units: mm				
arithmetic mean (standard deviation)	46.7 (± 31.03)	46.87 (± 24.56)		

Statistical analyses

Statistical analysis title	VAS Means Comparision
Comparison groups	Group I v Group II
Number of subjects included in analysis	226
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.873
Method	Wilcoxon (Mann-Whitney)

Secondary: Changes in visual analogue scale for pain after 4 weeks of treatment (intention to treat population)

End point title	Changes in visual analogue scale for pain after 4 weeks of treatment (intention to treat population)
End point description:	

End point type	Secondary
End point timeframe: After 4 weeks of treatment	

End point values	Group I	Group II		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	114		
Units: mm				
arithmetic mean (standard deviation)	39.83 (± 27.42)	38.78 (± 25.41)		

Statistical analyses

Statistical analysis title	VAS Means Comparision
Comparison groups	Group I v Group II
Number of subjects included in analysis	226
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.9
Method	Wilcoxon (Mann-Whitney)

Secondary: Chronic anal fissure cure after 4 weeks of treatment (intention to treat population)

End point title	Chronic anal fissure cure after 4 weeks of treatment (intention to treat population)

End point description:

End point type	Secondary

End point timeframe:

After 4 weeks of treatment

End point values	Group I	Group II		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	114		
Units: Subjects	14	18		

Statistical analyses

Statistical analysis title	Cure Proportion Comparision
Comparison groups	Group I v Group II
Number of subjects included in analysis	226
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.568
Method	Fisher exact

Secondary: Chronic anal fissure relapse (intention to treat population)

End point title	Chronic anal fissure relapse (intention to treat population)

End point description:

End point type	Secondary

End point timeframe:

During the 24-week follow-up period

End point values	Group I	Group II		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65	73		
Units: Subjects	8	14		

Statistical analyses

Statistical analysis title	Relapse Proportion Comparision
Comparison groups	Group I v Group II
Number of subjects included in analysis	138
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.351
Method	Fisher exact

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

The investigator was responsible for notifying the sponsor no later than 24 hours of all serious adverse events, except those not requiring immediate notification. This expedited reporting was followed by a detailed report, no later than 5 (five) days.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17

Reporting groups

Reporting group title	Group II
Reporting group description: -	
Reporting group title	Group I
Reporting group description: -	

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: Details were given above

Serious adverse events	Group II	Group I	
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 121 (7.44%)	6 / 117 (5.13%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Blood count abnormal			
subjects affected / exposed	1 / 121 (0.83%)	0 / 117 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Rectal adenoma			
subjects affected / exposed	0 / 121 (0.00%)	1 / 117 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal cancer			
subjects affected / exposed	0 / 121 (0.00%)	1 / 117 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			

Limb traumatic amputation			
subjects affected / exposed	1 / 121 (0.83%)	0 / 117 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	0 / 121 (0.00%)	1 / 117 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb crushing injury			
subjects affected / exposed	0 / 121 (0.00%)	1 / 117 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
subjects affected / exposed	0 / 121 (0.00%)	1 / 117 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Intervertebral disc operation			
subjects affected / exposed	1 / 121 (0.83%)	0 / 117 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Plastic surgery			
subjects affected / exposed	1 / 121 (0.83%)	0 / 117 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthopaedic procedure			
subjects affected / exposed	0 / 121 (0.00%)	1 / 117 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Dysplasia			
subjects affected / exposed	0 / 121 (0.00%)	1 / 117 (0.85%)	
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	2 / 121 (1.65%)	1 / 117 (0.85%)	
occurrences causally related to treatment / all	1 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 121 (0.00%)	1 / 117 (0.85%)	
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			
Intervertebral disc protrusion			
subjects affected / exposed	1 / 121 (0.83%)	0 / 117 (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			
Influenza			
subjects affected / exposed	1 / 121 (0.83%)	0 / 117 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal abscess			
subjects affected / exposed	0 / 121 (0.00%)	2 / 117 (1.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheobronchitis			
subjects affected / exposed	1 / 121 (0.83%)	0 / 117 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 121 (0.83%)	0 / 117 (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: 5 %

Non-serious adverse events	Group II	Group I	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 121 (0.00%)	0 / 117 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 September 2008	Clarification of the IMP circuit
11 September 2009	Clarification of the study procedures
24 January 2012	Alteration of the sample size

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported