# 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<br>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<br>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<br>Units: years | | | |
| arithmetic mean | 43.52 | 47.43 | |
| standard deviation | ± 14.79 | ± 14.89 | - |
| Gender categorical<br>Units: Subjects | | | |
| Female | 51 | 65 | 116 |
| Male | 61 | 49 | 110 |

## End points

| End points reporting groups | |
|---|---|
| Reporting group title | Group I |
| Reporting group description:<br>the DTZ 2% cutaneous paste and the PLC cutaneous cream | |
| Reporting group title | Group II |
| Reporting group description:<br>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:<br>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:<br>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:<br>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