



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 (\pm 29.60) | 44.08 (\pm 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 (\pm 26.46) | 46.82 (\pm 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 occurrences (all) | 5 / 105 (4.76%) 5 | 7 / 115 (6.09%) 7 | |
| Anal fissure subjects affected / exposed occurrences (all) | 1 / 105 (0.95%) 1 | 4 / 115 (3.48%) 4 | |
| Haemorrhoids subjects affected / exposed occurrences (all) | 5 / 105 (4.76%) 6 | 8 / 115 (6.96%) 8 | |
| Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all) | 3 / 105 (2.86%) 3 | 5 / 115 (4.35%) 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 acetaminophen is not enough. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported