# Clinical trial results:
# A phase 2 trial testing ZP1848 in patients with SBS

## A proof-of-concept, dose-finding, controlled, single-center, randomized, cross-over, double-blind, fixed dose trial

### Summary

| | |
|---|---|
| EudraCT number | 2015-002826-38 |
| Trial protocol | DK |
| Global end of trial date | 04 May 2017 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 01 June 2018 |
| First version publication date | 01 June 2018 |

### Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | ZP1848-15073 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02690025 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Zealand Pharma A/S |
| Sponsor organisation address | Smedeland 36, Glostrup, Denmark, 2600 |
| Public contact | Gertrud Koefoed Rasmussen, Zealand Pharma A/S, 0045 50603773, gkr@zealandpharma.com |
| Scientific contact | Gertrud Koefoed Rasmussen, Zealand Pharma A/S, 0045 50603773, gkr@zealandpharma.com |

Notes:

**Paediatric regulatory details**

| | |
|---|---|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 04 May 2017 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 04 May 2017 |
| Global end of trial reached? | Yes |
| Global end of trial date | 04 May 2017 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective is to evaluate the effect of three different doses of ZP1848 on intestinal absorption in SBS patients after three week treatment periods.

Protection of trial subjects:

The trial was conducted in accordance of the World Medical Association Declaration of Helsinki, current guidelines for GCP and local regulations.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 05 February 2016 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Denmark: 18 |
| Worldwide total number of subjects | 18 |
| EEA total number of subjects | 18 |

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) | 12 |
| From 65 to 84 years | 6 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

22 patients were screened at one Danish site. The first patient was screened on 5 Feb 2016 and the last patient was enrolled on 25 Jan 2017. 18 Patients were randomized in the trial and 16 patients completed the trial.

### Pre-assignment

Screening details:

4 patients failed screening. 18 patients were randomized and received treatment. 2 patients dropped out during their first treatment period (did not start the second treatment period). Hence, totally 34 treatment periods were started/32 were completed. The screening assessments occurred up to 27 days prior to baseline assessments.

### Period 1

| | |
|---|---|
| Period 1 title | Overall trial (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Investigator, Monitor, Data analyst, Subject |

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | No |
| **Arm title** | 0.1 mg/day |

Arm description: -

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | ZP1848 |
| Investigational medicinal product code | |
| Other name | glepaglutide |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

0.1 mg injected daily subcutaneously in abdomen or thighs for 3 weeks

| | |
|---|---|
| **Arm title** | 1 mg/day |

Arm description: -

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | ZP1848 |
| Investigational medicinal product code | |
| Other name | glepaglutide |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

1 mg injected daily subcutaneously in abdomen or thighs for 3 weeks

| | |
|---|---|
| **Arm title** | 10 mg/day |

Arm description: -

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | ZP1848 |
| Investigational medicinal product code | |
| Other name | glepaglutide |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:
10 mg injected daily subcutaneously in abdomen or thighs for 3 weeks

| **Number of subjects in period 1** | 0.1 mg/day | 1 mg/day | 10 mg/day |
|---|---|---|---|
| Started | 11 | 11 | 12 |
| Completed | 10 | 11 | 11 |
| Not completed | 1 | 0 | 1 |
| Consent withdrawn by subject | 1 | - | - |
| Adverse event, non-fatal | - | - | 1 |

## Baseline characteristics

### Reporting groups

| Reporting group title | Overall trial |
|---|---|

Reporting group description: -

| Reporting group values | Overall trial | Total | |
|---|---|---|---|
| Number of subjects | 18 | 18 | |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 12 | 12 | |
| From 65-84 years | 6 | 6 | |
| 85 years and over | 0 | 0 | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 9 | 9 | |
| Male | 9 | 9 | |

### Subject analysis sets

| Subject analysis set title | FAS |
|---|---|
| Subject analysis set type | Full analysis |

Subject analysis set description:

The full analysis set comprises all randomized patients delivering post-baseline efficacy data

| Reporting group values | FAS | | |
|---|---|---|---|
| Number of subjects | 16 | | |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | | |
| Preterm newborn infants (gestational age < 37 wks) | 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) | 11 | | |
| From 65-84 years | 5 | | |
| 85 years and over | 0 | | |

| Gender categorical<br>Units: Subjects | | | |
|---|---|---|---|
| Female | 8 | | |
| Male | 8 | | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | 0.1 mg/day |
| Reporting group description: - | |
| Reporting group title | 1 mg/day |
| Reporting group description: - | |
| Reporting group title | 10 mg/day |
| Reporting group description: - | |
| Subject analysis set title | FAS |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| The full analysis set comprises all randomized patients delivering post-baseline efficacy data | |

### Primary: Absolute change from baseline to the end of the 3-week treatment periods of wet weight output or diarrhea

| | |
|---|---|
| End point title | Absolute change from baseline to the end of the 3-week treatment periods of wet weight output or diarrhea |
| End point description: | |
| | |
| End point type | Primary |
| End point timeframe: | |
| Change measured between baseline and end of the 3-week treatment period | |

| End point values | 0.1 mg/day | 1 mg/day | 10 mg/day | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 10 | 11 | 11 | |
| Units: g per day | | | | |
| least squares mean (confidence interval 95%) | 173 (-160 to 506) | -592 (-913 to -272) | -833 (-1152 to -515) | |

### Statistical analyses

| Statistical analysis title | Test 1 Effect in the pooled 10 and 1 mg dose group |
|---|---|
| Statistical analysis description: | |
| Effect in the pooled medium and high dose groups | |
| Comparison groups | 10 mg/day v 1 mg/day |
| Number of subjects included in analysis | 22 |
| Analysis specification | Pre-specified |
| Analysis type | other[1] |
| P-value | < 0.0001 |
| Method | ANCOVA |

Notes:

[1] - The primary endpoint was analyzed using a linear model having period (1,2) and treatment doses (0.1, 1 and 10.0 mg) as fixed effects and patient as random effect, adjusting for the baseline value within each dosing period, the total oral intake (solid and liquid combined in grams) and the PS volume. The model was analyzed using a mixed-effects analysis of covariance (ANCOVA).

| Statistical analysis title | Test 2 Effect in the 10 mg dose |
|---|---|

Statistical analysis description:

Effect in the high dose group

| | |
|---|---|
| Comparison groups | 10 mg/day v 1 mg/day |
| Number of subjects included in analysis | 22 |
| Analysis specification | Pre-specified |
| Analysis type | other[2] |
| P-value | = 0.0002 [3] |
| Method | ANCOVA |

Notes:

[2] - The primary endpoint was analyzed using a linear model having period (1,2) and treatment doses (0.1, 1 and 10.0 mg) as fixed effects and patient as random effect, adjusting for the baseline value within each dosing period, the total oral intake (solid and liquid combined in grams) and the PS volume. The model was analyzed using a mixed-effects analysis of covariance (ANCOVA).

[3] - The primary hypotheses were tested sequentially in a hierarchical testing procedure.

| Statistical analysis title | Test 3 Effect in the 1 mg dose group |
|---|---|

Statistical analysis description:

Effect of the medium dose

| | |
|---|---|
| Comparison groups | 1 mg/day v 0.1 mg/day |
| Number of subjects included in analysis | 21 |
| Analysis specification | Pre-specified |
| Analysis type | other[4] |
| P-value | = 0.0021 [5] |
| Method | ANCOVA |

Notes:

[4] - The primary endpoint was analyzed using a linear model having period (1,2) and treatment doses (0.1, 1 and 10.0 mg) as fixed effects and patient as random effect, adjusting for the baseline value within each dosing period, the total oral intake (solid and liquid combined in grams) and the PS volume. The model was analyzed using a mixed-effects analysis of covariance (ANCOVA).

[5] - The primary hypotheses were tested sequentially in a hierarchical testing procedure.

| Statistical analysis title | Test 4 Effect in the 0.1 mg dose group |
|---|---|
| Comparison groups | 0.1 mg/day v 1 mg/day |
| Number of subjects included in analysis | 21 |
| Analysis specification | Pre-specified |
| Analysis type | other[6] |
| P-value | = 0.2743 [7] |
| Method | ANCOVA |

Notes:

[6] - The primary endpoint was analyzed using a linear model having period (1,2) and treatment doses (0.1, 1 and 10.0 mg) as fixed effects and patient as random effect, adjusting for the baseline value within each dosing period, the total oral intake (solid and liquid combined in grams) and the PS volume. The model was analyzed using a mixed-effects analysis of covariance (ANCOVA).

[7] - The primary hypotheses were tested sequentially in a hierarchical testing procedure. The test procedure stopped at test 4

## Secondary: Relative change from baseline to the end of treatment of wet weight of ostomy output or diarrhea

| | |
|---|---|
| End point title | Relative change from baseline to the end of treatment of wet weight of ostomy output or diarrhea |

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

Change measured between baseline and end of the 3 week treatment period

| **End point values** | 0.1 mg/day | 1 mg/day | 10 mg/day | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 10 | 11 | 11 | |
| Units: percent | | | | |
| least squares mean (confidence interval 95%) | 10 (-3 to 22) | -23 (-35 to -11) | -30 (-42 to -19) | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Absolute change from baseline to the end of treatment of urine weight

| End point title | Absolute change from baseline to the end of treatment of urine weight |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

Change measured between baseline and end of the 3 week treatment period

| **End point values** | 0.1 mg/day | 1 mg/day | 10 mg/day | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 10 | 11 | 11 | |
| Units: g per day | | | | |
| least squares mean (confidence interval 95%) | 90 (-208 to 389) | 530 (245 to 816) | 368 (82 to 654) | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Relative change from baseline to the end of treatment of urine weight

| End point title | Relative change from baseline to the end of treatment of urine weight |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

Change measured between baseline and end of the 3 week treatment period

| **End point values** | 0.1 mg/day | 1 mg/day | 10 mg/day | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 10 | 11 | 11 | |
| Units: percent | | | | |
| least squares mean (confidence interval 95%) | 11 (-11 to 34) | 40 (18 to 61) | 32 (11 to 54) | |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Absolute change from baseline to the end of treatment of wet weight absorption (measured by oral intake minus fecal excretion)**

| End point title | Absolute change from baseline to the end of treatment of wet weight absorption (measured by oral intake minus fecal excretion) |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

Change measured between baseline and end of the 3 week treatment period

| **End point values** | 0.1 mg/day | 1 mg/day | 10 mg/day | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 10 | 11 | 11 | |
| Units: g per day | | | | |
| least squares mean (confidence interval 95%) | -211 (-487 to 64) | 650 (385 to 914) | 786 (523 to 1049) | |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Relative change from baseline to the end of treatment of wet weight absorption (measured by oral intake minus fecal excretion)**

| End point title | Relative change from baseline to the end of treatment of wet |
|---|---|

| | |
|---|---|
| | weight absorption (measured by oral intake minus fecal excretion) |

End point description:

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

Change measured between baseline and end of the 3 week treatment period

| **End point values** | 0.1 mg/day | 1 mg/day | 10 mg/day | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 10 | 11 | 11 | |
| Units: percent | | | | |
| least squares mean (confidence interval 95%) | -34 (-228 to 159) | 21 (-165 to 207) | 87 (-98 to 272) | |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Absolute change from baseline to the end of treatment of urine weight minus oral intake**

| | |
|---|---|
| End point title | Absolute change from baseline to the end of treatment of urine weight minus oral intake |

End point description:

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

Change measured between baseline and end of the 3 week treatment period

| **End point values** | 0.1 mg/day | 1 mg/day | 10 mg/day | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 10 | 11 | 11 | |
| Units: g per day | | | | |
| least squares mean (confidence interval 95%) | 118 (-244 to 479) | 487 (140 to 833) | 411 (65 to 758) | |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Relative change from baseline to the end of treatment of urine weight minus oral intake**

| End point title | Relative change from baseline to the end of treatment of urine weight minus oral intake |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

Change measured between baseline and end of the 3 week treatment period

| **End point values** | 0.1 mg/day | 1 mg/day | 10 mg/day | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 10 | 11 | 11 | |
| Units: percent | | | | |
| least squares mean (confidence interval 95%) | -4 (-39 to 31) | -45 (-79 to -11) | -50 (-84 to -16) | |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Absolute change from baseline to the end of treatment of the intestinal absorption (oral intake minus fecal excretion) of sodium**

| End point title | Absolute change from baseline to the end of treatment of the intestinal absorption (oral intake minus fecal excretion) of sodium |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

Change measured between baseline and end of the 3 week treatment period

| **End point values** | 0.1 mg/day | 1 mg/day | 10 mg/day | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 10 | 11 | 11 | |
| Units: mmol per day | | | | |
| least squares mean (confidence interval 95%) | -17 (-58 to 24) | 47 (7 to 86) | 40 (1 to 80) | |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Absolute change from baseline to the end of treatment of the intestinal**

| absorption (oral intake minus fecal excretion) of magnesium | |
|---|---|
| End point title | Absolute change from baseline to the end of treatment of the intestinal absorption (oral intake minus fecal excretion) of magnesium |

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

Change measured between baseline and end of the 3 week treatment period

| End point values | 0.1 mg/day | 1 mg/day | 10 mg/day | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 10 | 11 | 11 | |
| Units: mmol per day | | | | |
| least squares mean (confidence interval 95%) | -3 (-6 to -1) | 1 (-2 to 3) | -1 (-4 to 1) | |

**Statistical analyses**

No statistical analyses for this end point

| Secondary: Absolute change from baseline to the end of treatment of the intestinal absorption (oral intake minus fecal excretion) of calcium | |
|---|---|
| End point title | Absolute change from baseline to the end of treatment of the intestinal absorption (oral intake minus fecal excretion) of calcium |

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

Change measured between baseline and end of the 3 week treatment period

| End point values | 0.1 mg/day | 1 mg/day | 10 mg/day | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 10 | 11 | 11 | |
| Units: mmol per day | | | | |
| least squares mean (confidence interval 95%) | -5 (-9 to -1) | 0 (-4 to 4) | 0 (-4 to 4) | |

**Statistical analyses**

No statistical analyses for this end point

## Secondary: Absolute change from baseline to the end of treatment of the intestinal absorption (oral intake minus fecal excretion) of potassium

| End point title | Absolute change from baseline to the end of treatment of the intestinal absorption (oral intake minus fecal excretion) of potassium |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

Change measured between baseline and end of the 3 week treatment period

| End point values | 0.1 mg/day | 1 mg/day | 10 mg/day | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 10 | 11 | 11 | |
| Units: mmol per day | | | | |
| least squares mean (confidence interval 95%) | 0 (-16 to 17) | 16 (0 to 31) | 10 (-5 to 25) | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Relative change from baseline to the end of treatment of the intestinal absorption (oral intake minus fecal excretion) of sodium

| End point title | Relative change from baseline to the end of treatment of the intestinal absorption (oral intake minus fecal excretion) of sodium |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

Change measured between baseline and end of the 3 week treatment period

| End point values | 0.1 mg/day | 1 mg/day | 10 mg/day | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 10 | 11 | 11 | |
| Units: percent | | | | |
| least squares mean (confidence interval 95%) | 13 (-235 to 260) | 60 (-176 to 295) | 131 (-102 to 364) | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Relative change from baseline to the end of treatment of the intestinal absorption (oral intake minus fecal excretion) of magnesium

| End point title | Relative change from baseline to the end of treatment of the intestinal absorption (oral intake minus fecal excretion) of magnesium |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

Change measured between baseline and end of the 3 week treatment period

| End point values | 0.1 mg/day | 1 mg/day | 10 mg/day | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 10 | 11 | 11 | |
| Units: percent | | | | |
| least squares mean (confidence interval 95%) | 128 (-200 to 457) | -90 (-403 to 223) | -109 (-418 to 200) | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Relative change from baseline to the end of treatment of the intestinal absorption (oral intake minus fecal excretion) of calcium

| End point title | Relative change from baseline to the end of treatment of the intestinal absorption (oral intake minus fecal excretion) of calcium |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

Change measured between baseline and end of the 3 week treatment period

| End point values | 0.1 mg/day | 1 mg/day | 10 mg/day | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 10 | 11 | 11 | |
| Units: percent | | | | |
| least squares mean (confidence interval 95%) | -242 (-453 to -30) | -17 (-220 to 186) | 74 (-127 to 276) | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Relative change from baseline to the end of treatment of the intestinal absorption (oral intake minus fecal excretion) of potassium

| End point title | Relative change from baseline to the end of treatment of the intestinal absorption (oral intake minus fecal excretion) of potassium |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

Change measured between baseline and end of the 3 week treatment period

| **End point values** | 0.1 mg/day | 1 mg/day | 10 mg/day | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 10 | 11 | 11 | |
| Units: percent | | | | |
| least squares mean (confidence interval 95%) | -90 (-326 to 146) | -80 (-306 to 146) | 57 (-164 to 279) | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Absolute change from baseline to the end of treatment of intestinal absorption (oral intake minus fecal excretion) of energy assessed by bomb calorimetry

| End point title | Absolute change from baseline to the end of treatment of intestinal absorption (oral intake minus fecal excretion) of energy assessed by bomb calorimetry |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

Change measured between baseline and end of the 3 week treatment period

| End point values | 0.1 mg/day | 1 mg/day | 10 mg/day | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 10 | 11 | 11 | |
| Units: kJ per day | | | | |
| least squares mean (confidence interval 95%) | -377 (-1234 to 481) | 435 (-393 to 1263) | 588 (-227 to 1403) | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Relative change from baseline to the end of treatment of intestinal absorption (oral intake minus fecal excretion) of energy assessed by bomb calorimetry

| End point title | Relative change from baseline to the end of treatment of intestinal absorption (oral intake minus fecal excretion) of energy assessed by bomb calorimetry |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

Change measured between baseline and end of the 3 week treatment period

| End point values | 0.1 mg/day | 1 mg/day | 10 mg/day | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 10 | 11 | 11 | |
| Units: percent | | | | |
| least squares mean (confidence interval 95%) | 6 (-66 to 78) | 24 (-46 to 94) | 21 (-48 to 90) | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Absolute change from baseline to the end of treatment of intestinal absorption (oral intake minus fecal excretion) of lipids

| End point title | Absolute change from baseline to the end of treatment of intestinal absorption (oral intake minus fecal excretion) of lipids |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

Change measured between baseline and end of the 3 week treatment period

| End point values | 0.1 mg/day | 1 mg/day | 10 mg/day | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 10 | 11 | 11 | |
| Units: kJ per day | | | | |
| least squares mean (confidence interval 95%) | -330 (-864 to 205) | 516 (3 to 1029) | 103 (-407 to 612) | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Relative change from baseline to the end of treatment of intestinal absorption (oral intake minus fecal excretion) of lipids

| End point title | Relative change from baseline to the end of treatment of intestinal absorption (oral intake minus fecal excretion) of lipids |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

Change measured between baseline and end of the 3 week treatment period

| End point values | 0.1 mg/day | 1 mg/day | 10 mg/day | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 10 | 11 | 11 | |
| Units: percent | | | | |
| least squares mean (confidence interval 95%) | -31 (-72 to 10) | 48 (9 to 87) | 0 (-38 to 39) | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Absolute change from baseline to the end of treatment of intestinal absorption (oral intake minus fecal excretion) of nitrogen (a marker of proteins)

| End point title | Absolute change from baseline to the end of treatment of intestinal absorption (oral intake minus fecal excretion) of nitrogen (a marker of proteins) |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

Change measured between baseline and end of the 3 week treatment period

| **End point values** | 0.1 mg/day | 1 mg/day | 10 mg/day | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 10 | 11 | 11 | |
| Units: g per day | | | | |
| least squares mean (confidence interval 95%) | -1 (-3 to 1) | 2 (0 to 3) | 1 (-1 to 2) | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Relative change from baseline to the end of treatment of intestinal absorption (oral intake minus fecal excretion) of nitrogen (a marker of proteins)

| End point title | Relative change from baseline to the end of treatment of intestinal absorption (oral intake minus fecal excretion) of nitrogen (a marker of proteins) |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

Change measured between baseline and end of the 3 week treatment period

| **End point values** | 0.1 mg/day | 1 mg/day | 10 mg/day | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 10 | 11 | 11 | |
| Units: percent | | | | |
| least squares mean (confidence interval 95%) | -83 (-220 to 55) | -63 (-196 to 70) | -42 (-173 to 89) | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Absolute change from baseline to the end of treatment of intestinal absorption (oral intake minus fecal excretion) of carbohydrates

| End point title | Absolute change from baseline to the end of treatment of intestinal absorption (oral intake minus fecal excretion) of carbohydrates |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

Change measured between baseline and end of the 3 week treatment period

| **End point values** | 0.1 mg/day | 1 mg/day | 10 mg/day | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 10 | 11 | 11 | |
| Units: kJ per day | | | | |
| least squares mean (confidence interval 95%) | -11 (-399 to 377) | 368 (-6 to 743) | 336 (-31 to 703) | |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Mean score change in mental component score (MCS)**

| End point title | Mean score change in mental component score (MCS) |
|---|---|

End point description:

SF-36v2 1 week-recall version

| End point type | Secondary |
|---|---|

End point timeframe:

Change measured between baseline and end of the 3 week treatment period

| **End point values** | 0.1 mg/day | 1 mg/day | 10 mg/day | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 10 | 11 | 11 | |
| Units: Score | | | | |
| arithmetic mean (standard deviation) | 2.7 (± 9.5) | 1.8 (± 7.0) | -4.8 (± 13.7) | |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Relative change from baseline to the end of treatment of intestinal absorption (oral intake minus fecal excretion) of carbohydrates**

| End point title | Relative change from baseline to the end of treatment of intestinal absorption (oral intake minus fecal excretion) of carbohydrates |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

Change measured between baseline and end of the 3 week treatment period

| **End point values** | 0.1 mg/day | 1 mg/day | 10 mg/day | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 10 | 11 | 11 | |
| Units: percent | | | | |
| least squares mean (confidence interval 95%) | -2 (-20 to 17) | 18 (-1 to 36) | 21 (3 to 39) | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Mean score change in physical component score (PCS)

| End point title | Mean score change in physical component score (PCS) |
|---|---|

End point description:

SF-36v2 1-week recall version used

| End point type | Secondary |
|---|---|

End point timeframe:

Change measured between baseline and end of the 3 week treatment period

| **End point values** | 0.1 mg/day | 1 mg/day | 10 mg/day | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 10 | 11 | 11 | |
| Units: Score | | | | |
| arithmetic mean (standard deviation) | 1.3 (± 6.1) | 2.5 (± 5.6) | -2.5 (± 6.8) | |

### Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Absolute change from baseline to the end of treatment of intestinal absorption (oral intake minus fecal excretion) of energy calculated as the sum of the energy content

| End point title | Absolute change from baseline to the end of treatment of intestinal absorption (oral intake minus fecal excretion) of energy calculated as the sum of the energy content |
|---|---|

End point description:

Energy was calculated as the sum of the energy content from lipids, nitrogen (as a marker for proteins) and carbohydrates and used as an approximation

| End point type | Other pre-specified |
|---|---|

End point timeframe:

Change measured between baseline and end of the 3 week treatment period

| **End point values** | 0.1 mg/day | 1 mg/day | 10 mg/day | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 10 | 10 | 10 | |
| Units: kJ per day | | | | |
| least squares mean (confidence interval 95%) | -491 (-1402 to 419) | 1099 (223 to 1976) | 544 (-317 to 1406) | |

## Statistical analyses

No statistical analyses for this end point

## Other pre-specified: Relative change from baseline to the end of treatment of intestinal absorption (oral intake minus fecal excretion) of energy calculated as the sum of the energy content

| End point title | Relative change from baseline to the end of treatment of intestinal absorption (oral intake minus fecal excretion) of energy calculated as the sum of the energy content |
|---|---|

End point description:

Energy was calculated as the sum of the energy content from lipids, nitrogen (as a marker for proteins) and carbohydrates and used as an approximation

| End point type | Other pre-specified |
|---|---|

End point timeframe:

Change measured between baseline and end of the 3 week treatment period

| **End point values** | 0.1 mg/day | 1 mg/day | 10 mg/day | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 10 | 11 | 11 | |
| Units: percent | | | | |
| least squares mean (confidence interval 95%) | -10 (-33 to 13) | 25 (3 to 47) | 11 (-11 to 34) | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

| Adverse events information | |
|---|---|
| Timeframe for reporting adverse events: | |
| Adverse event reporting was done from informed consent was signed and until the follow up visit | |
| Adverse event reporting additional description: | |
| Due to the size of the trial population any event reported would result in >5% frequency | |
| Assessment type | Systematic |

| Dictionary used | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 18.1 |

| Reporting groups | |
|---|---|
| Reporting group title | 0.1 mg/day |
| Reporting group description: - | |
| Reporting group title | Safety analysis set |
| Reporting group description: - | |
| Reporting group title | 10 mg/day |
| Reporting group description: - | |
| Reporting group title | 1 mg/day |
| Reporting group description: - | |

| Serious adverse events | 0.1 mg/day | Safety analysis set | 10 mg/day |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 7 / 18 (38.89%) | 6 / 12 (50.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | | 0 |
| Injury, poisoning and procedural complications | | | |
| Stoma obstruction | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 1 / 18 (5.56%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Thrombophlebitis superficial | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 18 (5.56%) | 1 / 12 (8.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Surgical and medical procedures | | | |
| Catheter removal | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 18 (5.56%) | 1 / 12 (8.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 18 (5.56%) | 1 / 12 (8.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 18 (5.56%) | 1 / 12 (8.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 1 / 18 (5.56%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mechanical ileus | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 18 (5.56%) | 1 / 12 (8.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Device related sepsis | Additional description: Cross-over design.One patient in group 0.1 mg is the same patient as in the 10 mg group, hence this patient experienced 2 events both of them assessed not related. | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 2 / 18 (11.11%) | 1 / 12 (8.33%) |
| occurrences causally related to treatment / all | 1 / 2 | 1 / 3 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 1 / 18 (5.56%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infection | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 12 (8.33%) | 2 / 18 (11.11%) | 1 / 12 (8.33%) |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 2 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 18 (5.56%) | 1 / 12 (8.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| **Serious adverse events** | 1 mg/day | | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |
| Injury, poisoning and procedural complications | | | |
| Stoma obstruction | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |
| Thrombophlebitis superficial | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Surgical and medical procedures | | | |
| Catheter removal | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Abdominal pain upper | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 12 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Mechanical ileus | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Device related sepsis | Additional description: Cross-over design.One patient in group 0.1 mg is the same patient as in the 10 mg group, hence this patient experienced 2 events both of them assessed not related. | | |
| subjects affected / exposed | 0 / 12 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sepsis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infection | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| **Non-serious adverse events** | 0.1 mg/day | Safety analysis set | 10 mg/day |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 11 / 12 (91.67%) | 18 / 18 (100.00%) | 12 / 12 (100.00%) |
| Vascular disorders | | | |
| Hot flush | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 3 / 18 (16.67%) | 3 / 12 (25.00%) |
| occurrences (all) | 0 | 4 | 4 |
| Peripheral coldness | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 1 / 18 (5.56%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Hypertension | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 18 (5.56%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 1 |
| Surgical and medical procedures | | | |
| Enterostomy | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 18 (5.56%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| General disorders and administration site conditions | | | |
| Injection site reaction | Additional description: This was a cross-over design, hence subjects may appear in 2 groups.<br>Injection site reactions (ISRs) were captured separately from AEs. ISRs were recorded on a symptom level: itching, redness, induration/infiltration, pain, edema and other | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 11 / 18 (61.11%) | 8 / 12 (66.67%) |
| occurrences (all) | 11 | 498 | 327 |
| Oedema peripheral | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 10 / 18 (55.56%) | 5 / 12 (41.67%) |
| occurrences (all) | 3 | 21 | 9 |
| Fatigue | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 6 / 18 (33.33%) | 4 / 12 (33.33%) |
| occurrences (all) | 1 | 7 | 4 |
| Malaise | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 3 / 18 (16.67%) | 2 / 12 (16.67%) |
| occurrences (all) | 3 | 5 | 2 |
| Thirst | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 18 (5.56%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 2 | 2 |
| Impaired healing | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 12 (8.33%) | 1 / 18 (5.56%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Device occlusion | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 1 / 18 (5.56%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Chills | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 18 (5.56%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 1 | 1 |
| Reproductive system and breast disorders | | | |
| Oedema genital | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 2 / 18 (11.11%) | 2 / 12 (16.67%) |
| occurrences (all) | 0 | 2 | 2 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 4 / 18 (22.22%) | 2 / 12 (16.67%) |
| occurrences (all) | 1 | 4 | 2 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 2 / 18 (11.11%) | 1 / 12 (8.33%) |
| occurrences (all) | 2 | 3 | 1 |
| Dyspnoea exertional | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 18 (5.56%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Psychiatric disorders | | | |
| Restlessness | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 2 / 18 (11.11%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Irritability | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 18 (5.56%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 1 | 1 |
| Insomnia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 18 (5.56%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Depressed mood | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 1 / 18 (5.56%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Investigations | | | |

| | | | |
|---|---|---|---|
| Gastrointestinal stoma output increased | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 3 / 18 (16.67%) | 3 / 12 (25.00%) |
| occurrences (all) | 0 | 4 | 4 |
| Weight increased | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 18 (5.56%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 1 | 1 |
| Weight decreased | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 1 / 18 (5.56%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Urine output increased | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 18 (5.56%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Serum ferritin decreased | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 18 (5.56%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 1 | 1 |
| International normalised ratio abnormal | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 18 (5.56%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 18 (5.56%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Gastrointestinal stoma output decreased | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 18 (5.56%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Injury, poisoning and procedural complications | | | |
| Stoma complication | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 13 / 18 (72.22%) | 10 / 12 (83.33%) |
| occurrences (all) | 2 | 20 | 12 |
| Gastrointestinal stoma complication | | | |
| subjects affected / exposed | 3 / 12 (25.00%) | 13 / 18 (72.22%) | 10 / 12 (83.33%) |
| occurrences (all) | 3 | 19 | 10 |
| Stoma obstruction | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 1 / 18 (5.56%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |

| | | | |
|---|---|---|---|
| Procedural pain | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 3 / 18 (16.67%) | 1 / 12 (8.33%) |
| occurrences (all) | 2 | 3 | 1 |
| Stoma site haemorrhage | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 1 / 18 (5.56%) | 0 / 12 (0.00%) |
| occurrences (all) | 2 | 2 | 0 |
| Stoma site oedema | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 18 (5.56%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Stoma site erythema | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 18 (5.56%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 1 | 1 |
| Ligament sprain | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 1 / 18 (5.56%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Scar | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 1 / 18 (5.56%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Excoriation | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 18 (5.56%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Accidental overdose | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 1 / 18 (5.56%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Cardiac disorders | | | |
| Tachycardia | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 3 / 18 (16.67%) | 2 / 12 (16.67%) |
| occurrences (all) | 1 | 5 | 3 |
| Palpitations | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 1 / 18 (5.56%) | 1 / 12 (8.33%) |
| occurrences (all) | 2 | 3 | 1 |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 3 / 18 (16.67%) | 2 / 12 (16.67%) |
| occurrences (all) | 2 | 13 | 5 |
| Dizziness | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 12 (16.67%) | 5 / 18 (27.78%) | 3 / 12 (25.00%) |
| occurrences (all) | 4 | 8 | 4 |
| Migraine | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 2 / 18 (11.11%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 3 | 1 |
| Paraesthesia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 18 (5.56%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Restless legs syndrome | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 18 (5.56%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hypoaesthesia | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 1 / 18 (5.56%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Eye disorders | | | |
| Conjunctival haemorrhage | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 18 (5.56%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 1 | 1 |
| Gastrointestinal disorders | | | |
| Nausea | | | |
| subjects affected / exposed | 4 / 12 (33.33%) | 8 / 18 (44.44%) | 6 / 12 (50.00%) |
| occurrences (all) | 6 | 21 | 14 |
| Abdominal pain | | | |
| subjects affected / exposed | 5 / 12 (41.67%) | 7 / 18 (38.89%) | 2 / 12 (16.67%) |
| occurrences (all) | 12 | 17 | 3 |
| Gastrointestinal sounds abnormal | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 1 / 18 (5.56%) | 0 / 12 (0.00%) |
| occurrences (all) | 10 | 11 | 0 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 4 / 18 (22.22%) | 3 / 12 (25.00%) |
| occurrences (all) | 2 | 8 | 5 |
| Vomiting | | | |
| subjects affected / exposed | 3 / 12 (25.00%) | 5 / 18 (27.78%) | 3 / 12 (25.00%) |
| occurrences (all) | 3 | 8 | 4 |
| Abdominal distension | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 3 / 12 (25.00%) | 5 / 18 (27.78%) | 2 / 12 (16.67%) |
| occurrences (all) | 3 | 7 | 2 |
| Dry mouth | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 2 / 18 (11.11%) | 2 / 12 (16.67%) |
| occurrences (all) | 0 | 2 | 2 |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 1 / 18 (5.56%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Abdominal pain lower | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 1 / 18 (5.56%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Abdominal tenderness | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 1 / 18 (5.56%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Abdominal discomfort | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 1 / 18 (5.56%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Skin and subcutaneous tissue disorders | | | |
| Erythema | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 18 (5.56%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 1 | 1 |
| Renal and urinary disorders | | | |
| Polyuria | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 6 / 18 (33.33%) | 3 / 12 (25.00%) |
| occurrences (all) | 1 | 7 | 3 |
| Pollakiuria | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 2 / 18 (11.11%) | 2 / 12 (16.67%) |
| occurrences (all) | 0 | 2 | 2 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 3 / 18 (16.67%) | 1 / 12 (8.33%) |
| occurrences (all) | 1 | 4 | 1 |
| Myalgia | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 2 / 18 (11.11%) | 1 / 12 (8.33%) |
| occurrences (all) | 1 | 2 | 1 |
| Muscular weakness | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 12 (8.33%) | 1 / 18 (5.56%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Fistula discharge | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 18 (5.56%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 1 | 1 |
| Infections and infestations | | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 3 / 18 (16.67%) | 2 / 12 (16.67%) |
| occurrences (all) | 1 | 5 | 2 |
| Influenza | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 3 / 18 (16.67%) | 1 / 12 (8.33%) |
| occurrences (all) | 1 | 3 | 1 |
| Infection | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 1 / 18 (5.56%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 2 / 18 (11.11%) | 0 / 12 (0.00%) |
| occurrences (all) | 2 | 2 | 0 |
| Tooth infection | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 18 (5.56%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 1 | 1 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 18 (5.56%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 18 (5.56%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Rhinitis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 18 (5.56%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 4 / 18 (22.22%) | 2 / 12 (16.67%) |
| occurrences (all) | 1 | 4 | 2 |
| Iron deficiency | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 18 (5.56%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hypokalaemia | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 1 / 18 (5.56%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Abnormal weight gain | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 18 (5.56%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 1 | 1 |
| Vitamin D deficiency | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 18 (5.56%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 1 | 1 |

| **Non-serious adverse events** | 1 mg/day | | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 11 / 12 (91.67%) | | |
| Vascular disorders | | | |
| Hot flush | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | | |
| occurrences (all) | 0 | | |
| Peripheral coldness | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hypertension | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | | |
| occurrences (all) | 1 | | |
| Surgical and medical procedures | | | |
| Enterostomy | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | | |
| occurrences (all) | 1 | | |
| General disorders and administration site conditions | | | |
| Injection site reaction | Additional description: This was a cross-over design, hence subjects may appear in 2 groups.<br>Injection site reactions (ISRs) were captured separately from AEs. ISRs were recorded on a symptom level: itching, redness, induration/infiltration, pain, edema and other | | |
| subjects affected / exposed | 7 / 12 (58.33%) | | |
| occurrences (all) | 160 | | |
| Oedema peripheral | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed<br>occurrences (all) | 6 / 12 (50.00%)<br>9 | | |
| Fatigue<br>subjects affected / exposed<br>occurrences (all) | 2 / 12 (16.67%)<br>2 | | |
| Malaise<br>subjects affected / exposed<br>occurrences (all) | 0 / 12 (0.00%)<br>0 | | |
| Thirst<br>subjects affected / exposed<br>occurrences (all) | 0 / 12 (0.00%)<br>0 | | |
| Impaired healing<br>subjects affected / exposed<br>occurrences (all) | 0 / 12 (0.00%)<br>0 | | |
| Device occlusion<br>subjects affected / exposed<br>occurrences (all) | 0 / 12 (0.00%)<br>0 | | |
| Chills<br>subjects affected / exposed<br>occurrences (all) | 0 / 12 (0.00%)<br>0 | | |
| Reproductive system and breast disorders | | | |
| Oedema genital<br>subjects affected / exposed<br>occurrences (all) | 0 / 12 (0.00%)<br>0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough<br>subjects affected / exposed<br>occurrences (all) | 1 / 12 (8.33%)<br>1 | | |
| Oropharyngeal pain<br>subjects affected / exposed<br>occurrences (all) | 0 / 12 (0.00%)<br>0 | | |
| Dyspnoea exertional<br>subjects affected / exposed<br>occurrences (all) | 1 / 12 (8.33%)<br>1 | | |
| Psychiatric disorders | | | |

| | | | |
|---|---|---|---|
| Restlessness | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | | |
| occurrences (all) | 2 | | |
| Irritability | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | | |
| occurrences (all) | 0 | | |
| Insomnia | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | | |
| occurrences (all) | 1 | | |
| Depressed mood | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | | |
| occurrences (all) | 0 | | |
| Investigations | | | |
| Gastrointestinal stoma output increased | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | | |
| occurrences (all) | 0 | | |
| Weight increased | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | | |
| occurrences (all) | 0 | | |
| Weight decreased | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | | |
| occurrences (all) | 0 | | |
| Urine output increased | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | | |
| occurrences (all) | 1 | | |
| Serum ferritin decreased | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | | |
| occurrences (all) | 0 | | |
| International normalised ratio abnormal | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | | |
| occurrences (all) | 1 | | |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | | |
| occurrences (all) | 1 | | |
| Gastrointestinal stoma output decreased | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 12 (8.33%) | | |
| occurrences (all) | 1 | | |
| Injury, poisoning and procedural complications | | | |
| Stoma complication | | | |
| subjects affected / exposed | 6 / 12 (50.00%) | | |
| occurrences (all) | 6 | | |
| Gastrointestinal stoma complication | | | |
| subjects affected / exposed | 6 / 12 (50.00%) | | |
| occurrences (all) | 6 | | |
| Stoma obstruction | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | | |
| occurrences (all) | 0 | | |
| Procedural pain | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | | |
| occurrences (all) | 0 | | |
| Stoma site haemorrhage | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | | |
| occurrences (all) | 0 | | |
| Stoma site oedema | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | | |
| occurrences (all) | 1 | | |
| Stoma site erythema | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | | |
| occurrences (all) | 0 | | |
| Ligament sprain | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | | |
| occurrences (all) | 0 | | |
| Scar | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | | |
| occurrences (all) | 0 | | |
| Excoriation | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | | |
| occurrences (all) | 1 | | |
| Accidental overdose | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 12 (0.00%) | | |
| occurrences (all) | 0 | | |
| Cardiac disorders | | | |
| Tachycardia | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | | |
| occurrences (all) | 1 | | |
| Palpitations | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | | |
| occurrences (all) | 0 | | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | | |
| occurrences (all) | 6 | | |
| Dizziness | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | | |
| occurrences (all) | 0 | | |
| Migraine | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | | |
| occurrences (all) | 2 | | |
| Paraesthesia | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | | |
| occurrences (all) | 2 | | |
| Restless legs syndrome | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | | |
| occurrences (all) | 1 | | |
| Hypoaesthesia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | | |
| occurrences (all) | 0 | | |
| Eye disorders | | | |
| Conjunctival haemorrhage | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | | |
| occurrences (all) | 0 | | |
| Gastrointestinal disorders | | | |
| Nausea | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | | |
| occurrences (all) | 1 | | |
| Abdominal pain | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 12 (16.67%) | | |
| occurrences (all) | 2 | | |
| Gastrointestinal sounds abnormal | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | | |
| occurrences (all) | 1 | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | | |
| occurrences (all) | 1 | | |
| Vomiting | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | | |
| occurrences (all) | 1 | | |
| Abdominal distension | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | | |
| occurrences (all) | 2 | | |
| Dry mouth | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | | |
| occurrences (all) | 0 | | |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | | |
| occurrences (all) | 0 | | |
| Abdominal pain lower | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | | |
| occurrences (all) | 0 | | |
| Abdominal tenderness | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | | |
| occurrences (all) | 0 | | |
| Abdominal discomfort | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | | |
| occurrences (all) | 0 | | |
| Skin and subcutaneous tissue disorders | | | |
| Erythema | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | | |
| occurrences (all) | 0 | | |
| Renal and urinary disorders | | | |
| Polyuria | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 3 / 12 (25.00%) | | |
| occurrences (all) | 3 | | |
| Pollakiuria | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | | |
| occurrences (all) | 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | | |
| occurrences (all) | 2 | | |
| Myalgia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | | |
| occurrences (all) | 0 | | |
| Muscular weakness | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | | |
| occurrences (all) | 0 | | |
| Fistula discharge | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | | |
| occurrences (all) | 0 | | |
| Infections and infestations | | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | | |
| occurrences (all) | 2 | | |
| Influenza | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | | |
| occurrences (all) | 1 | | |
| Infection | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | | |
| occurrences (all) | 0 | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | | |
| occurrences (all) | 0 | | |
| Tooth infection | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | | |
| occurrences (all) | 0 | | |
| Pneumonia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 12 (8.33%) | | |
| occurrences (all) | 1 | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | | |
| occurrences (all) | 1 | | |
| Rhinitis | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | | |
| occurrences (all) | 1 | | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | | |
| occurrences (all) | 1 | | |
| Iron deficiency | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | | |
| occurrences (all) | 1 | | |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | | |
| occurrences (all) | 0 | | |
| Abnormal weight gain | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | | |
| occurrences (all) | 0 | | |
| Vitamin D deficiency | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | | |
| occurrences (all) | 0 | | |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported