



Clinical trial results:

A Phase 2 Randomised, Double Blind, Placebo Controlled, Parallel Group, Multicentre Study to Evaluate the Safety and Efficacy of Repeated Oral Doses of Blautix™ in Adult Subjects with Irritable Bowel Syndrome (IBS) Subtypes IBS-C and IBS-D

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2018-001203-36 |
| Trial protocol | IE GB PL |
| Global end of trial date | 13 May 2020 |

Results information

| | |
|--------------------------------|-------------------|
| Result version number | v1 (current) |
| This version publication date | 24 September 2021 |
| First version publication date | 24 September 2021 |

Trial information

Trial identification

| | |
|-----------------------|------------|
| Sponsor protocol code | BHT-II-002 |
|-----------------------|------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03721107 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | 4D Pharma Plc |
| Sponsor organisation address | 9 Bond Court, Leeds, United Kingdom, LS1 2JZ |
| Public contact | Clinical Trials Department, 4D Pharma Plc, 44 0113895 0130, clinicaltrials@4dpharmapl.com |
| Scientific contact | Clinical Trials Department, 4D Pharma Plc, 44 0113895 0130, clinicaltrials@4dpharmapl.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 | 13 May 2020 |
| Is this the analysis of the primary completion data? | No |

| | |
|----------------------------------|-------------|
| Global end of trial reached? | Yes |
| Global end of trial date | 13 May 2020 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to assess the efficacy of repeated twice daily doses of Blautix > 1*10¹⁰ most probable number (MPN) for 8 weeks in adult subjects with either IBS-C (Cohort C) or IBS-D (Cohort D).

Protection of trial subjects:

The study was conducted in accordance with Good Clinical Practice (GCP) as required by Food and Drug Administration (FDA) regulations, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines, and standard operating procedures (SOPs) for clinical investigation and documentation provided by the sponsor, Parexel and Synteract. Compliance with these requirements also indicates conformity with the ethical principles that have their origins in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

| | |
|---|-----------------|
| Actual start date of recruitment | 11 October 2018 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|---------------------|
| Country: Number of subjects enrolled | United Kingdom: 122 |
| Country: Number of subjects enrolled | Ireland: 7 |
| Country: Number of subjects enrolled | United States: 237 |
| Worldwide total number of subjects | 366 |
| EEA total number of subjects | 7 |

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) | 335 |
| From 65 to 84 years | 31 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

A total of 366 subjects were randomised across 30 study centers in Ireland, United Kingdom, and United States between 11 October 2018 (first subject enrolled) and 13 May 2020 (last subject completed study).

Pre-assignment

Screening details:

Subjects who met the eligibility criteria were randomised to receive Blautix or Placebo in either Cohort C or Cohort D depending on classification of IBS subtype by the study doctor.

Period 1

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

Arms

| | |
|------------------------------|-------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Cohort C: Blautix |

Arm description:

Subjects diagnosed with Irritable Bowel Syndrome Subtype-C (IBS-C) received two capsules of Blautix orally, twice daily for 8 weeks. Maximum daily dose of Blautix (strain of *Blautia hydrogenotrophica*) was 10^{10} to 10^{11} most probable number (MPN).

| | |
|--|---|
| Arm type | Experimental |
| Investigational medicinal product name | Blautix |
| Investigational medicinal product code | MRx1234 |
| Other name | <i>Blautia hydrogenotrophica</i> , DSMZ n°14294 |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects diagnosed with IBS-C received two capsules of Blautix orally, twice daily for 8 weeks.

| | |
|------------------|-------------------|
| Arm title | Cohort C: Placebo |
|------------------|-------------------|

Arm description:

Subjects diagnosed with IBS-C received two capsules of placebo matched to Blautix orally, twice daily for 8 weeks.

| | |
|--|----------|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects diagnosed with IBS-C received two capsules of placebo matched to Blautix orally, twice daily for 8 weeks.

| | |
|------------------|-------------------|
| Arm title | Cohort D: Blautix |
|------------------|-------------------|

Arm description:

Subjects diagnosed with Irritable Bowel Syndrome Subtype-D (IBS-D) received two capsules of Blautix orally, twice daily for 8 weeks. Maximum daily dose of Blautix (strain of *Blautia hydrogenotrophica*) was 10^{10} to 10^{11} MPN.

| | |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

| | |
|---|---|
| Investigational medicinal product name | Blautix |
| Investigational medicinal product code | MRx1234 |
| Other name | Blautia hydrogenotrophica, DSMZ n°14294 |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Subjects diagnosed with IBS-D received two capsules of Blautix orally, twice daily for 8 weeks. | |
| Arm title | Cohort D: Placebo |

Arm description:

Subjects diagnosed with IBS-D received two capsules of placebo matched to Blautix orally, twice daily for 8 weeks.

| | |
|--|----------|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects diagnosed with IBS-D received two capsules of placebo matched to Blautix orally, twice daily for 8 weeks.

| Number of subjects in period 1^[1] | Cohort C: Blautix | Cohort C: Placebo | Cohort D: Blautix |
|---|-------------------|-------------------|-------------------|
| Started | 80 | 84 | 97 |
| Completed | 75 | 81 | 83 |
| Not completed | 5 | 3 | 14 |
| Consent withdrawn by subject | 1 | 1 | 5 |
| Physician decision | - | 1 | - |
| Adverse event, non-fatal | 1 | 1 | 6 |
| Unspecified | 1 | - | - |
| Lost to follow-up | 2 | - | 3 |
| Inclusion/Exclusion Criteria not Met | - | - | - |

| Number of subjects in period 1^[1] | Cohort D: Placebo |
|---|-------------------|
| Started | 104 |
| Completed | 92 |
| Not completed | 12 |
| Consent withdrawn by subject | 5 |
| Physician decision | - |
| Adverse event, non-fatal | 5 |
| Unspecified | 1 |
| Lost to follow-up | - |
| Inclusion/Exclusion Criteria not Met | 1 |

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: A total of 366 subjects were enrolled, out of which 365 subjects were treated and presented in subject disposition and baseline characteristics.

Baseline characteristics

Reporting groups

| | |
|---|-------------------|
| Reporting group title | Cohort C: Blautix |
| Reporting group description: Subjects diagnosed with Irritable Bowel Syndrome Subtype-C (IBS-C) received two capsules of Blautix orally, twice daily for 8 weeks. Maximum daily dose of Blautix (strain of <i>Blautia hydrogenotrophica</i>) was 10^{10} to 10^{11} most probable number (MPN). | |
| Reporting group title | Cohort C: Placebo |
| Reporting group description: Subjects diagnosed with IBS-C received two capsules of placebo matched to Blautix orally, twice daily for 8 weeks. | |
| Reporting group title | Cohort D: Blautix |
| Reporting group description: Subjects diagnosed with Irritable Bowel Syndrome Subtype-D (IBS-D) received two capsules of Blautix orally, twice daily for 8 weeks. Maximum daily dose of Blautix (strain of <i>Blautia hydrogenotrophica</i>) was 10^{10} to 10^{11} MPN. | |
| Reporting group title | Cohort D: Placebo |
| Reporting group description: Subjects diagnosed with IBS-D received two capsules of placebo matched to Blautix orally, twice daily for 8 weeks. | |

| Reporting group values | Cohort C: Blautix | Cohort C: Placebo | Cohort D: Blautix |
|---|-------------------|-------------------|-------------------|
| Number of subjects | 80 | 84 | 97 |
| Age categorical Units: Subjects | | | |
| Age continuous Units: years | | | |
| arithmetic mean | 44.6 | 45.3 | 43.1 |
| standard deviation | ± 13.04 | ± 13.41 | ± 13.65 |
| Gender categorical Units: Subjects | | | |
| Female | 67 | 69 | 60 |
| Male | 13 | 15 | 37 |
| Ethnicity Units: Subjects | | | |
| Hispanic or Latino | 20 | 21 | 10 |
| Not Hispanic or Latino | 60 | 63 | 87 |
| Unknown or Not Reported | 0 | 0 | 0 |
| Race Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | 2 |
| Asian | 1 | 0 | 2 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| Black or African American | 30 | 33 | 7 |
| White | 48 | 50 | 86 |
| More than one race | 0 | 0 | 0 |
| Unknown or Not Reported | 1 | 1 | 0 |

| Reporting group values | Cohort D: Placebo | Total | |
|---|-------------------|-------|--|
| Number of subjects | 104 | 365 | |
| Age categorical Units: Subjects | | | |
| Age continuous Units: years arithmetic mean standard deviation | 44.9 ± 14.40 | - | |
| Gender categorical Units: Subjects | | | |
| Female | 73 | 269 | |
| Male | 31 | 96 | |
| Ethnicity Units: Subjects | | | |
| Hispanic or Latino | 10 | 61 | |
| Not Hispanic or Latino | 94 | 304 | |
| Unknown or Not Reported | 0 | 0 | |
| Race Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 2 | |
| Asian | 1 | 4 | |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | |
| Black or African American | 11 | 81 | |
| White | 90 | 274 | |
| More than one race | 1 | 1 | |
| Unknown or Not Reported | 1 | 3 | |

End points

End points reporting groups

| | |
|---|-------------------|
| Reporting group title | Cohort C: Blautix |
| Reporting group description: Subjects diagnosed with Irritable Bowel Syndrome Subtype-C (IBS-C) received two capsules of Blautix orally, twice daily for 8 weeks. Maximum daily dose of Blautix (strain of <i>Blautia hydrogenotrophica</i>) was 10^{10} to 10^{11} most probable number (MPN). | |
| Reporting group title | Cohort C: Placebo |
| Reporting group description: Subjects diagnosed with IBS-C received two capsules of placebo matched to Blautix orally, twice daily for 8 weeks. | |
| Reporting group title | Cohort D: Blautix |
| Reporting group description: Subjects diagnosed with Irritable Bowel Syndrome Subtype-D (IBS-D) received two capsules of Blautix orally, twice daily for 8 weeks. Maximum daily dose of Blautix (strain of <i>Blautia hydrogenotrophica</i>) was 10^{10} to 10^{11} MPN. | |
| Reporting group title | Cohort D: Placebo |
| Reporting group description: Subjects diagnosed with IBS-D received two capsules of placebo matched to Blautix orally, twice daily for 8 weeks. | |

Primary: Percentage of Subjects With Overall Response

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|---|--|
| End point title | Percentage of Subjects With Overall Response |
| End point description: Overall responder was a subject who has at least 7 evaluable weeks of data and has reported an improvement in their weekly symptoms (abdominal pain intensity [API] and stool frequency [SF] or consistency [SC]) for greater than or equal to (\geq) 50 percent (%) of the treatment period. API: decrease in weekly average of worst abdominal pain in the past 24 hours score of at least 30% compared with baseline for Cohort C and D; SF: increase of 1 or more CSBM per week compared with baseline for Cohort C; SC: decrease at least 50% in the proportion of days per week with at least one stool that has a consistency of Type 6 or 7 compared with baseline for Cohort D. Subjects with <4 weeks available were considered non-responders. Full Analysis Set (FAS): all subjects in the safety analysis set who were appropriately randomized into the study. Here, "Number of subjects analysed" signifies subjects who were evaluable for this endpoint. | |
| End point type | Primary |
| End point timeframe: Baseline up to Week 8 | |

| End point values | Cohort C: Blautix | Cohort C: Placebo | Cohort D: Blautix | Cohort D: Placebo |
|-------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 76 | 82 | 94 | 101 |
| Units: Percentage of subjects | | | | |
| number (not applicable) | 25.0 | 17.1 | 23.4 | 17.8 |

Statistical analyses

| | |
|---|---------------------------------------|
| Statistical analysis title | Cohort C: Blautix, Cohort C: Placebo |
| Comparison groups | Cohort C: Placebo v Cohort C: Blautix |
| Number of subjects included in analysis | 158 |
| Analysis specification | Post-hoc |
| Analysis type | superiority |
| P-value | = 0.152 ^[1] |
| Method | Chi-squared corrected |
| Parameter estimate | Difference in Percentage |
| Point estimate | 7.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -6 |
| upper limit | 21.9 |

Notes:

[1] - P-value is from a 1-sided Pearson chi-square test with Yates' correction with null hypothesis that the difference in proportions Blautix - placebo ≤ 0 versus the difference is > 0 . The significance level for rejection of the null hypotheses is 0.10.

| | |
|---|---------------------------------------|
| Statistical analysis title | Cohort D: Blautix, Cohort D: Placebo |
| Comparison groups | Cohort D: Blautix v Cohort D: Placebo |
| Number of subjects included in analysis | 195 |
| Analysis specification | Post-hoc |
| Analysis type | superiority |
| P-value | = 0.216 ^[2] |
| Method | Chi-squared corrected |
| Parameter estimate | Difference in Percentage |
| Point estimate | 5.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -6.8 |
| upper limit | 18 |

Notes:

[2] - P-value is from a 1-sided Pearson chi-square test with Yates' correction with null hypothesis that the difference in proportions Blautix - placebo ≤ 0 versus the difference is > 0 . The significance level for rejection of the null hypotheses is 0.10.

Secondary: Number of Subjects With Treatment-Related Treatment Emergent Adverse Events (TEAEs)

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|---|---|
| End point title | Number of Subjects With Treatment-Related Treatment Emergent Adverse Events (TEAEs) |
| End point description: | |
| An adverse event (AE) was any untoward medical occurrence in a subject administered study medication and which does not necessarily have a causal relationship with this treatment. TEAE was defined as an AE that started or worsened in severity on or after the start date of the study treatment and includes all AEs recorded through the follow-up visit. A treatment-related TEAE is a TEAE possibly related to the study treatment. Safety analysis set (SAF) included all subjects randomised into the study who received at least one dose of Blautix or Placebo. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline up to follow-up visit (up to Week 14) | |

| End point values | Cohort C: Blautix | Cohort C: Placebo | Cohort D: Blautix | Cohort D: Placebo |
|-----------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 80 | 84 | 97 | 104 |
| Units: Subjects | 5 | 4 | 16 | 14 |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Response to Subject Global Assessment of Relief

| | |
|-----------------|---|
| End point title | Number of Subjects With Response to Subject Global Assessment of Relief |
|-----------------|---|

End point description:

The Subject Global Assessment of Relief was collected weekly through the electronic clinical outcome assessment (eCOA) system. It was a comparison of how the subject has felt over the past week with regards to their IBS to the way they felt before entering the study. It was measured on a 5-point Likert scale with the following responses: Completely relieved; considerably relieved; somewhat relieved; unchanged; worse. The total score ranged from 0-20, where higher scores indicated worsening of condition. FAS included all subjects in the safety analysis set who were appropriately randomised into the study. Here, "number of subjects analysed" signifies subjects who were evaluable for this endpoint.

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

End point timeframe:

Week 1, 4, 8, follow-up visit (Week 12, 13 and 14)

| End point values | Cohort C: Blautix | Cohort C: Placebo | Cohort D: Blautix | Cohort D: Placebo |
|-------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 66 | 70 | 84 | 86 |
| Units: Subjects | | | | |
| Week 1: Completely Relieved | 0 | 2 | 2 | 0 |
| Week 1: Considerably Relieved | 1 | 3 | 1 | 0 |
| Week 1: Somewhat Relieved | 6 | 6 | 3 | 8 |
| Week 1: Unchanged | 58 | 56 | 72 | 76 |
| Week 1: Worse | 1 | 3 | 6 | 2 |
| Week 4: Completely Relieved | 1 | 1 | 2 | 1 |
| Week 4: Considerably Relieved | 13 | 7 | 13 | 14 |
| Week 4: Somewhat Relieved | 31 | 31 | 26 | 24 |
| Week 4: Unchanged | 17 | 19 | 28 | 28 |
| Week 4: Worse | 1 | 5 | 4 | 4 |
| Week 8: Completely Relieved | 2 | 3 | 5 | 3 |
| Week 8: Considerably Relieved | 20 | 13 | 14 | 16 |
| Week 8: Somewhat Relieved | 24 | 23 | 22 | 26 |
| Week 8: Unchanged | 18 | 19 | 21 | 20 |

| | | | | |
|--------------------------------|----|----|----|----|
| Week 8: Worse | 1 | 2 | 6 | 5 |
| Week 12: Completely Relieved | 5 | 5 | 5 | 2 |
| Week 12: Considerably Relieved | 6 | 11 | 10 | 5 |
| Week 12: Somewhat Relieved | 13 | 17 | 14 | 16 |
| Week 12: Unchanged | 14 | 16 | 19 | 24 |
| Week 12: Worse | 2 | 3 | 2 | 5 |
| Week 13: Completely Relieved | 4 | 4 | 4 | 3 |
| Week 13: Considerably Relieved | 9 | 12 | 4 | 3 |
| Week 13: Somewhat Relieved | 12 | 9 | 12 | 14 |
| Week 13: Unchanged | 7 | 12 | 15 | 18 |
| Week 13: Worse | 1 | 4 | 5 | 4 |
| Week 14: Completely Relieved | 2 | 0 | 0 | 1 |
| Week 14: Considerably Relieved | 2 | 2 | 0 | 1 |
| Week 14: Somewhat Relieved | 2 | 1 | 3 | 1 |
| Week 14: Unchanged | 0 | 5 | 8 | 4 |
| Week 14: Worse | 0 | 0 | 0 | 3 |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Stool Consistency Assessed by Bristol Stool Form Scale (BSFS) at Week 1, 4, 8, Follow-up Visit (Week 12, 13 and 14)

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|-----------------|---|
| End point title | Change From Baseline in Stool Consistency Assessed by Bristol Stool Form Scale (BSFS) at Week 1, 4, 8, Follow-up Visit (Week 12, 13 and 14) |
|-----------------|---|

End point description:

Stool consistency of each bowel movement was assessed by subjects using the 7-point BSFS from 1 to 7 where Type 1 = separate hard lumps, like nuts (hard to pass), Type 2 = sausage-shaped but lumpy, Type 3 = like a sausage but with cracks on the surface, Type 4 = like a sausage or snake, smooth and soft, Type 5 = soft blobs with clear-cut edges (passed easily), Type 6 = fluffy pieces with ragged edges, a mushy stool, Type 7 = watery, no solid pieces; entirely liquid. A score of 1 or 2 indicates constipation and a score of 6 or 7 indicates diarrhea. FAS included all subjects in the safety analysis set who were appropriately randomised into the study. Here, "number of subjects analysed" signifies subjects who were evaluable for this endpoint and "n=number analysed" signifies subjects who were evaluable at specified time points.

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

End point timeframe:

Baseline, Week 1, 4, 8, follow-up visit (Week 12, 13 and 14)

| End point values | Cohort C: Blautix | Cohort C: Placebo | Cohort D: Blautix | Cohort D: Placebo |
|--------------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 64 | 73 | 83 | 94 |
| Units: Score on a Scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Change at Week 1 (n=64, 73, 83, 94) | 0.13 (± 22.859) | 3.38 (± 24.412) | -25.67 (± 28.078) | -23.70 (± 30.730) |
| Change at Week 4 (n=57, 63, 74, 76) | -4.23 (± 24.470) | -1.99 (± 24.077) | -32.43 (± 33.627) | -33.73 (± 33.615) |

| | | | | |
|--------------------------------------|------------------|------------------|-------------------|-------------------|
| Change at Week 8 (n=53, 56, 67, 70) | -5.93 (± 26.705) | -0.10 (± 22.852) | -40.36 (± 37.595) | -36.91 (± 35.753) |
| Change at Week 12 (n=33, 46, 51, 57) | -5.66 (± 23.063) | 1.06 (± 27.027) | -34.09 (± 41.128) | -42.13 (± 31.500) |
| Change at Week 13 (n=7, 15, 17, 25) | 10.88 (± 26.517) | -5.16 (± 19.868) | -29.38 (± 35.002) | -32.21 (± 39.679) |
| Change at Week 14 (n=2, 2, 4, 6) | -15.48 (± 1.684) | -2.98 (± 15.994) | -40.00 (± 36.216) | -38.10 (± 36.608) |

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Stool Consistency Assessed by Bristol Stool Form Scale (BSFS) at Week 1, 4, 8, Follow-up Visit (Week 12, 13 and 14)

| | |
|-----------------|---|
| End point title | Percent Change From Baseline in Stool Consistency Assessed by Bristol Stool Form Scale (BSFS) at Week 1, 4, 8, Follow-up Visit (Week 12, 13 and 14) |
|-----------------|---|

End point description:

Stool consistency of each bowel movement was assessed by subjects using the 7-point BSFS from 1 to 7 where Type 1 = separate hard lumps, like nuts (hard to pass), Type 2 = sausage-shaped but lumpy, Type 3 = like a sausage but with cracks on the surface, Type 4 = like a sausage or snake, smooth and soft, Type 5 = soft blobs with clear-cut edges (passed easily), Type 6 = fluffy pieces with ragged edges, a mushy stool, Type 7 = watery, no solid pieces; entirely liquid. A score of 1 or 2 indicates constipation and a score of 6 or 7 indicates diarrhea. Lower numbers represented more formed stools and higher numbers represented less formed stools. FAS included all subjects in the safety analysis set who were appropriately randomised into the study. Here, "number of subjects analysed" signifies subjects who were evaluable for this endpoint and "n=number analysed" signifies subjects who were evaluable at specified time points.

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

End point timeframe:

Baseline, Week 1, 4, 8, follow-up visit (Week 12, 13 and 14)

| End point values | Cohort C: Blautix | Cohort C: Placebo | Cohort D: Blautix | Cohort D: Placebo |
|--|--------------------|--------------------|-------------------|-------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 63 | 70 | 83 | 94 |
| Units: Percent Change | | | | |
| arithmetic mean (standard deviation) | | | | |
| Percent Change at Week 1 (n=63, 70, 83, 94) | 15.05 (± 126.940) | 27.65 (± 129.217) | -32.30 (± 36.887) | -27.27 (± 38.590) |
| Percent Change at Week 4 (n=57, 61, 74, 76) | -6.36 (± 122.165) | -7.18 (± 112.425) | -40.14 (± 42.757) | -40.60 (± 40.128) |
| Percent Change at Week 8 (n=52, 54, 67, 70) | -12.00 (± 145.174) | -4.64 (± 103.202) | -49.32 (± 45.798) | -42.64 (± 39.801) |
| Percent Change at Week 12 (n=33, 44, 51, 57) | -7.45 (± 125.537) | 14.75 (± 144.064) | -36.96 (± 50.023) | -49.94 (± 34.638) |
| Percent Change at Week 13 (n=7, 14, 17, 25) | 41.07 (± 143.017) | -40.31 (± 89.914) | -33.29 (± 40.067) | -35.91 (± 44.635) |
| Percent Change at Week 14 (n=2, 2, 4, 6) | -100.00 (± 0.000) | -25.00 (± 106.066) | -52.50 (± 49.319) | -43.53 (± 44.353) |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Weekly Average Stool Frequency Assessed by Bristol Stool Form Scale (BSFS) at Week 1, 4, 8, Follow-up Visit (Week 12, 13 and 14)

| | |
|-----------------|--|
| End point title | Change From Baseline in Weekly Average Stool Frequency Assessed by Bristol Stool Form Scale (BSFS) at Week 1, 4, 8, Follow-up Visit (Week 12, 13 and 14) |
|-----------------|--|

End point description:

Stool frequency was defined as a sum of weekly CSBMs. Stool types were assessed using the 7-point BSFS where 1 = separate hard lumps, like nuts, 2 = sausage-shaped but lumpy, 3 = like a sausage but with cracks on the surface, 4 = like a sausage or snake, smooth and soft, 5 = soft blobs with clear-cut edges, 6 = fluffy pieces with ragged edges, a mushy stool, 7 = watery, no solid pieces; entirely liquid. Score of 1 or 2 indicates constipation and 6 or 7 indicates diarrhea. Weekly stool frequency based on the daily stool frequency (DSF) which was calculated as follows: if there was 1 or more entry for BSC, the number of BSC entries was summed up. If on that day laxative was used, daily stool frequency was set to 0. If an answer to CSBMs, but no BSC entry was provided, the DSF was set to 0 on that day. FAS Analysis. "Number of subjects analysed" signifies subjects were evaluable for this endpoint; "n=number analysed" signifies subjects were evaluable at specified time point.

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

End point timeframe:

Baseline, Week 1, 4, 8, follow-up visit (Week 12, 13 and 14)

| End point values | Cohort C: Blautix | Cohort C: Placebo | Cohort D: Blautix | Cohort D: Placebo |
|--------------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 64 | 73 | 83 | 94 |
| Units: Score on a Scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Change at Week 1 (n=64, 73, 83, 94) | 1.33 (± 2.202) | 1.61 (± 2.416) | -1.07 (± 2.441) | -1.02 (± 3.119) |
| Change at Week 4 (n=57, 63, 74, 76) | 2.14 (± 2.348) | 1.87 (± 2.809) | -1.60 (± 2.543) | -1.83 (± 3.389) |
| Change at Week 8 (n=53, 56, 67, 70) | 2.00 (± 2.289) | 2.42 (± 2.751) | -2.59 (± 3.012) | -1.97 (± 3.048) |
| Change at Week 12 (n=33, 46, 51, 57) | 1.76 (± 2.547) | 2.18 (± 2.762) | -2.29 (± 2.599) | -2.43 (± 3.299) |
| Change at Week 13 (n=7, 15, 17, 25) | 2.09 (± 2.489) | 1.98 (± 2.539) | -2.05 (± 3.242) | -1.77 (± 2.804) |
| Change at Week 14 (n=2, 2, 4, 6) | 2.56 (± 0.507) | 1.19 (± 0.860) | -4.71 (± 2.626) | -3.54 (± 4.063) |

Statistical analyses

Secondary: Change From Baseline in IBS Quality of Life (IBS-QOL) Questionnaire Subscale and Total Scores at Week 4, 8, and Follow-up Visit (Weeks 12-14)

| | |
|-----------------|---|
| End point title | Change From Baseline in IBS Quality of Life (IBS-QOL) Questionnaire Subscale and Total Scores at Week 4, 8, and Follow-up Visit (Weeks 12-14) |
|-----------------|---|

End point description:

Subjects were asked to complete a QOL questionnaire of 34 items each with an individual 5-point response on an ordinal scale. Responses to these items were summed and averaged for a total score (TS) and then transformed to a 100-point scale for ease of interpretation. Sub-scales included dysphoria score (DS [8 items]), interference of activity (IAS [7 items]), body image (BIS [4 items]), health worry (HWS [3 items]), food avoidance (FAS [3 items]), social reaction (SRS [4 items]), sexual (SS [2 items]) and relationship (RS [3 items]) were numbered as 1-5 with: 1 = not at all, 2 = slightly, 3 = moderately, 4 = quite a bit, 5 = extremely or a great deal. IBS-QOL was measured on a scale range of 0-100 with (0=worst; 100=better). Higher scores indicates better IBS-specific quality of life. FAS analysis population. Here, "number of subjects analysed" signifies subjects who were evaluable for this endpoint; "n=number analysed" signifies subjects who were evaluable at specified time points.

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

End point timeframe:

Baseline, Week 4, 8, follow-up visit (Week 12-14)

| End point values | Cohort C: Blautix | Cohort C: Placebo | Cohort D: Blautix | Cohort D: Placebo |
|--|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 41 | 41 | 47 | 64 |
| Units: Score on a Scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Change at Week 4: TS (n=41, 41, 45, 64) | 5.67 (± 16.858) | 5.79 (± 21.908) | 5.62 (± 18.087) | 5.93 (± 13.113) |
| Change at Week 4: DS (n=41, 41, 45, 64) | 5.95 (± 20.561) | 5.34 (± 22.881) | 9.17 (± 22.627) | 5.81 (± 17.429) |
| Change at Week 4: IAS (n=41, 41, 45, 64) | 4.79 (± 16.952) | 6.71 (± 22.633) | 7.54 (± 18.230) | 8.26 (± 16.008) |
| Change at Week 4: BIS (n=41, 41, 45, 64) | 4.88 (± 23.779) | 7.62 (± 23.239) | 5.83 (± 20.703) | 4.10 (± 17.860) |
| Change at Week 4: HWS (n=41, 41, 45, 64) | 10.98 (± 23.082) | 10.57 (± 26.940) | 6.85 (± 19.727) | 7.55 (± 19.056) |
| Change at Week 4: FAS (n=41, 41, 45, 64) | 6.50 (± 20.625) | 4.88 (± 29.461) | 5.56 (± 19.624) | 7.55 (± 19.960) |
| Change at Week 4: SRS (n=41, 41, 45, 64) | 4.12 (± 16.922) | 2.44 (± 24.402) | 0.42 (± 23.963) | 6.64 (± 14.935) |
| Change at Week 4: SS (n=41, 41, 45, 64) | 7.32 (± 29.445) | 1.52 (± 24.716) | -0.56 (± 20.288) | 0.39 (± 19.284) |
| Change at Week 4: RS (n=41, 41, 45, 64) | 2.85 (± 21.214) | 5.89 (± 26.170) | 1.30 (± 23.500) | 2.73 (± 17.509) |
| Change at Week 8: TS (n=38, 35, 47, 53) | 12.27 (± 20.969) | 8.09 (± 18.318) | 11.89 (± 20.933) | 8.37 (± 18.043) |
| Change at Week 8: DS (n=38, 35, 47, 53) | 13.40 (± 21.044) | 7.59 (± 20.085) | 14.23 (± 26.241) | 12.21 (± 20.403) |
| Change at Week 8: IAS (n=38, 35, 47, 53) | 10.15 (± 26.120) | 10.31 (± 21.529) | 15.12 (± 22.944) | 8.96 (± 20.247) |
| Change at Week 8: BIS (n=38, 35, 47, 53) | 12.83 (± 22.696) | 8.93 (± 18.890) | 13.70 (± 22.217) | 7.43 (± 23.096) |
| Change at Week 8: HWS (n=38, 35, 47, 53) | 17.32 (± 27.834) | 12.38 (± 22.810) | 7.80 (± 22.947) | 7.23 (± 19.614) |

| | | | | |
|---|------------------|------------------|------------------|------------------|
| Change at Week 8: FAS (n=38, 35, 47, 53) | 17.54 (± 27.522) | 7.38 (± 29.412) | 14.01 (± 22.327) | 6.60 (± 24.534) |
| Change at Week 8: SRS (n=38, 35, 47, 53) | 10.69 (± 21.401) | 3.21 (± 17.960) | 8.78 (± 24.473) | 7.55 (± 20.669) |
| Change at Week 8: SS (n=38, 35, 47, 53) | 10.53 (± 24.406) | 3.57 (± 22.600) | 3.46 (± 26.797) | 3.30 (± 26.420) |
| Change at Week 8: RS (n=38, 35, 47, 53) | 6.36 (± 19.800) | 9.05 (± 22.721) | 7.45 (± 21.858) | 5.35 (± 20.155) |
| Change at Follow-up: TS (n=34, 36, 37, 38) | 15.55 (± 21.368) | 8.09 (± 16.647) | 7.93 (± 23.919) | 10.80 (± 19.950) |
| Change at Follow-up: DS (n=34, 36, 37, 38) | 15.99 (± 23.957) | 8.07 (± 17.236) | 10.47 (± 30.336) | 11.43 (± 21.236) |
| Change at Follow-up: IAS (n=34, 36, 37, 38) | 14.50 (± 23.195) | 12.00 (± 21.278) | 9.75 (± 25.417) | 14.94 (± 26.243) |
| Change at Follow-up: BIS (n=34, 36, 37, 38) | 17.10 (± 21.777) | 9.38 (± 17.772) | 8.95 (± 24.409) | 9.38 (± 25.200) |
| Change at Follow-up: HWS (n=34, 36, 37, 38) | 19.36 (± 28.701) | 9.26 (± 23.382) | 10.14 (± 23.663) | 14.25 (± 18.371) |
| Change at Follow-up: FAS (n=34, 36, 37, 38) | 16.91 (± 23.524) | 9.72 (± 21.776) | 7.43 (± 24.594) | 9.21 (± 26.408) |
| Change at Follow-up: SRS (n=34, 36, 37, 38) | 13.79 (± 24.942) | 1.04 (± 15.917) | 6.59 (± 27.676) | 9.38 (± 23.554) |
| Change at Follow-up: SS (n=34, 36, 37, 38) | 15.07 (± 26.253) | 3.13 (± 23.599) | -1.69 (± 27.507) | 4.93 (± 25.425) |
| Change at Follow-up: RS (n=34, 36, 37, 38) | 12.25 (± 22.774) | 7.18 (± 22.900) | 2.03 (± 24.799) | 5.26 (± 22.041) |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in IBS Symptom Severity Score (IBS-SSS) at Week 4, 8 and Follow-up Visit (Weeks 12-14)

| | |
|-----------------|---|
| End point title | Change From Baseline in IBS Symptom Severity Score (IBS-SSS) at Week 4, 8 and Follow-up Visit (Weeks 12-14) |
|-----------------|---|

End point description:

Subjects were asked to complete a questionnaire on the severity of abdominal distension and pain, frequency of abdominal pain, dissatisfaction with bowel habits, and interference of IBS symptoms with daily life. The IBS-SSS was measured on a Visual Analog Scale (VAS scale) in combination with reported numeric values which equated to an overall score. The scale range was from 0 (no symptoms) to 500 (maximum severity). Subjects were categorized as having mild (74-174), moderate (175-299), or severe (greater than [$>$] 300) IBS symptoms based on symptomology. Higher scores were indicative of greater disease severity (worse outcome). FAS included all subjects in the safety analysis set who were appropriately randomised into the study. Here, "number of subjects analysed" signifies subjects who were evaluable for this endpoint and "n=number analysed" signifies subjects who were evaluable at specified time points.

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

End point timeframe:

Baseline, Week 4, 8, follow-up visit (Week 12-14)

| End point values | Cohort C: Blautix | Cohort C: Placebo | Cohort D: Blautix | Cohort D: Placebo |
|--|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 77 | 81 | 83 | 93 |
| Units: Score on a Scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Change at Week 4 (n=77, 81, 83, 93) | -128.87 (± 143.885) | -141.30 (± 139.439) | -125.75 (± 135.258) | -100.97 (± 114.939) |
| Change at Week 8 (n=73, 79, 81, 85) | -168.46 (± 157.300) | -173.53 (± 155.253) | -143.55 (± 143.781) | -133.63 (± 139.290) |
| Change at Follow up visit (n=77, 80, 83, 90) | -142.49 (± 149.678) | -160.66 (± 150.174) | -113.47 (± 135.064) | -104.76 (± 146.447) |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Hospital Anxiety and Depression (HADS) Total Score at Week 4, 8 and Follow-up Visit (Weeks 12-14)

| | |
|-----------------|---|
| End point title | Change From Baseline in Hospital Anxiety and Depression (HADS) Total Score at Week 4, 8 and Follow-up Visit (Weeks 12-14) |
|-----------------|---|

End point description:

Subjects were asked to complete the HADS which was a 14-item scale that generated ordinal data. Seven of the items were related to anxiety and seven were related to depression. Each item on the questionnaire was scored from 0-3 which means that a subject total score (TS) ranges from 0 and 21 each are derived by summing the individual scores under each category for anxiety or depression. Total Scores are interpreted as: 0-7 = Normal, 8-10 = Borderline abnormal and 11-21 = Abnormal. Higher HADS scores were indicative of more severe depression and anxiety. FAS included all subjects in the safety analysis set who were appropriately randomised into the study. Here, "number of subjects analysed" signifies subjects who were evaluable for this endpoint and "n=number analysed" signifies subjects who were evaluable at specified time points.

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

End point timeframe:

Baseline, Week 4, 8, follow-up visit (Week 12-14)

| End point values | Cohort C: Blautix | Cohort C: Placebo | Cohort D: Blautix | Cohort D: Placebo |
|--|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 41 | 41 | 47 | 64 |
| Units: Score on a Scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Change at Week 4: Anxiety TS (n=41, 41, 45, 64) | -0.02 (± 2.612) | 0.22 (± 2.954) | 0.09 (± 2.827) | -0.27 (± 3.243) |
| Change at Week 4: Depression TS (n=41, 41, 45, 64) | 0.24 (± 3.527) | -0.29 (± 3.303) | 0.22 (± 2.566) | 0.00 (± 2.410) |
| Change at Week 8: Anxiety TS (n=38, 35, 47, 53) | 0.08 (± 2.981) | -0.09 (± 3.320) | -0.32 (± 3.251) | -0.40 (± 3.213) |
| Change at Week 8: Depression TS (n=38, 35, 47, 53) | -0.18 (± 3.432) | -0.06 (± 3.556) | 0.19 (± 2.787) | -0.36 (± 3.169) |
| Change at Follow-up: Anxiety TS (n=34, 36, 37, 38) | -0.53 (± 3.360) | 0.06 (± 2.714) | -0.14 (± 3.029) | -0.55 (± 3.375) |

| | | | | |
|--|--------------------|--------------------|----------------|--------------------|
| Change at Follow-up: Depression TS(n=34,36,37,38) | -0.85 (± 3.735) | -0.14 (± 2.939) | 0.51 (± 3.024) | -0.68 (± 2.886) |
|--|--------------------|--------------------|----------------|--------------------|

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to follow-up visit (up to Week 14)

Adverse event reporting additional description:

SAF included all subjects randomized into the study who received at least one dose of Blautix or Placebo.

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 23.0 |

Reporting groups

| | |
|-----------------------|-------------------|
| Reporting group title | Cohort C: Blautix |
|-----------------------|-------------------|

Reporting group description:

Subjects diagnosed with IBS-C received two capsules of Blautix orally, twice daily for 8 weeks. Maximum daily dose of Blautix (strain of *Blautia hydrogenotrophica*) was 10^{10} to 10^{11} MPN.

| | |
|-----------------------|-------------------|
| Reporting group title | Cohort C: Placebo |
|-----------------------|-------------------|

Reporting group description:

Subjects diagnosed with IBS-C received two capsules of placebo matched to Blautix orally, twice daily for 8 weeks.

| | |
|-----------------------|-------------------|
| Reporting group title | Cohort D: Blautix |
|-----------------------|-------------------|

Reporting group description:

Subjects diagnosed with IBS-D received two capsules of Blautix orally, twice daily for 8 weeks. Maximum daily dose of Blautix (strain of *Blautia hydrogenotrophica*) was 10^{10} to 10^{11} MPN.

| | |
|-----------------------|-------------------|
| Reporting group title | Cohort D: Placebo |
|-----------------------|-------------------|

Reporting group description:

Subjects diagnosed with IBS-D received two capsules of placebo matched to Blautix orally, twice daily for 8 weeks.

| Serious adverse events | Cohort C: Blautix | Cohort C: Placebo | Cohort D: Blautix |
|---|-------------------|-------------------|-------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 84 (0.00%) | 1 / 97 (1.03%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Cardiac disorders | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 84 (0.00%) | 1 / 97 (1.03%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Cellulitis | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 84 (0.00%) | 0 / 97 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-------------------|--|--|
| Serious adverse events | Cohort D: Placebo | | |
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 104 (0.96%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |
| Cardiac disorders | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 104 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Cellulitis | | | |
| subjects affected / exposed | 1 / 104 (0.96%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| | | | |
|---|-------------------|-------------------|-------------------|
| Non-serious adverse events | Cohort C: Blautix | Cohort C: Placebo | Cohort D: Blautix |
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 17 / 80 (21.25%) | 19 / 84 (22.62%) | 41 / 97 (42.27%) |
| Vascular disorders | | | |
| Hot flush | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 84 (0.00%) | 1 / 97 (1.03%) |
| occurrences (all) | 0 | 0 | 1 |
| Hypertension | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 0 / 84 (0.00%) | 0 / 97 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| General disorders and administration site conditions | | | |
| Chest pain | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 84 (0.00%) | 1 / 97 (1.03%) |
| occurrences (all) | 0 | 0 | 1 |

| | | | |
|---|---------------------|---------------------|---------------------|
| Early satiety subjects affected / exposed occurrences (all) | 0 / 80 (0.00%) 0 | 0 / 84 (0.00%) 0 | 1 / 97 (1.03%) 1 |
| Fatigue subjects affected / exposed occurrences (all) | 0 / 80 (0.00%) 0 | 3 / 84 (3.57%) 3 | 0 / 97 (0.00%) 0 |
| Influenza like illness subjects affected / exposed occurrences (all) | 0 / 80 (0.00%) 0 | 0 / 84 (0.00%) 0 | 1 / 97 (1.03%) 1 |
| Thirst subjects affected / exposed occurrences (all) | 0 / 80 (0.00%) 0 | 0 / 84 (0.00%) 0 | 0 / 97 (0.00%) 0 |
| Reproductive system and breast disorders Breast mass subjects affected / exposed occurrences (all) | 0 / 80 (0.00%) 0 | 1 / 84 (1.19%) 1 | 0 / 97 (0.00%) 0 |
| Postmenopausal haemorrhage subjects affected / exposed occurrences (all) | 0 / 80 (0.00%) 0 | 0 / 84 (0.00%) 0 | 1 / 97 (1.03%) 1 |
| Respiratory, thoracic and mediastinal disorders Asthma subjects affected / exposed occurrences (all) | 0 / 80 (0.00%) 0 | 0 / 84 (0.00%) 0 | 0 / 97 (0.00%) 0 |
| Cough subjects affected / exposed occurrences (all) | 0 / 80 (0.00%) 0 | 0 / 84 (0.00%) 0 | 1 / 97 (1.03%) 1 |
| Oropharyngeal pain subjects affected / exposed occurrences (all) | 0 / 80 (0.00%) 0 | 0 / 84 (0.00%) 0 | 2 / 97 (2.06%) 2 |
| Rhinitis allergic subjects affected / exposed occurrences (all) | 0 / 80 (0.00%) 0 | 0 / 84 (0.00%) 0 | 0 / 97 (0.00%) 0 |
| Psychiatric disorders Anxiety subjects affected / exposed occurrences (all) | 0 / 80 (0.00%) 0 | 1 / 84 (1.19%) 1 | 0 / 97 (0.00%) 0 |

| | | | |
|--|----------------|----------------|----------------|
| Insomnia | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 84 (0.00%) | 2 / 97 (2.06%) |
| occurrences (all) | 0 | 0 | 2 |
| Irritability | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 84 (0.00%) | 1 / 97 (1.03%) |
| occurrences (all) | 0 | 0 | 1 |
| Post-traumatic stress disorder | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 84 (0.00%) | 1 / 97 (1.03%) |
| occurrences (all) | 0 | 0 | 1 |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 84 (0.00%) | 0 / 97 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| C-reactive protein increased | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 84 (0.00%) | 0 / 97 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 84 (0.00%) | 0 / 97 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 1 / 84 (1.19%) | 0 / 97 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| White blood cell count decreased | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 1 / 84 (1.19%) | 0 / 97 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Injury, poisoning and procedural complications | | | |
| Ankle fracture | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 0 / 84 (0.00%) | 0 / 97 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Ligament sprain | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 0 / 84 (0.00%) | 1 / 97 (1.03%) |
| occurrences (all) | 1 | 0 | 1 |
| Muscle strain | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 84 (0.00%) | 0 / 97 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Post-traumatic pain | | | |

| | | | |
|--------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 84 (0.00%) | 0 / 97 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Radius fracture | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 84 (0.00%) | 0 / 97 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Road traffic accident | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 84 (0.00%) | 0 / 97 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Sunburn | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 84 (0.00%) | 1 / 97 (1.03%) |
| occurrences (all) | 0 | 0 | 1 |
| Thermal burn | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 84 (0.00%) | 1 / 97 (1.03%) |
| occurrences (all) | 0 | 0 | 1 |
| Wrist fracture | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 84 (0.00%) | 0 / 97 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Cardiac disorders | | | |
| Palpitations | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 84 (0.00%) | 1 / 97 (1.03%) |
| occurrences (all) | 0 | 0 | 1 |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 1 / 84 (1.19%) | 0 / 97 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Headache | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 2 / 84 (2.38%) | 4 / 97 (4.12%) |
| occurrences (all) | 1 | 2 | 4 |
| Hypoaesthesia | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 84 (0.00%) | 1 / 97 (1.03%) |
| occurrences (all) | 0 | 0 | 1 |
| Tremor | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 84 (0.00%) | 1 / 97 (1.03%) |
| occurrences (all) | 0 | 0 | 1 |
| Blood and lymphatic system disorders | | | |

| | | | |
|--|---------------------|---------------------|---------------------|
| Normocytic anaemia subjects affected / exposed occurrences (all) | 1 / 80 (1.25%) 1 | 0 / 84 (0.00%) 0 | 0 / 97 (0.00%) 0 |
| Thrombocytosis subjects affected / exposed occurrences (all) | 0 / 80 (0.00%) 0 | 1 / 84 (1.19%) 1 | 0 / 97 (0.00%) 0 |
| Ear and labyrinth disorders Tinnitus subjects affected / exposed occurrences (all) | 0 / 80 (0.00%) 0 | 0 / 84 (0.00%) 0 | 0 / 97 (0.00%) 0 |
| Gastrointestinal disorders Abdominal distension subjects affected / exposed occurrences (all) | 0 / 80 (0.00%) 0 | 0 / 84 (0.00%) 0 | 0 / 97 (0.00%) 0 |
| Abdominal pain subjects affected / exposed occurrences (all) | 2 / 80 (2.50%) 2 | 1 / 84 (1.19%) 1 | 2 / 97 (2.06%) 2 |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 0 / 80 (0.00%) 0 | 0 / 84 (0.00%) 0 | 1 / 97 (1.03%) 1 |
| Abnormal faeces subjects affected / exposed occurrences (all) | 0 / 80 (0.00%) 0 | 0 / 84 (0.00%) 0 | 0 / 97 (0.00%) 0 |
| Anal fissure subjects affected / exposed occurrences (all) | 0 / 80 (0.00%) 0 | 0 / 84 (0.00%) 0 | 0 / 97 (0.00%) 0 |
| Anorectal discomfort subjects affected / exposed occurrences (all) | 0 / 80 (0.00%) 0 | 0 / 84 (0.00%) 0 | 0 / 97 (0.00%) 0 |
| Constipation subjects affected / exposed occurrences (all) | 0 / 80 (0.00%) 0 | 1 / 84 (1.19%) 1 | 1 / 97 (1.03%) 1 |
| Diarrhoea subjects affected / exposed occurrences (all) | 1 / 80 (1.25%) 1 | 0 / 84 (0.00%) 0 | 5 / 97 (5.15%) 5 |
| Dyspepsia | | | |

| | | | |
|----------------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 84 (0.00%) | 3 / 97 (3.09%) |
| occurrences (all) | 0 | 0 | 3 |
| Flatulence | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 84 (0.00%) | 1 / 97 (1.03%) |
| occurrences (all) | 0 | 0 | 1 |
| Frequent bowel movements | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 84 (0.00%) | 0 / 97 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastritis | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 84 (0.00%) | 1 / 97 (1.03%) |
| occurrences (all) | 0 | 0 | 1 |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 2 / 84 (2.38%) | 0 / 97 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Glossodynia | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 84 (0.00%) | 0 / 97 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Haemorrhoids | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 2 / 84 (2.38%) | 0 / 97 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Haemorrhoids thrombosed | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 84 (0.00%) | 0 / 97 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Irritable bowel syndrome | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 84 (0.00%) | 3 / 97 (3.09%) |
| occurrences (all) | 0 | 0 | 3 |
| Nausea | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 84 (0.00%) | 1 / 97 (1.03%) |
| occurrences (all) | 0 | 0 | 1 |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 84 (0.00%) | 1 / 97 (1.03%) |
| occurrences (all) | 0 | 0 | 1 |
| Toothache | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 0 / 84 (0.00%) | 0 / 97 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Vomiting | | | |

| | | | |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 1 / 80 (1.25%) 1 | 0 / 84 (0.00%) 0 | 1 / 97 (1.03%) 1 |
| Skin and subcutaneous tissue disorders | | | |
| Brachioradial pruritus | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 0 / 84 (0.00%) | 0 / 97 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Dermatitis contact | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 1 / 84 (1.19%) | 0 / 97 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Rash | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 84 (0.00%) | 0 / 97 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rash macular | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 84 (0.00%) | 0 / 97 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Renal and urinary disorders | | | |
| Dysuria | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 1 / 84 (1.19%) | 0 / 97 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Haematuria | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 1 / 84 (1.19%) | 0 / 97 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Pollakiuria | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 84 (0.00%) | 1 / 97 (1.03%) |
| occurrences (all) | 0 | 0 | 1 |
| Urine odour abnormal | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 84 (0.00%) | 0 / 97 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthritis | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 84 (0.00%) | 0 / 97 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Back pain | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 84 (0.00%) | 1 / 97 (1.03%) |
| occurrences (all) | 0 | 0 | 1 |
| Musculoskeletal pain | | | |

| | | | |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 84 (0.00%) | 1 / 97 (1.03%) |
| occurrences (all) | 0 | 0 | 1 |
| Neck pain | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 1 / 84 (1.19%) | 0 / 97 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 84 (0.00%) | 1 / 97 (1.03%) |
| occurrences (all) | 0 | 0 | 1 |
| Rotator cuff syndrome | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 0 / 84 (0.00%) | 0 / 97 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Infections and infestations | | | |
| Acute sinusitis | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 84 (0.00%) | 0 / 97 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 1 / 84 (1.19%) | 0 / 97 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 84 (0.00%) | 0 / 97 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Ear infection | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 84 (0.00%) | 0 / 97 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 1 / 84 (1.19%) | 4 / 97 (4.12%) |
| occurrences (all) | 0 | 1 | 4 |
| Herpes zoster | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 84 (0.00%) | 1 / 97 (1.03%) |
| occurrences (all) | 0 | 0 | 1 |
| Influenza | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 0 / 84 (0.00%) | 1 / 97 (1.03%) |
| occurrences (all) | 1 | 0 | 1 |
| Lice infestation | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 84 (0.00%) | 0 / 97 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|---|---------------------|---------------------|---------------------|
| Lower respiratory tract infection subjects affected / exposed occurrences (all) | 0 / 80 (0.00%) 0 | 0 / 84 (0.00%) 0 | 0 / 97 (0.00%) 0 |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 2 / 80 (2.50%) 2 | 1 / 84 (1.19%) 1 | 5 / 97 (5.15%) 5 |
| Oral herpes subjects affected / exposed occurrences (all) | 0 / 80 (0.00%) 0 | 0 / 84 (0.00%) 0 | 1 / 97 (1.03%) 1 |
| Otitis media subjects affected / exposed occurrences (all) | 0 / 80 (0.00%) 0 | 0 / 84 (0.00%) 0 | 0 / 97 (0.00%) 0 |
| Pharyngitis subjects affected / exposed occurrences (all) | 0 / 80 (0.00%) 0 | 0 / 84 (0.00%) 0 | 1 / 97 (1.03%) 1 |
| Rhinitis subjects affected / exposed occurrences (all) | 0 / 80 (0.00%) 0 | 0 / 84 (0.00%) 0 | 1 / 97 (1.03%) 1 |
| Sinusitis subjects affected / exposed occurrences (all) | 0 / 80 (0.00%) 0 | 1 / 84 (1.19%) 1 | 0 / 97 (0.00%) 0 |
| Tonsillitis subjects affected / exposed occurrences (all) | 0 / 80 (0.00%) 0 | 0 / 84 (0.00%) 0 | 1 / 97 (1.03%) 1 |
| Tooth infection subjects affected / exposed occurrences (all) | 0 / 80 (0.00%) 0 | 0 / 84 (0.00%) 0 | 1 / 97 (1.03%) 1 |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 4 / 80 (5.00%) 4 | 3 / 84 (3.57%) 3 | 3 / 97 (3.09%) 3 |
| Urinary tract infection subjects affected / exposed occurrences (all) | 0 / 80 (0.00%) 0 | 1 / 84 (1.19%) 1 | 1 / 97 (1.03%) 1 |
| Vaginal infection subjects affected / exposed occurrences (all) | 0 / 80 (0.00%) 0 | 1 / 84 (1.19%) 1 | 0 / 97 (0.00%) 0 |

| | | | |
|---|----------------|----------------|----------------|
| Viral infection | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 84 (0.00%) | 0 / 97 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Viral rhinitis | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 84 (0.00%) | 0 / 97 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 84 (0.00%) | 1 / 97 (1.03%) |
| occurrences (all) | 0 | 0 | 1 |
| Vulvovaginal candidiasis | | | |
| subjects affected / exposed | 2 / 80 (2.50%) | 1 / 84 (1.19%) | 0 / 97 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Vulvovaginal mycotic infection | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 84 (0.00%) | 0 / 97 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Metabolism and nutrition disorders | | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 1 / 84 (1.19%) | 0 / 97 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |

| | | | |
|---|-------------------|--|--|
| Non-serious adverse events | Cohort D: Placebo | | |
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 43 / 104 (41.35%) | | |
| Vascular disorders | | | |
| Hot flush | | | |
| subjects affected / exposed | 1 / 104 (0.96%) | | |
| occurrences (all) | 1 | | |
| Hypertension | | | |
| subjects affected / exposed | 0 / 104 (0.00%) | | |
| occurrences (all) | 0 | | |
| General disorders and administration site conditions | | | |
| Chest pain | | | |
| subjects affected / exposed | 0 / 104 (0.00%) | | |
| occurrences (all) | 0 | | |
| Early satiety | | | |
| subjects affected / exposed | 0 / 104 (0.00%) | | |
| occurrences (all) | 0 | | |

| | | | |
|--|--|--|--|
| <p>Fatigue</p> <p>subjects affected / exposed</p> <p>0 / 104 (0.00%)</p> <p>occurrences (all)</p> <p>0</p> <p>Influenza like illness</p> <p>subjects affected / exposed</p> <p>1 / 104 (0.96%)</p> <p>occurrences (all)</p> <p>1</p> <p>Thirst</p> <p>subjects affected / exposed</p> <p>1 / 104 (0.96%)</p> <p>occurrences (all)</p> <p>1</p> | | | |
| <p>Reproductive system and breast disorders</p> <p>Breast mass</p> <p>subjects affected / exposed</p> <p>0 / 104 (0.00%)</p> <p>occurrences (all)</p> <p>0</p> <p>Postmenopausal haemorrhage</p> <p>subjects affected / exposed</p> <p>0 / 104 (0.00%)</p> <p>occurrences (all)</p> <p>0</p> | | | |
| <p>Respiratory, thoracic and mediastinal disorders</p> <p>Asthma</p> <p>subjects affected / exposed</p> <p>1 / 104 (0.96%)</p> <p>occurrences (all)</p> <p>1</p> <p>Cough</p> <p>subjects affected / exposed</p> <p>0 / 104 (0.00%)</p> <p>occurrences (all)</p> <p>0</p> <p>Oropharyngeal pain</p> <p>subjects affected / exposed</p> <p>1 / 104 (0.96%)</p> <p>occurrences (all)</p> <p>1</p> <p>Rhinitis allergic</p> <p>subjects affected / exposed</p> <p>1 / 104 (0.96%)</p> <p>occurrences (all)</p> <p>1</p> | | | |
| <p>Psychiatric disorders</p> <p>Anxiety</p> <p>subjects affected / exposed</p> <p>0 / 104 (0.00%)</p> <p>occurrences (all)</p> <p>0</p> <p>Insomnia</p> <p>subjects affected / exposed</p> <p>0 / 104 (0.00%)</p> <p>occurrences (all)</p> <p>0</p> | | | |

| | | | |
|--|----------------------|--|--|
| Irritability subjects affected / exposed occurrences (all) | 0 / 104 (0.00%) 0 | | |
| Post-traumatic stress disorder subjects affected / exposed occurrences (all) | 0 / 104 (0.00%) 0 | | |
| Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 1 / 104 (0.96%) 1 | | |
| C-reactive protein increased subjects affected / exposed occurrences (all) | 1 / 104 (0.96%) 1 | | |
| Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all) | 1 / 104 (0.96%) 1 | | |
| Neutrophil count decreased subjects affected / exposed occurrences (all) | 0 / 104 (0.00%) 0 | | |
| White blood cell count decreased subjects affected / exposed occurrences (all) | 0 / 104 (0.00%) 0 | | |
| Injury, poisoning and procedural complications Ankle fracture subjects affected / exposed occurrences (all) | 0 / 104 (0.00%) 0 | | |
| Ligament sprain subjects affected / exposed occurrences (all) | 0 / 104 (0.00%) 0 | | |
| Muscle strain subjects affected / exposed occurrences (all) | 2 / 104 (1.92%) 2 | | |
| Post-traumatic pain subjects affected / exposed occurrences (all) | 1 / 104 (0.96%) 1 | | |
| Radius fracture | | | |

| | | | |
|--------------------------------------|-----------------|--|--|
| subjects affected / exposed | 1 / 104 (0.96%) | | |
| occurrences (all) | 1 | | |
| Road traffic accident | | | |
| subjects affected / exposed | 1 / 104 (0.96%) | | |
| occurrences (all) | 1 | | |
| Sunburn | | | |
| subjects affected / exposed | 0 / 104 (0.00%) | | |
| occurrences (all) | 0 | | |
| Thermal burn | | | |
| subjects affected / exposed | 0 / 104 (0.00%) | | |
| occurrences (all) | 0 | | |
| Wrist fracture | | | |
| subjects affected / exposed | 1 / 104 (0.96%) | | |
| occurrences (all) | 1 | | |
| Cardiac disorders | | | |
| Palpitations | | | |
| subjects affected / exposed | 0 / 104 (0.00%) | | |
| occurrences (all) | 0 | | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 1 / 104 (0.96%) | | |
| occurrences (all) | 1 | | |
| Headache | | | |
| subjects affected / exposed | 5 / 104 (4.81%) | | |
| occurrences (all) | 5 | | |
| Hypoaesthesia | | | |
| subjects affected / exposed | 0 / 104 (0.00%) | | |
| occurrences (all) | 0 | | |
| Tremor | | | |
| subjects affected / exposed | 0 / 104 (0.00%) | | |
| occurrences (all) | 0 | | |
| Blood and lymphatic system disorders | | | |
| Normocytic anaemia | | | |
| subjects affected / exposed | 0 / 104 (0.00%) | | |
| occurrences (all) | 0 | | |
| Thrombocytosis | | | |

| | | | |
|--|----------------------|--|--|
| subjects affected / exposed occurrences (all) | 0 / 104 (0.00%) 0 | | |
| Ear and labyrinth disorders Tinnitus subjects affected / exposed occurrences (all) | 1 / 104 (0.96%) 1 | | |
| Gastrointestinal disorders Abdominal distension subjects affected / exposed occurrences (all) | 2 / 104 (1.92%) 2 | | |
| Abdominal pain subjects affected / exposed occurrences (all) | 3 / 104 (2.88%) 3 | | |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 0 / 104 (0.00%) 0 | | |
| Abnormal faeces subjects affected / exposed occurrences (all) | 1 / 104 (0.96%) 1 | | |
| Anal fissure subjects affected / exposed occurrences (all) | 1 / 104 (0.96%) 1 | | |
| Anorectal discomfort subjects affected / exposed occurrences (all) | 1 / 104 (0.96%) 1 | | |
| Constipation subjects affected / exposed occurrences (all) | 2 / 104 (1.92%) 2 | | |
| Diarrhoea subjects affected / exposed occurrences (all) | 2 / 104 (1.92%) 2 | | |
| Dyspepsia subjects affected / exposed occurrences (all) | 1 / 104 (0.96%) 1 | | |
| Flatulence | | | |

| | | | |
|--|-----------------|--|--|
| subjects affected / exposed | 0 / 104 (0.00%) | | |
| occurrences (all) | 0 | | |
| Frequent bowel movements | | | |
| subjects affected / exposed | 1 / 104 (0.96%) | | |
| occurrences (all) | 1 | | |
| Gastritis | | | |
| subjects affected / exposed | 0 / 104 (0.00%) | | |
| occurrences (all) | 0 | | |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 1 / 104 (0.96%) | | |
| occurrences (all) | 1 | | |
| Glossodynia | | | |
| subjects affected / exposed | 1 / 104 (0.96%) | | |
| occurrences (all) | 1 | | |
| Haemorrhoids | | | |
| subjects affected / exposed | 1 / 104 (0.96%) | | |
| occurrences (all) | 1 | | |
| Haemorrhoids thrombosed | | | |
| subjects affected / exposed | 1 / 104 (0.96%) | | |
| occurrences (all) | 1 | | |
| Irritable bowel syndrome | | | |
| subjects affected / exposed | 1 / 104 (0.96%) | | |
| occurrences (all) | 1 | | |
| Nausea | | | |
| subjects affected / exposed | 2 / 104 (1.92%) | | |
| occurrences (all) | 2 | | |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 0 / 104 (0.00%) | | |
| occurrences (all) | 0 | | |
| Toothache | | | |
| subjects affected / exposed | 0 / 104 (0.00%) | | |
| occurrences (all) | 0 | | |
| Vomiting | | | |
| subjects affected / exposed | 0 / 104 (0.00%) | | |
| occurrences (all) | 0 | | |
| Skin and subcutaneous tissue disorders | | | |

| | | | |
|--|----------------------|--|--|
| Brachioradial pruritus subjects affected / exposed occurrences (all) | 0 / 104 (0.00%) 0 | | |
| Dermatitis contact subjects affected / exposed occurrences (all) | 0 / 104 (0.00%) 0 | | |
| Rash subjects affected / exposed occurrences (all) | 1 / 104 (0.96%) 1 | | |
| Rash macular subjects affected / exposed occurrences (all) | 1 / 104 (0.96%) 1 | | |
| Renal and urinary disorders Dysuria subjects affected / exposed occurrences (all) | 0 / 104 (0.00%) 0 | | |
| Haematuria subjects affected / exposed occurrences (all) | 0 / 104 (0.00%) 0 | | |
| Pollakiuria subjects affected / exposed occurrences (all) | 0 / 104 (0.00%) 0 | | |
| Urine odour abnormal subjects affected / exposed occurrences (all) | 1 / 104 (0.96%) 1 | | |
| Musculoskeletal and connective tissue disorders Arthritis subjects affected / exposed occurrences (all) | 1 / 104 (0.96%) 1 | | |
| Back pain subjects affected / exposed occurrences (all) | 0 / 104 (0.00%) 0 | | |
| Musculoskeletal pain subjects affected / exposed occurrences (all) | 0 / 104 (0.00%) 0 | | |
| Neck pain | | | |

| | | | |
|-----------------------------------|-----------------|--|--|
| subjects affected / exposed | 1 / 104 (0.96%) | | |
| occurrences (all) | 1 | | |
| Pain in extremity | | | |
| subjects affected / exposed | 1 / 104 (0.96%) | | |
| occurrences (all) | 1 | | |
| Rotator cuff syndrome | | | |
| subjects affected / exposed | 0 / 104 (0.00%) | | |
| occurrences (all) | 0 | | |
| Infections and infestations | | | |
| Acute sinusitis | | | |
| subjects affected / exposed | 1 / 104 (0.96%) | | |
| occurrences (all) | 1 | | |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 104 (0.96%) | | |
| occurrences (all) | 1 | | |
| Cellulitis | | | |
| subjects affected / exposed | 2 / 104 (1.92%) | | |
| occurrences (all) | 2 | | |
| Ear infection | | | |
| subjects affected / exposed | 1 / 104 (0.96%) | | |
| occurrences (all) | 1 | | |
| Gastroenteritis | | | |
| subjects affected / exposed | 4 / 104 (3.85%) | | |
| occurrences (all) | 4 | | |
| Herpes zoster | | | |
| subjects affected / exposed | 0 / 104 (0.00%) | | |
| occurrences (all) | 0 | | |
| Influenza | | | |
| subjects affected / exposed | 0 / 104 (0.00%) | | |
| occurrences (all) | 0 | | |
| Lice infestation | | | |
| subjects affected / exposed | 1 / 104 (0.96%) | | |
| occurrences (all) | 1 | | |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 1 / 104 (0.96%) | | |
| occurrences (all) | 1 | | |

| | | | |
|-----------------------------------|-----------------|--|--|
| Nasopharyngitis | | | |
| subjects affected / exposed | 1 / 104 (0.96%) | | |
| occurrences (all) | 1 | | |
| Oral herpes | | | |
| subjects affected / exposed | 0 / 104 (0.00%) | | |
| occurrences (all) | 0 | | |
| Otitis media | | | |
| subjects affected / exposed | 1 / 104 (0.96%) | | |
| occurrences (all) | 1 | | |
| Pharyngitis | | | |
| subjects affected / exposed | 1 / 104 (0.96%) | | |
| occurrences (all) | 1 | | |
| Rhinitis | | | |
| subjects affected / exposed | 0 / 104 (0.00%) | | |
| occurrences (all) | 0 | | |
| Sinusitis | | | |
| subjects affected / exposed | 0 / 104 (0.00%) | | |
| occurrences (all) | 0 | | |
| Tonsillitis | | | |
| subjects affected / exposed | 0 / 104 (0.00%) | | |
| occurrences (all) | 0 | | |
| Tooth infection | | | |
| subjects affected / exposed | 1 / 104 (0.96%) | | |
| occurrences (all) | 1 | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 4 / 104 (3.85%) | | |
| occurrences (all) | 4 | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 104 (0.96%) | | |
| occurrences (all) | 1 | | |
| Vaginal infection | | | |
| subjects affected / exposed | 0 / 104 (0.00%) | | |
| occurrences (all) | 0 | | |
| Viral infection | | | |
| subjects affected / exposed | 1 / 104 (0.96%) | | |
| occurrences (all) | 1 | | |

| | | | |
|---|-----------------|--|--|
| Viral rhinitis | | | |
| subjects affected / exposed | 1 / 104 (0.96%) | | |
| occurrences (all) | 1 | | |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 104 (0.96%) | | |
| occurrences (all) | 1 | | |
| Vulvovaginal candidiasis | | | |
| subjects affected / exposed | 0 / 104 (0.00%) | | |
| occurrences (all) | 0 | | |
| Vulvovaginal mycotic infection | | | |
| subjects affected / exposed | 1 / 104 (0.96%) | | |
| occurrences (all) | 1 | | |
| Metabolism and nutrition disorders | | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 104 (0.00%) | | |
| occurrences (all) | 0 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 06 April 2018 | Protocol Version 1.1: <ul style="list-style-type: none">- Amended an administrative error regarding the timing of the dosing by adding approximately 30 minutes to be consistent with other sections of the protocol.- Removal of erythrocyte sedimentation rate and replacement with C-reactive protein [CRP] test within the haematology panel as this is a more accurate measurement for investigator review.- Additional testing for hepatitis B surface antigen, a hepatitis B surface antibody, and a hepatitis core antibody test was added for all subjects at the Screening Visit.- Removal of bile acid analysis of fasting serum from the planned per-protocol assessments. |
| 31 May 2018 | Protocol Version 2.0: <ul style="list-style-type: none">- Changed the primary endpoint responder symptom definition for stool consistency from number of days per week to proportion of days per week.- Changed the timing for the collection of stool samples from within 48 hours before or on the morning of baseline to the night before or the morning of the next clinic visit.- Added a 24-hour window for completion of IBS QOL before the clinic visit.- Re-added hepatitis C to the safety assessment as it was removed in error during the changes to Version 1.1.- Added the requirement for the subject to record stool frequency of up to 10 bowel movements daily to ensure data required to meet the primary endpoint is sufficient. |
| 13 February 2019 | Protocol version 3.0: <ul style="list-style-type: none">- Added text to inclusion criterion 4 for clarity: Have a moderate or severe IBS symptom severity score: >175 at the Screening Visit as defined by IBS-SSS. A tolerance of -10% (\geq an IBS-SSS score of 157.5) will be allowable at the baseline (Visit 1).- Added a definition for the ranges of mild, moderate, and severe IBS symptom scores. |
| 31 March 2020 | Protocol version 3.1: <ul style="list-style-type: none">- Planned futility analysis following the randomisation of approximately 250 subjects was cancelled as the study had stopped enrolment before the interim analysis was reported.- An informal interim analysis was conducted once all recruited subjects had completed the primary efficacy analysis 8-week treatment period.- This interim analysis was planned to enable 4D pharma plc to expedite the clinical development strategy based on the outcome of the interim analysis. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported