



Clinical trial results:

Double-blind, randomised, placebo-controlled, parallel-group phase II study to evaluate the effect of oral ibodutant in irritable bowel syndrome with diarrhoea (IBS-D) - The Iris-2 Study.

Summary

| | |
|--------------------------|----------------------|
| EudraCT number | 2010-018300-85 |
| Trial protocol | CZ DE ES SE IT DK BG |
| Global end of trial date | 11 May 2012 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 15 November 2018 |
| First version publication date | 15 November 2018 |

Trial information

Trial identification

| | |
|-----------------------|--------|
| Sponsor protocol code | NAK-04 |
|-----------------------|--------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01303224 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Menarini Ricerche S.p.A. |
| Sponsor organisation address | Via Sette Santi 1, Florence, Italy, 50131 |
| Public contact | Corporate Director of Clinical Sciences, Corporate Clinical Sciences, +39 05556809990, acapriati@menarini-ricerche.it |
| Scientific contact | Corporate Director of Clinical Sciences, Corporate Clinical Sciences, +39 05556809990, acapriati@menarini-ricerche.it |

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 | 11 May 2012 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 11 May 2012 |
| Global end of trial reached? | Yes |
| Global end of trial date | 11 May 2012 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of 3 oral doses of ibodutant on IBS symptoms relief and abdominal pain/discomfort relief as compared to placebo in IBS-D patients following an 8-week oral treatment course.

Protection of trial subjects:

If any event(s) related to the conduct of the study or the development of the IMP which affected the safety of the study participants, the sponsor and the investigator were to take appropriate urgent safety measures to protect the patients against any immediate hazard. The CAs and IRB/ECs were to be informed forthwith about these new events and the measures taken.

For patients participating in the study, Menarini Ricerche S.p.A. had stipulated an insurance policy in accordance with local regulatory requirements.

Background therapy: -

Evidence for comparator:

The choice of placebo as control group also complied with requirements of institutional and academic guidelines and was justified because there was unison agreement that there were no standard therapy for IBS. Moreover, the "placebo effect" in IBS was known to be high with response rates ranging from 0% to 84% (median: 47%) so that demonstration of superiority over placebo was most likely to reflect a true advantage for the patient.

| | |
|---|-----------------|
| Actual start date of recruitment | 06 October 2010 |
| 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 | Poland: 188 |
| Country: Number of subjects enrolled | Spain: 23 |
| Country: Number of subjects enrolled | Sweden: 26 |
| Country: Number of subjects enrolled | Bulgaria: 162 |
| Country: Number of subjects enrolled | Czech Republic: 50 |
| Country: Number of subjects enrolled | Denmark: 67 |
| Country: Number of subjects enrolled | Germany: 35 |
| Country: Number of subjects enrolled | Italy: 14 |
| Worldwide total number of subjects | 565 |
| EEA total number of subjects | 565 |

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) | 519 |
| From 65 to 84 years | 46 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

The first patient was screened on 06 Oct 2010 and the first subject was randomised on 22 Oct 2010. The last patient completed the study on 11 May 2012. The study was conducted at 78 investigational sites in 8 European countries.

Pre-assignment

Screening details:

A total of 1054 entered into the 2-week screening period. Of these, 565 patients were eligible for randomisation, indicating a screening failure rate of 53.6%.

A total of 559 patients took at least one dose of study medication and provided at least one primary endpoint assessment (ITT-population)

Period 1

| | |
|------------------------------|---|
| Period 1 title | 8-week Double-blind Treatment (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Data analyst, Carer, Assessor |

Blinding implementation details:

Double-blind conditions were ensured by the identical appearance and weight of the three different strengths of ibodutant tablets as well as the placebo tablets.

In order to preserve the double-blind conditions of the study, persons who were involved in the preparation or the handling of the randomisation list were not involved in the study conduct and statistical analysis. This remained in effect until the database was completed and locked.

Arms

| | |
|------------------------------|---------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Ibodutant 1mg |

Arm description:

Ibodutant 1mg, oral tablet to be given once daily for 8 weeks of treatment.

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | Ibodutant |
| Investigational medicinal product code | MEN 15596 |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Ibodutant 1 mg oral tablet, to be given once daily in fasting conditions.

| | |
|------------------|---------------|
| Arm title | Ibodutant 3mg |
|------------------|---------------|

Arm description:

Ibodutant 3mg, oral tablet to be given once daily for 8 weeks of treatment.

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | Ibodutant |
| Investigational medicinal product code | MEN 15596 |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Ibodutant 3 mg oral tablet, to be given once daily in fasting conditions.

| | |
|------------------|----------------|
| Arm title | Ibodutant 10mg |
|------------------|----------------|

Arm description:

Ibodutant 10mg, oral tablet to be given once daily for 8 weeks of treatment.

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | Ibodutant |
| Investigational medicinal product code | MEN 15596 |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Other use |

Dosage and administration details:

Ibodutant 10 mg oral tablet, to be given once daily in fasting conditions.

| | |
|------------------|---------|
| Arm title | Placebo |
|------------------|---------|

Arm description:

Placebo, oral tablet to be given once daily for 8 weeks of treatment.

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

Dosage and administration details:

Placebo oral tablet (identical in appearance and weight to ibodutant tablets) to be given once daily in fasting conditions.

| Number of subjects in period 1 | Ibodutant 1mg | Ibodutant 3mg | Ibodutant 10mg |
|---------------------------------------|---------------|---------------|----------------|
| Started | 141 | 142 | 139 |
| Completed | 130 | 131 | 133 |
| Not completed | 11 | 11 | 6 |
| Consent withdrawn by subject | 4 | 8 | 2 |
| unk | 2 | 1 | 2 |
| Adverse event, non-fatal | 2 | 1 | 1 |
| Sponsor request | 1 | - | - |
| Lost to follow-up | 1 | 1 | 1 |
| Protocol deviation | 1 | - | - |

| Number of subjects in period 1 | Placebo |
|---------------------------------------|---------|
| Started | 143 |
| Completed | 133 |
| Not completed | 10 |
| Consent withdrawn by subject | 4 |
| unk | 3 |
| Adverse event, non-fatal | - |
| Sponsor request | - |
| Lost to follow-up | 3 |

| | |
|--------------------|---|
| Protocol deviation | - |
|--------------------|---|

Baseline characteristics

Reporting groups

| | |
|--|----------------|
| Reporting group title | Ibodutant 1mg |
| Reporting group description: Ibodutant 1mg, oral tablet to be given once daily for 8 weeks of treatment. | |
| Reporting group title | Ibodutant 3mg |
| Reporting group description: Ibodutant 3mg, oral tablet to be given once daily for 8 weeks of treatment. | |
| Reporting group title | Ibodutant 10mg |
| Reporting group description: Ibodutant 10mg, oral tablet to be given once daily for 8 weeks of treatment. | |
| Reporting group title | Placebo |
| Reporting group description: Placebo, oral tablet to be given once daily for 8 weeks of treatment. | |

| Reporting group values | Ibodutant 1mg | Ibodutant 3mg | Ibodutant 10mg |
|--|---------------|---------------|----------------|
| Number of subjects | 141 | 142 | 139 |
| Age categorical Units: Subjects | | | |
| Adults (18-70 years) | 141 | 142 | 139 |
| Age continuous Units: years | | | |
| arithmetic mean | 46.1 | 46.8 | 47.0 |
| standard deviation | ± 13.3 | ± 13.5 | ± 12.8 |
| Gender categorical Units: Subjects | | | |
| Female | 89 | 89 | 79 |
| Male | 52 | 53 | 60 |
| Time since onset of IBS symptoms Units: Years | | | |
| arithmetic mean | | | |
| standard deviation | ± | ± | ± |
| IBS symptoms at baseline/randomisation: abdominal pain | | | |
| Abdominal pain | | | |
| Units: Scores on a scale | | | |
| arithmetic mean | | | |
| standard deviation | ± | ± | ± |
| IBS symptoms at baseline/randomisation: bloating | | | |
| Bloating | | | |
| Units: Scores on a scale | | | |
| arithmetic mean | | | |
| standard deviation | ± | ± | ± |
| IBS symptoms at baseline/randomisation: urgency | | | |
| Urgency | | | |
| Units: Scores on a scale | | | |
| arithmetic mean | | | |

| | | | |
|--|---|---|---|
| standard deviation | ± | ± | ± |
| IBS symptoms at baseline/randomisation: severity | | | |
| IBS symptom severity rate | | | |
| Units: Scores on a scale | | | |
| arithmetic mean | | | |
| standard deviation | ± | ± | ± |
| Stool frequency/day | | | |
| Units: Bowel movements/day | | | |
| arithmetic mean | | | |
| standard deviation | ± | ± | ± |
| Stool consistency | | | |
| Units: Scores on a scale | | | |
| arithmetic mean | | | |
| standard deviation | ± | ± | ± |
| IBS symptoms severity scale score | | | |
| IBS symptoms severity scale score | | | |
| Units: Scores on a scale | | | |
| arithmetic mean | | | |
| standard deviation | ± | ± | ± |
| QoL questionnaire EQ-5D VAS | | | |
| Quality of Life questionnaire EQ-5D Visual analog scales | | | |
| Units: Scores on a scale | | | |
| arithmetic mean | | | |
| standard deviation | ± | ± | ± |

| | | | |
|--|---------|-------|--|
| Reporting group values | Placebo | Total | |
| Number of subjects | 143 | 565 | |
| Age categorical | | | |
| Units: Subjects | | | |
| Adults (18-70 years) | 143 | 565 | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 44.2 | - | |
| standard deviation | ± 14.0 | | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 79 | 336 | |
| Male | 64 | 229 | |
| Time since onset of IBS symptoms | | | |
| Units: Years | | | |
| arithmetic mean | | - | |
| standard deviation | ± | | |
| IBS symptoms at baseline/randomisation: abdominal pain | | | |
| Abdominal pain | | | |
| Units: Scores on a scale | | | |
| arithmetic mean | | - | |
| standard deviation | ± | | |
| IBS symptoms at baseline/randomisation: bloating | | | |
| Bloating | | | |

| | | | |
|--|-------|---|--|
| Units: Scores on a scale arithmetic mean standard deviation | \pm | - | |
| IBS symptoms at baseline/randomisation: urgency | | | |
| Urgency | | | |
| Units: Scores on a scale arithmetic mean standard deviation | \pm | - | |
| IBS symptoms at baseline/randomisation: severity | | | |
| IBS symptom severity rate | | | |
| Units: Scores on a scale arithmetic mean standard deviation | \pm | - | |
| Stool frequency/day Units: Bowel movements/day arithmetic mean standard deviation | \pm | - | |
| Stool consistency Units: Scores on a scale arithmetic mean standard deviation | \pm | - | |
| IBS symptoms severity scale score | | | |
| IBS symptoms severity scale score | | | |
| Units: Scores on a scale arithmetic mean standard deviation | \pm | - | |
| QoL questionnaire EQ-5D VAS | | | |
| Quality of Life questionnaire EQ-5D Visual analog scales | | | |
| Units: Scores on a scale arithmetic mean standard deviation | \pm | - | |

Subject analysis sets

| | |
|---|--------------------|
| Subject analysis set title | ITT 1 mg |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: All patients randomised to the 1 mg Ibudutant group who took at least one dose of the study medication and provided at least one primary endpoint assessment. | |
| Subject analysis set title | ITT 3 mg |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: All patients randomised to the 3 mg Ibudutant group who took at least one dose of the study medication and provided at least one primary endpoint assessment. | |
| Subject analysis set title | ITT 10 mg |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: All patients randomised to the 10 mg Ibudutant group who took at least one dose of the study medication and provided at least one primary endpoint assessment. | |
| Subject analysis set title | ITT placebo |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

All patients randomised to the placebo group who took at least one dose of the study medication and provided at least one primary endpoint assessment.

| Reporting group values | ITT 1 mg | ITT 3 mg | ITT 10 mg |
|--|----------|----------|-----------|
| Number of subjects | 140 | 138 | 139 |
| Age categorical | | | |
| Units: Subjects | | | |
| Adults (18-70 years) | 140 | 138 | 139 |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 45.9 | 47.1 | 47.0 |
| standard deviation | ± 13.7 | ± 13.4 | ± 12.8 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 89 | 87 | 79 |
| Male | 51 | 51 | 60 |
| Time since onset of IBS symptoms | | | |
| Units: Years | | | |
| arithmetic mean | 6.2 | 6.3 | 6.3 |
| standard deviation | ± 7.3 | ± 7.5 | ± 6.9 |
| IBS symptoms at baseline/randomisation: abdominal pain | | | |
| Abdominal pain | | | |
| Units: Scores on a scale | | | |
| arithmetic mean | 2.5 | 2.3 | 2.3 |
| standard deviation | ± 0.6 | ± 0.5 | ± 0.5 |
| IBS symptoms at baseline/randomisation: bloating | | | |
| Bloating | | | |
| Units: Scores on a scale | | | |
| arithmetic mean | 2.4 | 2.2 | 2.2 |
| standard deviation | ± 0.8 | ± 0.7 | ± 0.7 |
| IBS symptoms at baseline/randomisation: urgency | | | |
| Urgency | | | |
| Units: Scores on a scale | | | |
| arithmetic mean | 2.5 | 2.5 | 2.4 |
| standard deviation | ± 0.7 | ± 0.6 | ± 0.6 |
| IBS symptoms at baseline/randomisation: severity | | | |
| IBS symptom severity rate | | | |
| Units: Scores on a scale | | | |
| arithmetic mean | 2.7 | 2.6 | 2.6 |
| standard deviation | ± 0.7 | ± 0.6 | ± 0.6 |
| Stool frequency/day | | | |
| Units: Bowel movements/day | | | |
| arithmetic mean | 4.6 | 4.4 | 4.4 |
| standard deviation | ± 1.5 | ± 1.3 | ± 1.5 |
| Stool consistency | | | |
| Units: Scores on a scale | | | |
| arithmetic mean | 5.7 | 5.7 | 5.7 |
| standard deviation | ± 0.6 | ± 0.5 | ± 0.6 |

| | | | |
|--|--------|--------|--------|
| IBS symptoms severity scale score | | | |
| IBS symptoms severity scale score | | | |
| Units: Scores on a scale | | | |
| arithmetic mean | 343.4 | 333.3 | 332.6 |
| standard deviation | ± 68.8 | ± 78.3 | ± 74.3 |
| QoL questionnaire EQ-5D VAS | | | |
| Quality of Life questionnaire EQ-5D Visual analog scales | | | |
| Units: Scores on a scale | | | |
| arithmetic mean | 54.5 | 55.5 | 58.1 |
| standard deviation | ± 22.9 | ± 21.9 | ± 22.9 |

| | | | |
|--|-------------|--|--|
| Reporting group values | ITT placebo | | |
| Number of subjects | 142 | | |
| Age categorical | | | |
| Units: Subjects | | | |
| Adults (18-70 years) | 142 | | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 44.1 | | |
| standard deviation | ± 14.0 | | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 78 | | |
| Male | 64 | | |
| Time since onset of IBS symptoms | | | |
| Units: Years | | | |
| arithmetic mean | 4.6 | | |
| standard deviation | ± 6.2 | | |
| IBS symptoms at baseline/randomisation: abdominal pain | | | |
| Abdominal pain | | | |
| Units: Scores on a scale | | | |
| arithmetic mean | 2.3 | | |
| standard deviation | ± 0.6 | | |
| IBS symptoms at baseline/randomisation: bloating | | | |
| Bloating | | | |
| Units: Scores on a scale | | | |
| arithmetic mean | 2.2 | | |
| standard deviation | ± 0.6 | | |
| IBS symptoms at baseline/randomisation: urgency | | | |
| Urgency | | | |
| Units: Scores on a scale | | | |
| arithmetic mean | 2.4 | | |
| standard deviation | ± 0.6 | | |
| IBS symptoms at baseline/randomisation: severity | | | |
| IBS symptom severity rate | | | |
| Units: Scores on a scale | | | |
| arithmetic mean | 2.6 | | |
| standard deviation | ± 0.6 | | |
| Stool frequency/day | | | |

| | | | |
|--|-----------------|--|--|
| Units: Bowel movements/day arithmetic mean standard deviation | 4.4 ± 1.2 | | |
| Stool consistency Units: Scores on a scale arithmetic mean standard deviation | 5.7 ± 0.6 | | |
| IBS symptoms severity scale score | | | |
| IBS symptoms severity scale score | | | |
| Units: Scores on a scale arithmetic mean standard deviation | 335.7 ± 69.4 | | |
| QoL questionnaire EQ-5D VAS | | | |
| Quality of Life questionnaire EQ-5D Visual analog scales | | | |
| Units: Scores on a scale arithmetic mean standard deviation | 55.3 ± 22.3 | | |

End points

End points reporting groups

| | |
|---|--------------------|
| Reporting group title | Ibodutant 1mg |
| Reporting group description: Ibodutant 1mg, oral tablet to be given once daily for 8 weeks of treatment. | |
| Reporting group title | Ibodutant 3mg |
| Reporting group description: Ibodutant 3mg, oral tablet to be given once daily for 8 weeks of treatment. | |
| Reporting group title | Ibodutant 10mg |
| Reporting group description: Ibodutant 10mg, oral tablet to be given once daily for 8 weeks of treatment. | |
| Reporting group title | Placebo |
| Reporting group description: Placebo, oral tablet to be given once daily for 8 weeks of treatment. | |
| Subject analysis set title | ITT 1 mg |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: All patients randomised to the 1 mg Ibodutant group who took at least one dose of the study medication and provided at least one primary endpoint assessment. | |
| Subject analysis set title | ITT 3 mg |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: All patients randomised to the 3 mg Ibodutant group who took at least one dose of the study medication and provided at least one primary endpoint assessment. | |
| Subject analysis set title | ITT 10 mg |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: All patients randomised to the 10 mg Ibodutant group who took at least one dose of the study medication and provided at least one primary endpoint assessment. | |
| Subject analysis set title | ITT placebo |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: All patients randomised to the placebo group who took at least one dose of the study medication and provided at least one primary endpoint assessment. | |

Primary: Response for Relief of Overall IBS Symptoms and of Abdominal Pain/Discomfort at the End of 8 Weeks of Treatment, Where the Response is Defined as at Least 6 Weeks With Satisfactory Relief During 8 Weeks of Treatment (75% Rule)

| | |
|--|--|
| End point title | Response for Relief of Overall IBS Symptoms and of Abdominal Pain/Discomfort at the End of 8 Weeks of Treatment, Where the Response is Defined as at Least 6 Weeks With Satisfactory Relief During 8 Weeks of Treatment (75% Rule) |
| End point description: Weekly binary questions (yes/no) from Interactive Voice/Web Response (IV/WRS) diary records: "Did you have satisfactory relief of your overall IBS symptoms during the last week?" and "Did you have satisfactory relief of your abdominal pain or discomfort during the last week?" Responder: Report of satisfactory overall IBS symptom relief = "Yes" and of satisfactory abdominal pain/discomfort relief = "Yes" 6/8 weeks (75% rule) | |
| End point type | Primary |
| End point timeframe: Eight weeks | |

| End point values | ITT 1 mg | ITT 3 mg | ITT 10 mg | ITT placebo |
|-----------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 140 | 138 | 139 | 142 |
| Units: Number of Responders | | | | |
| Responder | 45 | 46 | 55 | 39 |
| Non Responder | 95 | 92 | 84 | 103 |

Statistical analyses

| Statistical analysis title | Cochran-Mantel-Haenszel Test |
|----------------------------|------------------------------|
|----------------------------|------------------------------|

Statistical analysis description:

Mantel-Haenszel-Test was used to compare separately each of the 3 active treatment groups with placebo using a two-sided overall significance level of 5%. The proportion of responders was tested with the following hypotheses: H0 (placebo) vs H1(Ibodutant:1mg/3mg/10mg). Approximately 80% power based on the assumptions: rate placebo 40%, expected mean therapeutic gain over placebo 15% for at least one dose of Ibodutant.

| | |
|---|---|
| Comparison groups | ITT 3 mg v ITT 1 mg v ITT 10 mg v ITT placebo |
| Number of subjects included in analysis | 559 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.05 ^[1] |
| Method | t-test, 2-sided |

Notes:

[1] - Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
Multiplicity was adjusted by using the Hochberg Procedure.

Secondary: Response of satisfactory relief of overall IBS symptoms AND abdominal pain/discomfort during 8 weeks of treatment according to the 50% rule

| | |
|-----------------|---|
| End point title | Response of satisfactory relief of overall IBS symptoms AND abdominal pain/discomfort during 8 weeks of treatment according to the 50% rule |
|-----------------|---|

End point description:

Weekly binary questions (yes/no) from IV/WRS diary records: "Did you have satisfactory relief of your overall IBS symptoms during the last week?" and "Did you have satisfactory relief of your abdominal pain or discomfort during the last week?"

Responder: Report of satisfactory overall IBS symptom relief ="Yes" and of satisfactory abdominal pain/discomfort relief = "Yes" 4/8 weeks with at least 2 consecutive weeks of satisfactory relief during Week 5 to Week 8(50% rule)

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Eight weeks | |

| End point values | ITT 1 mg | ITT 3 mg | ITT 10 mg | ITT placebo |
|-----------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 140 | 138 | 139 | 142 |
| Units: Number of responders | | | | |
| Responder | 72 | 61 | 74 | 55 |
| Non-Responder | 68 | 77 | 65 | 87 |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Mantel Haenszel |
| Comparison groups | ITT 1 mg v ITT 3 mg v ITT 10 mg v ITT placebo |
| Number of subjects included in analysis | 559 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.05 [2] |
| Method | Mantel-Haenszel |

Notes:

[2] - Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
Multiplicity was adjusted using the Hochberg procedure.

Secondary: Quality of Life Changes

| | |
|-----------------|-------------------------|
| End point title | Quality of Life Changes |
|-----------------|-------------------------|

End point description:

Change in EQ-5D Quality of Life (visual analogue scale) score at the end of 8 weeks of treatment versus baseline (at randomisation). EQ-5D quality of life visual analogue scale ranges from "0"= worst imaginable health state to "100"=best imaginable health state.

all ITT patients who provided EQ-5D data at Visit 2 (start of treatment) and Visit 4 (end of treatment).

No statistical analysis provided for Quality of Life Changes (Using EuroQoL EQ-5D Questionnaire).

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

End point timeframe:

Eight weeks

| End point values | ITT 1 mg | ITT 3 mg | ITT 10 mg | ITT placebo |
|--------------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 131 | 133 | 133 | 131 |
| Units: VAS | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline | 56.4 (± 20.6) | 58.2 (± 22.0) | 57.2 (± 22.0) | 58.7 (± 21.5) |
| Visit 4 | 71.3 (± 17.2) | 72.1 (± 18.7) | 66.7 (± 20.7) | 72.2 (± 17.0) |

Statistical analyses

Other pre-specified: Subgroup Analysis: Response for Relief of Overall IBS Symptoms and of Abdominal Pain/Discomfort According to the 75% Rule in the Female ITT Population

| | |
|-----------------|--|
| End point title | Subgroup Analysis: Response for Relief of Overall IBS Symptoms and of Abdominal Pain/Discomfort According to the 75% Rule in the Female ITT Population |
|-----------------|--|

End point description:

Weekly binary questions (yes/no) from IV/WRS diary records: "Did you have satisfactory relief of your overall IBS symptoms during the last week?" and "Did you have satisfactory relief of your abdominal pain or discomfort during the last week?"

Responder: Report of satisfactory overall IBS symptom relief = "Yes" and of satisfactory abdominal pain/discomfort relief = "Yes" 6/8 weeks (75% rule)

Population: Female ITT Population

No statistical analysis provided for Subgroup Analysis

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

End point timeframe:

Eight weeks

| End point values | ITT 1 mg | ITT 3 mg | ITT 10 mg | ITT placebo |
|-----------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 89 | 87 | 79 | 78 |
| Units: Participants | | | | |
| Responders | 32 | 35 | 37 | 19 |
| Non-Responders | 57 | 52 | 42 | 59 |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Subgroup Analysis: Response for Relief of Overall IBS Symptoms and of Abdominal Pain/Discomfort According to the 75% Rule in the Male ITT Population

| | |
|-----------------|--|
| End point title | Subgroup Analysis: Response for Relief of Overall IBS Symptoms and of Abdominal Pain/Discomfort According to the 75% Rule in the Male ITT Population |
|-----------------|--|

End point description:

Weekly binary questions (yes/no) from IV/WRS diary records: "Did you have satisfactory relief of your overall IBS symptoms during the last week?" and "Did you have satisfactory relief of your abdominal pain or discomfort during the last week?"

Responder: Report of satisfactory overall IBS symptom relief = "Yes" and of satisfactory abdominal pain/discomfort relief = "Yes" 6/8 weeks (75% rule)

Population: Intention-to-Treat in the male population

No statistical analysis provided for Subgroup Analysis.

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

End point timeframe:

Eight weeks

| End point values | ITT 1 mg | ITT 3 mg | ITT 10 mg | ITT placebo |
|-----------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 51 | 51 | 60 | 64 |
| Units: Participants | | | | |
| Responders | 13 | 11 | 18 | 20 |
| Non-Responders | 38 | 40 | 42 | 44 |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events (AEs) for 12 weeks

Treatment Emergent Signs and Symptoms (TESS) for 8 weeks

Adverse event reporting additional description:

TESS (collected from first drug intake at Visit 2 (randomisation) during the treatment period of 8 weeks) were analysed for the Safety Population (all patients who took at least one dose of study medication, N = 565).

Generally, Adverse Events were reported/patient for a period of 12 weeks (during the total individual study period).

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

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 13.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------------|
| Reporting group title | Ibodutant 1mg |
|-----------------------|---------------|

Reporting group description:

Ibodutant 1mg, oral tablet to be given once daily for 8 weeks of treatment.

| | |
|-----------------------|---------------|
| Reporting group title | Ibodutant 3mg |
|-----------------------|---------------|

Reporting group description:

Ibodutant 3mg, oral tablet to be given once daily for 8 weeks of treatment.

| | |
|-----------------------|----------------|
| Reporting group title | Ibodutant 10mg |
|-----------------------|----------------|

Reporting group description:

Ibodutant 10mg, oral tablet to be given once daily for 8 weeks of treatment.

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Placebo, oral tablet to be given once daily for 8 weeks of treatment.

| Serious adverse events | Ibodutant 1mg | Ibodutant 3mg | Ibodutant 10mg |
|---|-----------------|-----------------|-----------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 141 (0.00%) | 1 / 142 (0.70%) | 1 / 139 (0.72%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Uterus myomatosus | | | |
| subjects affected / exposed | 0 / 141 (0.00%) | 0 / 142 (0.00%) | 0 / 139 (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 |
| Eye disorders | | | |
| Mydriasis | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 141 (0.00%) | 0 / 142 (0.00%) | 0 / 139 (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 |
| Gastrointestinal disorders | | | |
| Worsened abdominal pain | | | |
| subjects affected / exposed | 0 / 141 (0.00%) | 0 / 142 (0.00%) | 0 / 139 (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 |
| Infections and infestations | | | |
| Acute appendicitis | | | |
| subjects affected / exposed | 0 / 141 (0.00%) | 1 / 142 (0.70%) | 0 / 139 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Diabetes Mellitus type II | | | |
| subjects affected / exposed | 0 / 141 (0.00%) | 0 / 142 (0.00%) | 1 / 139 (0.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|--|-----------------|--|--|
| Serious adverse events | Placebo | | |
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 3 / 143 (2.10%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Uterus myomatosus | | | |
| subjects affected / exposed | 1 / 143 (0.70%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Eye disorders | | | |
| Mydriasis | | | |
| subjects affected / exposed | 1 / 143 (0.70%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |

| | | | |
|---|-----------------------------------|--|--|
| Worsened abdominal pain subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 143 (0.70%) 0 / 1 0 / 0 | | |
| Infections and infestations Acute appendicitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 143 (0.00%) 0 / 0 0 / 0 | | |
| Metabolism and nutrition disorders Diabetes Mellitus type II subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 143 (0.00%) 0 / 0 0 / 0 | | |

Frequency threshold for reporting non-serious adverse events: 2 %

| Non-serious adverse events | Ibodutant 1mg | Ibodutant 3mg | Ibodutant 10mg |
|---|--|--|---|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 42 / 141 (29.79%) | 40 / 142 (28.17%) | 42 / 139 (30.22%) |
| Investigations Blood creatine phosphokinase increased subjects affected / exposed occurrences (all) | 3 / 141 (2.13%) 3 | 0 / 142 (0.00%) 0 | 1 / 139 (0.72%) 1 |
| Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) | 3 / 141 (2.13%) 3 7 / 141 (4.96%) 7 | 2 / 142 (1.41%) 2 3 / 142 (2.11%) 3 | 1 / 139 (0.72%) 1 8 / 139 (5.76%) 11 |
| Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Nausea | 1 / 141 (0.71%) 1 | 2 / 142 (1.41%) 2 | 0 / 139 (0.00%) 0 |

| | | | |
|--|----------------------|----------------------|----------------------|
| subjects affected / exposed occurrences (all) | 1 / 141 (0.71%) 1 | 4 / 142 (2.82%) 4 | 5 / 139 (3.60%) 5 |
| Infections and infestations | | | |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 141 (0.00%) | 2 / 142 (1.41%) | 3 / 139 (2.16%) |
| occurrences (all) | 0 | 2 | 3 |
| Influenza | | | |
| subjects affected / exposed | 0 / 141 (0.00%) | 2 / 142 (1.41%) | 3 / 139 (2.16%) |
| occurrences (all) | 0 | 2 | 3 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 5 / 141 (3.55%) | 4 / 142 (2.82%) | 5 / 139 (3.60%) |
| occurrences (all) | 6 | 4 | 5 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 141 (0.00%) | 0 / 142 (0.00%) | 3 / 139 (2.16%) |
| occurrences (all) | 0 | 0 | 3 |

| | | | |
|---|-------------------|--|--|
| Non-serious adverse events | Placebo | | |
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 29 / 143 (20.28%) | | |
| Investigations | | | |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 1 / 143 (0.70%) | | |
| occurrences (all) | 1 | | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 0 / 143 (0.00%) | | |
| occurrences (all) | 0 | | |
| Headache | | | |
| subjects affected / exposed | 4 / 143 (2.80%) | | |
| occurrences (all) | 4 | | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 3 / 143 (2.10%) | | |
| occurrences (all) | 4 | | |
| Nausea | | | |
| subjects affected / exposed | 3 / 143 (2.10%) | | |
| occurrences (all) | 3 | | |

| | | | |
|--|----------------------|--|--|
| Infections and infestations Gastroenteritis subjects affected / exposed occurrences (all) | 0 / 143 (0.00%) 0 | | |
| Influenza subjects affected / exposed occurrences (all) | 5 / 143 (3.50%) 5 | | |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 3 / 143 (2.10%) 3 | | |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 1 / 143 (0.70%) 1 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|--------------|---|
| 05 July 2010 | substantial; effective in the Czech Republic modified inclusion criterion no 2 in such a way that all patients older than 50 years OR patients with positive family history of colorectal cancer had to have normal results from a colonoscopy or flexible sigmoidoscopy that has been performed after onset of IBS symptoms and within one year before Screening. Moreover, amendment required all Czech patients to have a documented negative IgA antibodies against tissue transglutaminase and endomysium within the last 24 months in order to ascertain the absence of gluten enteropathy |
| 06 July 2010 | substantial; effective in Germany modified inclusion criterion no 2 in such a way that all study participants, irrespective of their age, had to have normal results from colonoscopy or flexible sigmoidoscopy performed within the last 5 years and after the onset of IBS symptoms, and completed before Screening |
| 12 July 2011 | non-substantial, administrative became necessary because of the changes in responsibilities resulting from the fact that on July 12, 2011 INC Research, LLC, a therapeutically focused Contract Research Organization (CRO) privately held by Avista Capital Partners and Ontario Teachers' Pension Plan, announced its completed acquisition of Kendle International Inc. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/27196574>