Synopsis of Clinical Study Report

A 12-week double-blind, randomised, placebo-controlled, parallel group Phase III study, followed by a 4-week randomised withdrawal period to evaluate the efficacy and safety of oral ibodutant 10 mg once daily in female patients with irritable bowel syndrome with diarrhoea (IBS-D)

Test Product:	Ibodutant
Indication:	Irritable bowel syndrome with diarrhoea
Sponsor:	Menarini Ricerche S.p.A. Clinical Research Via Sette Santi, 1 50131 Florence Italy Tel: +39 055 5680 9990 Fax: +39 055 5680 597
Protocol No.:	NAK-06
EudraCT number:	2013-000894-56
Development Phase:	III
Study Initiation Date:	27 Feb 2014
Study Completion Date:	22 Jun 2015
Co-ordinating Investigator:	Professor Jan Tack Department of Internal Medicine Division of Gastroenterology Katholieke Universiteit Leuven University Hospital Gasthuisberg Herestraat 49 3000 Leuven, Belgium
Responsible Medical Officer:	Angela Capriati MD, PhD Corporate Director of Clinical Research Menarini Ricerche S.p.A. 50131 Florence - Italy

This study was performed in accordance with Good Clinical Practice (GCP), including the archiving of essential documents.

Statement of Confidentiality

Date of Synopsis of Clinical Study Report: 21 JUNE 2016

APPROVAL SIGNATURE(S)

A 12-week double-blind, randomised, placebo-controlled, parallel group Phase III study, followed by a 4-week randomised withdrawal period to evaluate the efficacy and safety of oral ibodutant 10 mg once daily in female patients with irritable bowel syndrome with diarrhoea (IBS-D)

Synopsis of Clinical Report of Study Code NAK-06

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Co-Ordinating Investigator Signatory:

..... 21/6/16

Professor Dr Jan Tack, Date

Head of Division of Gastroenterology, Department of Internal Medicine

Katholieke Universiteit Leuven University,

Leuven, Belgium

Sponsor Signatory:

..... 21 June 2016

Angela Capriati, MD, PhD Date

Corporate Director of Clinical Research

Menarini Ricerche S.p.A.

Florence, Italy

Name of Company: Menarini Ricerche S.p.A. **Name of Finished Product:** Ibodutant **Name of Active Ingredient:** Ibodutant	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use only)*

Title of Study: A 12-week double-blind, randomised, placebo-controlled, parallel group Phase III study, followed by a 4-week randomised withdrawal period to evaluate the efficacy and safety of oral ibodutant 10 mg once daily in female patients with irritable bowel syndrome with diarrhoea (IBS-D). The IRIS-3 study (**I**bodutant for **R**elief of **I**rritable Bowel **S**yndrome)

Principal Investigator:
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Study Centre(s):
A total of 158 centres in 11 countries participated in the study, of which 130 centres screened patients and 99 centres randomised patients.

Publication: None.

Study Period:	**Phase of Development:**
27 Feb 2014 to 22 Jun 2015	Phase III

Objectives:

Primary Objective:

The primary objective of this study was to evaluate the efficacy of ibodutant on irritable bowel syndrome (IBS) symptoms as compared to placebo in IBS-D female patients over a 12-week oral (PO) treatment period.

Secondary Objectives:

The secondary objectives of this study were:

- To assess the safety and tolerability of ibodutant on 12- and 16-week treatment course with PO 10 mg dose once daily (QD) in IBS-D female patients.
- To evaluate the rebound effect on IBS symptoms in IBS-D female patients after treatment discontinuation.
- To evaluate ibodutant population pharmacokinetics (PK) in IBS-D female patients.

Methodology:

This was a Phase III multicentre study consisting of a 12-week randomised double-blind parallel group treatment period followed by a 4-week randomised withdrawal (RW) period. It compared ibodutant 10 mg QD PO with placebo for the treatment of IBS-D.

Following the screening period (Visit 1) of up to 2 weeks, patients entered a 2-week run-in period (Visit 2) which served as a treatment-free prospective baseline period to characterise IBS symptom severity. Patients received treatment for a total of 16 weeks across 2 periods. At randomisation (Visit 3), patients commenced 12 weeks of double-blind treatment in a 1:1 ibodutant : placebo ratio, during which Visits 4 (Day 29) and 5 (Day 57) occurred. Patients were re-randomised for the 4-week RW period at Visit 6 (Day 85): those previously randomised to placebo were mock-randomised to ibodutant; those previously randomised to ibodutant were re-randomised in a 1:1 ibodutant : placebo ratio. The 4-week RW period ended at Visit 7 (Day 113) and patients then entered a 2-week safety follow-up period. The final visit (Visit 8) occurred on Day 126.

From the start of the 12-week double-blind treatment period onwards, rescue medication was permitted in the form of loperamide, administered at up to 6 capsules per day for a maximum of 4 consecutive days.

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Number of Patients (Planned and Analysed): It was planned that 1000 patients would be screened to ensure completion of 500 patients. The enrolment was competitive. A total of 1237 patients were actually screened, of whom 535 patients were randomised and 448 patients completed the study. A total of 271 patients were randomised to ibodutant and 264 patients to placebo.

Diagnosis and Main Criteria for Inclusion:

Inclusion criteria:

A patient was eligible for inclusion in the study if all of the following criteria were met:

1. Female patients aged ≥18 years.
2. Clinical diagnosis of IBS-D according to the following symptom-based criteria as per Rome III modular questionnaire criteria:
   - Recurrent abdominal pain or discomfort for at least 3 days per month in the last 3 months associated with at least 2 of the following characteristics: a) improvement with defecation; b) onset associated with a change in the frequency of stool; c) onset associated with a change in form (appearance) of stool.
   - Symptom onset at least 6 months prior to diagnosis.
   - Loose or watery stools at least 25% of the time in the last 3 months AND hard or lumpy stools less than 25% of the time in the last 3 months.
   - Additional criterion: more than 3 bowel movements per day for at least 25% of the time in the last 3 months.
3. For patients >50 years of age OR patients with positive family history of colorectal cancer: normal results from colonoscopy/flexible sigmoidoscopy performed within the last 5 years and after the onset of IBS symptoms, and completed before the start of the screening period.
4. For patients aged ≥65 years: absence of ischaemic colitis, microscopy colitis or any other organic gastrointestinal (GI) disease as evidenced by the results of a colonoscopy/flexible sigmoidoscopy with biopsy performed within 6 months before the start of the screening period.
5. For women of childbearing potential (i.e. not postmenopausal [postmenopausal was defined as ≥52 years of age and amenorrhoeic for at least 2 years at screening], not surgically sterile [i.e. through hysterectomy or bilateral oophorectomy, tubal ligation] or otherwise incapable of pregnancy) and sexually active: use of a highly effective contraceptive method with a failure rate <1% per year throughout the entire study period and up to 30 days post-treatment. Oral contraceptives were allowed provided that they had not been changed in the previous 6 months.
6. Physical examination without clinically relevant abnormalities during the screening period.
7. No clinically relevant abnormalities in 12-Lead ECG during the screening period.
8. No clinically relevant abnormalities in laboratory findings during the screening period.
9. Willing to be compliant with study procedures including completing the daily electronic diary (i.e. e-diary through an Interactive Voice Response System [IVRS]) for 18 weeks from the beginning of the run-in period.
10. Mentally competent, able to give written informed consent prior to any study-related procedure and compliant to undergo all visits and procedures scheduled in the study.
11. Patient had unrestricted access to a working touch-tone telephone for the entire trial.
12. Patient was willing to refrain from using any anti-diarrhoeal loperamide within 3 days prior to run-in visit and during the run-in period (this was re-checked prior to randomisation).

At the end of the run-in period, ONLY patients meeting the following e-diary criteria and all the other inclusion criteria were eligible to progress to randomisation:

13. Patient had during both weeks of the run-in period a weekly average score for worst abdominal pain in the past 24 hours of at least 3.0 on a 0 to 10 point scale (abdominal pain intensity).
14. Patient had during both weeks of the run-in period at least 1 bowel movement on each day.
15. Patient had during both weeks of the run-in period a weekly average of at least 3 bowel movements per day.

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16. Patient had during both weeks of the run-in period at least 1 stool with a consistency of Type 6 or Type 7 according to the Bristol Stool Scale (BSS) on at least 2 days per week (stool consistency).
17. Patient had during both weeks of the run-in period fewer than 2 bowel movements per week with a consistency of Type 1 or Type 2 according to the BSS.
18. Adequate compliance with the e-diary recording procedure, defined as at least 11 of 14 days (≥75%) of the nominal daily data entry considering the last consecutive 14 days prior to the randomisation. NOTE: run-in duration was 14 days [+3 days].

Exclusion criteria:

A patient was not eligible for inclusion in the study if any of the following criteria were met:

NOTE: A patient with any alarm signs (e.g. fever, rectal bleeding other than haemorrhoids, unintentional weight loss, anaemia) warranted special consideration to exclude any organic GI disease.

1. Male gender.
2. Patient had a diagnosis of IBS with a subtype of constipation, mixed IBS, or unsubtyped IBS according to the Rome III criteria.
3. Patient had undergone surgery that met any of the following criteria:
   a) Colonic or major abdominal surgery, i.e. bariatric surgery and stomach, small/large bowel or large vessel abdominal surgery (except appendectomy, hysterectomy, cholecystectomy, caesarean section, or laparoscopic surgery).
   b) Any other major abdominal surgery in the previous 6 months.
4. Patient had any elective major surgery planned or expected at any time during the study.
5. Patient had a history of inflammatory bowel diseases, complicated diverticulosis (i.e. diverticulitis), ischaemic colitis, microscopic colitis.
6. Patient had a history of organic abnormalities of the GI tract, intestinal obstruction, stricture, toxic megacolon, GI perforation, faecal impaction, gastric banding, adhesions or impaired intestinal circulation (e.g., aortoiliac disease).
7. Patient had a history of pancreatitis of any aetiology, cholecystitis or symptomatic gallbladder stone disease in the previous 6 months.
8. Patient had an active biliary duct disease or a history of Sphincter of Oddi dysfunction.
9. Patient had a history of gluten enteropathy.
10. Patient had a history of lactose intolerance as assessed by response to diet.
11. Patient had a current or previous diagnosis of neoplasia (except non-GI neoplasia in complete remission ≥5 years, squamous and basal cell carcinomas, and cervical carcinoma *in situ*).
12. Patient had a history of ectopic endometriosis.
13. Patient had a history of positive tests for ova or parasites, or *Clostridium difficile* toxin or occult blood in the stool in the previous 6 months.
14. Patient had a history of human immunodeficiency virus infection.
15. Patient had a history of a cardiovascular event, including stroke, myocardial infarction, congestive heart failure (New York Heart Association class >2), or transient ischaemic attack in the previous 6 months.
16. Patient had uncontrolled hypertension, defined as systolic blood pressure (BP) >180 mmHg or a diastolic BP >100 mmHg.
17. Patient had insulin-dependent diabetes mellitus.
18. Patient had a major psychiatric or neurological disorder.
19. Patient had an unstable medical condition which could compromise the efficacy and safety assessments as required in the study and/or require change in concomitant medication.
20. Patient had a history of abnormal thyroid function. A patient was still a candidate for the study if thyroid hormone replacement therapy was stable for at least 2 months.
21. Patient had evidence of clinically significant hepatic disease as defined by alanine aminotransferase (ALT) or

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aspartate aminotransferase (AST) >3 times the upper limit of normal or total bilirubin >3 mg/dL (>51.3 mmoL/L), with the exception of Gilbert's syndrome or albumin <2.8 g/dL during the screening period.

22. Patient had a severe renal insufficiency (glomerular filtration rate <30 mL/min/1.73 m^2 calculated by the Cockcroft-Gault formula adjusted for the body surface area) during the screening period.
23. Patient had evidence of anaemia as confirmed by haemoglobin (Hb) <9 g/dL during the screening period.
24. Relevant changes in dietary habits, lifestyle, or exercise regimen in the previous 2 months. NOTE: dietary habits, lifestyle and exercise regimen were to be maintained for the duration of the study.
25. Use of prohibited concurrent medication within the previous month, namely:
    - Antibiotics (4 months in the case of rifaximin).
    - 5-HT_3 antagonist alosetron.
26. Use of prohibited concurrent medication in the previous 7 days, namely:
    - Antimuscarinic drugs.
    - Drugs enhancing GI motility such as prokinetic agents and other stimulants of GI contractility drugs, laxatives, or anti-diarrhoeal agents (except for loperamide).
    - Analgesic drugs (opioids or non-steroidal anti-inflammatory drugs). NOTE: Short-term use of paracetamol was allowed for a maximum of 2 consecutive days.
    - Fibre products and herbal preparations.
    - Antidepressants. NOTE: The use of a single antidepressant was only allowed when the drug type and its dose regimen had not been changed in the previous 6 months.
    - Benzodiazepines. NOTE: The use of a single benzodiazepine was only allowed when it was administered as a sleep inducer and the drug type and its dose regimen had not been changed in the previous 6 months.
27. Pregnancy or breastfeeding.
28. Hypersensitivity to the drug excipients.
29. Patient was not able to understand or collaborate throughout the study.
30. Patient was unable to swallow solid, oral dosage forms whole with the aid of liquid (patients were not allowed to chew, divide, dissolve, or crush the study drug).
31. Participation in other clinical studies in the previous 4 weeks or the patient was currently enrolled in a clinical study with another investigational drug.
32. Patient had any condition that, in the opinion of the Investigator, would compromise the wellbeing of the patient or the requirements of the study.

Test Product, Dose and Mode of Administration, Batch Number(s):

Ibodutant tablets were administered PO at a dose of one 10 mg tablet QD. The batch numbers were 5021901, 5124501 and 521001C.

Duration of Study Drug Treatment:

Twelve-week double-blind treatment period: 12 weeks

Four-week Randomised Withdrawal (RW) period: 4 weeks

Reference Product, Dose and Mode of Administration, Batch Number(s):

Placebo tablets were administered PO at a dose of 1 tablet QD. The batch numbers were 5022001C and 5124601. Placebo tablets were identical to ibodutant in appearance and weight.

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Criteria for Evaluation:

Efficacy:

The primary evaluation of efficacy was based on the weekly response for abdominal pain intensity AND stool consistency over 12 weeks of treatment in ≥50% of the weeks of treatment (6 out of 12 weeks).

In addition, the following secondary efficacy endpoints were measured: weekly response for abdominal pain intensity over 12 weeks of treatment in ≥50% of the weeks of treatment, weekly response for stool consistency over 12 weeks of treatment in ≥50% of the weeks of treatment, weekly abdominal pain responders, weekly stool consistency responders, weekly response for relief of overall IBS signs and symptoms, evaluation of rebound effect between baseline and 4-week RW period in patients who were re-randomised to placebo after having received ibodutant, change in IBS-SSS from baseline, change in weekly average of specific symptoms of IBS-D.

Pharmacokinetics:

Population PK parameters of ibodutant following repeated oral administration at steady state, including systemic clearance (CL/F), apparent volume of distribution (V/F) and first order absorption rate constant (Ka) were measured. Individual PK parameters (i.e. area under the plasma concentration-time curve_AUC, minimum plasma concentration_Cmin, maximum plasma concentration_Cmax, and terminal elimination half-life_($t_{1/2}$) were estimated from population parameters.

The estimates of the PK parameters were based on multiple regressions using Non-Linear Mixed Effect Models (NONMEM).

Safety:

The safety of the study treatment was evaluated by assessments of adverse events, laboratory parameters (haematology, biochemistry and urinalysis), ECG, physical examinations and vital signs.

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Statistical Methods:

Populations analysed

Safety Population: all enrolled patients who received at least 1 dose of study drug.

Intent-to-treat (ITT) Population: all randomised patients who received at least 1 dose of study drug.

Modified ITT (mITT) Population: all patients included in the ITT Population excluding patients from site 00123, where a serious breach of Good Clinical Practice was reported, and site 00134, where disqualification proceedings against the Investigator were initiated by the Food and Drug Administration.

Per-protocol Population: all patients from the mITT Population who did not experience relevant protocol violations related to the efficacy endpoints, such as administration of prohibited medications, lack of clinical diagnosis of IBS-D as per Rome III modular questionnaire criteria at screening, drug compliance <80% or >120%, or any patients randomised to a treatment group who received other treatment group drug.

RW Population: all patients entered into the 4-week RW period who received at least 1 dose of ibodutant or placebo during this period.

Modified RW Population: all patients included in the RW Population, excluding patients from sites 00123 and 00134.

PK Population: all randomised patients who had at least 1 evaluable ibodutant plasma concentration data available with complete dosing and sampling history, and covariate documentation.

Modified PK Population: all patients from the PK population excluding patients from sites 00123 and 00134. Additionally, patients showing ibodutant plasma concentration values inconsistent either with the assumption of steady state attainment or dosing history were excluded.

PK/Pharmacodynamic Population: patients from the PK Population and placebo patients from the ITT Population.

Primary endpoint

The primary endpoint was composed of the weekly response for abdominal pain intensity and stool consistency over 12 weeks of treatment in ≥50% of the weeks of treatment. It was analysed using a Cochran-Mantel-Haenszel (CMH) test in a 2 × 2 contingency table to compare ibodutant with placebo. The number and percentage of responders and non-responders for each treatment group, the difference in responder rates between the treatment groups, the odds ratio with corresponding 95% two-sided confidence interval for each, and p-value associated with the CMH test were presented.

Secondary endpoints

Weekly responses for abdominal pain intensity, stool consistency and relief of overall IBS signs and symptoms were analysed in the same way as the primary efficacy endpoint; the same analyses were also performed by each week time-point for weekly abdominal pain and stool consistency response. Rebound effect was evaluated by a paired t-test. For the evaluation of change in IBS-SSS, and change in weekly average for IBS-D specific symptoms, if assumptions of normality were not violated, analysis was performed using an analysis of covariance (ANCOVA) for each planned week. The ANCOVA model included treatment group and the patient's corresponding baseline value for the parameter as a covariate. If the assumption of normality was violated, a Kruskal-Wallis test was to be performed. For the 4-week RW period, the same method was used as for as for the 12-week double-blind treatment period, with the exception that treatment sequence replaced treatment group in the ANCOVA model and the analysis compared the ibodutant-placebo and ibodutant-ibodutant treatment sequences.

Summary of Results:

Efficacy Results:

The primary endpoint consisted of the weekly response for abdominal pain intensity and stool consistency over 12 weeks of treatment in ≥50% of the weeks of treatment (6 out of 12 weeks). A total of 79 (35.7%) patients in the ibodutant group were responders, compared with 75 (34.7%) patients in the placebo group. The odds ratio (OR; 95% confidence interval [CI]) was 1.046 (0.71, 1.55); the difference between treatment groups was not statistically significant (p=0.823).

There were similar numbers of responders in both groups for abdominal pain intensity (OR [95% CI] 1.011 [0.69,

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1.47], p=0.954), stool consistency (OR [95% CI] 1.073 [0.74, 1.57], p=0.714), weekly abdominal pain response, i.e. pain decrease from baseline of ≥30% (OR [95% CI] 1.128 [0.78, 1.64], p=0.529), ≥40% (OR [95% CI] 0.944 [0.64, 1.38], p=0.768) or ≥50% (OR [95% CI] 0.946 [0.64, 1.41], p=0.785), weekly stool consistency response for decrease from baseline of ≥50% (OR [95% CI] 1.151 [0.79, 1.68], p=0.463) and weekly response for overall IBS signs and symptoms (OR [95% CI] 1.153 [0.72, 1.84], p=0.552). There was no rebound effect observed (p<0.001) and no significant differences between groups in the change from baseline in IBS-SSS score (p=0.542). In general, similar improvements from baseline in IBS-D symptoms were observed in both treatment groups, although there was an isolated significant result favouring ibodutant (p=0.026) for abdominal discomfort at Week 1 of the 12-week double-blind treatment period.

There were no notable results in the subgroup analyses, with the exception of stool consistency: for weekly response over 12 weeks of treatment in patients aged ≥65 years, a statistically significantly greater number of patients receiving ibodutant were responders compared with patients receiving placebo (OR [95% CI] 10.000 [1.59, 62.73], p=0.011); for weekly response by week time-point, the age subgroup analysis for stool consistency response was statistically significant for 5 of the 12 weeks.

Pharmacokinetic Results:

- *Population pharmacokinetic (pop-PK) analysis*

A population pharmacokinetic model was built to describe the PK of ibodutant at steady state. The dataset used for the NONMEM population PK and PK/PD analyses encompassed data from 174 patients (aged 18-77 years) representing the modified PK population.

In the final population PK model, ibodutant plasma concentrations were described by a two compartment model with first order absorption rate (Ka) and linear elimination from the central compartment. The population PK model estimated the population means for apparent clearance (CL/F), apparent volume of distribution of central compartment (Vc/F), apparent volume of distribution of peripheral compartment (Vp/F), apparent inter-compartmental clearance (Q/F), and Ka. The between-subject variability was also estimated for CL/F and Vc/F. In addition, the two components of the residual variability, proportional and additive (σ_{prop} and σ_{add}) were estimated for ibodutant plasma concentrations. Age was found to influence the volume of the central compartment, with lower volume (and higher exposure) for those of advanced age. Hepatic function (AST) was found to affect apparent clearance, with lower clearance (approximately 50%) and higher exposure for those with AST levels exceeding the limit of 40 U/L. For a typical patient aged 47 years and normal hepatic function, the estimated apparent volume of distribution of central compartment and the apparent clearance at steady state were 1180 L and 223 L/h, respectively, with a high between-subject variability (>50%) associated with both parameters. Secondary steady state PK parameters i.e., Cmax, AUC and $t_{1/2}$ were 6393.7 pg/mL, 52012.5 pg*h/mL and 33.7 h, respectively.

Pharmacokinetics of ibodutant was similar in IBS-D female patients and healthy female subjects (Company Report: NAK-05). Overall, these results suggest that no apparent accumulation of ibodutant occurred, and that drug steady-state concentrations were predictable from single-dose pharmacokinetics for both healthy female subjects and IBS-D female patients.

- *Exposure-response (PK/PD) analysis*

No exposure-response relationship could be statistically demonstrated between the rate of responders and ibodutant exposure.

Safety and Tolerability Results:

In the 12-week double-blind treatment period, 211 treatment-emergent signs and symptoms (TESSs) were reported in 120 (22.4%) patients in the Safety Population. Slightly more TESSs were reported in the ibodutant group (119 TESSs in 66 [24.4%] patients) compared with the placebo group (92 TESSs in 54 [20.5%] patients). Of these, 2 (0.4%) patients experienced 2 serious TESSs (placebo, 2 TESSs in 2 [0.8%] patients) and 22 (4.1%) patients experienced 32 treatment-related TESSs (ibodutant, 20 TESSs in 12 [4.4%] patients; placebo, 12 TESSs in 10 [3.8%] patients). A total of 10 [1.7%] patients experienced 10 TESSs which led to treatment/study

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discontinuation (ibodutant, 6 TESSs in 6 [2.2%] patients; placebo, 4 TESSs in 4 [1.5%] patients). One of these patients was discontinued in the RW period but is included here as the event onset was in the 12-week double-blind treatment period; another patient who experienced a TESS leading to discontinuation was re-randomised but did not receive any study drug following re-randomisation. Therefore, she was also included in the first period. Finally, one of these patients experienced 2 TESSs for which the action taken was reported as "drug withdrawn" but it was not possible to include both as the reason for discontinuation (therefore, only one of them was included as event leading to discontinuation). There were no deaths and the majority of TESSs were mild. By System Organ Class (SOC), the most commonly reported TESSs were infections and infestations (60 TESSs in 50 [9.3%] patients overall) and GI disorders (28 TESSs in 24 [4.5%] patients overall). By preferred term (PT), no TESS was reported in ≥3% of patients. There were no notable differences between treatment groups.

From the start of the RW period to end of study, 70 TESSs were reported in 52 (11.5%) patients in the RW Population (ibodutant-placebo, 21 TESSs in 12 [10.5%] patients; ibodutant-ibodutant, 21 TESSs in 16 [14.2%] patients; placebo-ibodutant, 28 TESSs in 24 [10.7%] patients). Of these, 1 patient allocated to placebo-ibodutant treatment sequence experienced a serious TESS and 3 [0.7%] patients experienced a treatment-related TESS (ibodutant-ibodutant, 1 [0.9%] patient; placebo-ibodutant, 2 [0.9%] patients). One (0.4%) patient who received the placebo-ibodutant treatment sequence experienced 1 TESS which led to treatment/study discontinuation. There were no deaths and the majority of TESSs were mild. By SOC, the most commonly reported TESSs were infections and infestations (24 TESSs in 22 [4.9%] patients overall). By PT, no TESS was reported in ≥1% of patients overall. No notable differences were observed between treatment sequences.

There were no notable changes over time of significant differences between treatment groups in haematology, biochemistry, urinalysis, physical examination, vital signs, ECG, diet, lifestyle and exercise regimens, or therapeutic and diagnostic procedures.

Conclusions:

- Ibodutant 10 mg QD did not demonstrate efficacy over placebo in the treatment of IBS-D in female patients with at least moderate abdominal pain.
- Ibodutant 10 mg QD was safe and well tolerated.

Date of Synopsis of Clinical Study Report: 21 JUNE 2016