Synopsis of Clinical Study Report
A 52-week, double-blind, randomised, placebo-controlled, parallel-group phase III study with re-randomisation at week 25 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
Study Code:	NAK-07
EudraCT number:	2013-000895-14
Development Phase:	III
Study Initiation Date:	26 Feb 2014
Study Completion Date:	03 Nov 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.

Date of Synopsis of Clinical Study Report: 02 NOV 2016

APPROVAL SIGNATURES

A 52-week, double-blind, randomised, placebo-controlled, parallel-group phase III study with re-randomisation at week 25 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 Study Report - Study Code: NAK-07

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:

2/11/2016

.....

Professor Dr Jan Tack. Date

Head of Division of Gastroenterology. Department of Internal Medicine

Katholieke Universiteit Leuven University.

Leuven. Belgium

Sponsor Signatory:

.....

02 NOV 2016

Angela Capriati, MD. PhD Date

Corporate Director of Clinical Research

Menarini Ricerche S.p.A.

Florence. Italy

1 SYNOPSIS

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

Title of Study: A 52-week, double-blind, randomised, placebo-controlled, parallel-group phase III study with re-randomisation at week 25 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-4 study (**I**bodutant for **R**elief of **I**rritable Bowel **S**yndrome)

Principal Investigator:
Professor Jan Tack
Department of Internal Medicine
Division of Gastroenterology
Katholieke Universiteit Leuven
University Hospital Gasthuisberg
Herestraat 49
3000 Leuven
Belgium

Study Centre(s):
A total of 139 centres in 9 countries participated in the study, of which 118 centres screened patients and 94 centres randomised patients.

Publication (reference): None.

Study Period:	**Phase of Development:**
26 February 2014 to 03 November 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 24-week oral (PO) treatment period.

Secondary Objectives:

The secondary objectives of this study were:

- To assess the safety and tolerability of ibodutant on 12, 24 and 52-week treatment course with PO 10 mg dose once daily (QD) in IBS-D female patients.
- To evaluate the sustained effect of ibodutant on IBS symptoms in IBS-D female patients.
- To evaluate ibodutant population pharmacokinetics (PK) in IBS-D female patients.

Methodology:

This was a phase III multicentre study comparing ibodutant 10 mg QD PO with placebo in female patients with at least moderate IBS-D.

The study consisted of a first 24-week randomised double-blind parallel group treatment period and a second re-randomised double-blind treatment period of 28 weeks (total treatment duration: 52 weeks) for a total of 14 Study Visits, as detailed below.

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. At randomisation (Visit 3), patients commenced 24 weeks of double-blind treatment in a 1:1 ibodutant:placebo ratio, during which five on-treatment visits occurred: Visit 4 (Day 29), 5 (Day 57), 6 (Day 85), 7 (Day 113) and 8 (Day 141). Patients were to be re-randomised for the second 28-week double-blind treatment period at Visit 9 (Day 169): those previously randomised to ibodutant were to be mock-randomised to ibodutant; those previously randomised to placebo were to be re-randomised in a 1:1 ibodutant:placebo ratio. Three on-treatment visits were scheduled during the second 28-week treatment period: Visit 10 (Day 197), 11 (Day 253), and 12 (Day 309). The second treatment period ended at Visit 13 (Day 365) with the final Visit 14 (Day 379) to occur after completion of a 2-week safety follow-up period. From the start of the double-blind treatment period onwards, rescue medication was permitted in the form of loperamide 2mg, administered at up to 6 capsules per day for a maximum of 4 consecutive days.

When the negative results of the contemporaneous sister study NAK-06 (comparing ibodutant 10 mg QD PO with placebo over 12 weeks followed by a 4-week randomised withdrawal period in the same population included in the NAK-07 study, namely female patients with at least moderate IBS-D) became available, **the Sponsor decided on 03 September 2015 to prematurely terminate the stud**y, also in light of the definitely lower than expected overall (ibodutant/placebo) response rate at week 24.

Number of Patients (Planned and Analysed):

It was planned that 1000 patients would have been screened to ensure completion of 500 patients. A total of 1300 patients were actually screened, of whom 558 patients were randomised (n=277 and n=281 patients randomised to ibodutant and placebo, respectively). Two patients randomised to placebo never took the study medication. At time point of premature study termination, a total of 366 patients had completed study treatment during the first 24-week treatment period and 72 patients have taken the study treatment during the entire second 28-week study period, of whom 37 were allocated to 'Ibodutant – Ibodutant', 17 to 'Placebo – Ibodutant' and 18 to 'Placebo – Placebo' treatment sequences.

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 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 [post-menopausal 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 54 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).

<u>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:</u>

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.
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].

<u>Exclusion criteria</u>

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 with history of inflammatory bowel diseases, complicated diverticulosis (i.e. diverticulitis), ischaemic colitis, microscopic colitis.
6) Patient with 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 with 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 with 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 with history of ectopic endometriosis.
13) Patient with 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 with history of human immunodeficiency virus infection.
15) Patient with history of a cardiovascular event, including stroke, myocardial infarction, congestive heart failure (New York Heart Association class >2), or transient ischemic 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 with history of insulin-dependent diabetes mellitus.
18) Patient with history of 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 with 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 aspartate aminotransferase (AST) >3 times the upper limit of normal or total bilirubin >3 mg/dL (>51.3 µmoL/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 had 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 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 well-being of the patient or the requirements of the study.

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

Ibodutant tablets were administered PO at a dose of one 10 mg tablet QD. The bulk batch numbers were 5021901, 5124501 and 5210001C.

Duration of Study Drug Treatment:

First double-blind treatment period: 24 weeks

Second double-blind treatment period: 28 weeks

Note: At the early study termination date (3rd SEP 2015) randomised patients had all the opportunity to complete study treatment during the first 24-week double-blind treatment period, 321 were re-randomised to the second double-blind 28-week treatment period, while only 72 completed it.

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

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

Criteria for Evaluation:

Efficacy:

The primary evaluation of efficacy was based on the weekly response for abdominal pain intensity AND stool consistency over the first 24 weeks of treatment in ≥50% of the weeks (12 out of 24 weeks).

In addition, the following secondary efficacy endpoints were measured: sustained efficacy evaluated as weekly response for abdominal pain intensity AND stool consistency over the first 24 weeks of treatment applying the 50% rule with at least 2 weeks in the last 4 weeks of treatment (weeks 21-24), weekly response for abdominal pain intensity over the first 24 weeks of treatment in ≥50% of the weeks (12 out of 24 weeks), weekly response in stool consistency over the first 24 weeks of treatment in ≥50% of the weeks (12 out of 24 weeks), weekly abdominal pain responders defined as patients with a ≥30% (≥40%, ≥50%) weekly abdominal pain decrease vs. baseline, weekly stool consistency responders defined as patients with ≥50% decrease in number of days per week with stool types 6 or 7 vs. baseline, weekly response for relief of overall IBS signs and symptoms over 24 weeks of treatment in at least 50% of the weeks of treatment (12 out of 24 weeks), change in IBS signs and symptoms (IBS-SSS) from baseline to weeks 12 and 24, change in weekly average of specific IBS-D symptoms during the first 24-week treatment period, weekly response for abdominal pain intensity AND stool consistency over the first 12 weeks of treatment in ≥50% of the weeks (6 out of 12 weeks).

Pharmacokinetic variables:

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 to be 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 [t1/2] were to be estimated from population parameters.

Note: According to the statistical analysis plan, PK analysis was to be performed ONLY in case that efficacy analysis demonstrated the superiority of ibodutant *versus* placebo.

Pharmacodynamics: Not applicable.

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.

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 00179 (N=48), where a potential serious breach of Good Clinical Practice was reported, and site 00186 (N=34), where disqualification proceedings against the Investigator were initiated by the US Food and Drug Administration.

Per-protocol Population: all patients from the mITT Population who did not experience relevant protocol violations especially 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 who received treatment group drug other than the randomised one.

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

PK/Pharmacodynamic Population: patients from the PK population and placebo subjects from the mITT population.

Primary efficacy endpoint:

The primary endpoint was composed of the weekly response for abdominal pain intensity AND stool consistency over 24 weeks of treatment in ≥50% of the weeks of treatment (12 out of 24 weeks). A patient with less than 4 valid e-diary entries for the corresponding assessments (i.e. abdominal pain intensity and stool consistency) during a week was considered a non-responder for that week. If a patient prematurely discontinued the study, she was considered as a non-responder for the subsequent missing weeks. 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 (OR) with corresponding 95% two-sided confidence interval (CI) for each, and p-value associated with the CMH test were presented.

Secondary and exploratory efficacy endpoints:

- During the first 24-week double-blind treatment period:
  Weekly responses for abdominal pain intensity, stool consistency and relief of overall IBS-SSS were analysed in the same way as the primary efficacy endpoint; the same analyses were also performed each week for weekly abdominal pain and stool consistency response; a patient with missing assessment was to be considered a non-responder for that week. 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 performed.
- During the second double-blind treatment period (28-week period):
  Descriptive statistics, by treatment sequences, were provided for weekly abdominal pain responder (defined as a patient with a decrease versus baseline of at least 30% in the weekly average of abdominal pain intensity from the start to the end of the second 28-week treatment period), stool consistency responder (defined as a patient with a decrease versus baseline of at least 50% in the number of days per week with at least one stool that has a consistency of Type 6 or 7 from the start to the end of the second double-blind treatment period), change in IBS-SSS and in each specific symptoms of IBS-D from baseline to the end of treatment period.

Safety endpoints: AEs were categorized as Treatment-Emergent Signs and Symptoms (TESS) or Non-TESS for each of the study periods based on the onset date/time of AE. Number of events and number of patients (%) were presented by categories (severity, outcome, relationship, seriousness) and by System Organ Class (SOC) and Preferred Term (PT).

Summary of Results:

Efficacy Results:

For the primary endpoint: a total of 51 (21.6%) patients in the ibodutant group were responders, compared with 52 (21.8%) patients in the placebo group. The OR (95% CI) was 0.986 (0.64, 1.53); the difference between treatment groups was not statistically significant (p=0.949) (see Table 1).

Table 1. Number of responders (responder rate %) over the 24-week double-blind treatment period (mITT Population, N=474)

Efficacy Variable	Ibodutant (N=236)	Placebo (N=238)	OR (95% CI)*	p-value[*]
Composite Primary Endpoint				
Response for abdominal pain AND stool consistency	51 (21.6%)	52 (21.8%)	0.986 (0.64, 1.53)	0.949
Main Secondary Endpoints				
Response for abdominal pain intensity	96 (40.7%)	83 (34.9%)	1.280 (0.88,1.86)	0.193
Response for stool consistency	72 (30.5%)	71 (29.8%)	1.032 (0.70,1.53)	0.872
Weekly responders for relief of overall IBS signs and symptoms in ≥50% of the weeks *at week 24*	37 (15.7%)	29 (12.2%)	1.339 (0.79, 2.26)	0.272

Source: Final SAR Tables 14.2.1.1, 14.2.2.1, 14.2.2.3.1 and 14.2.2.6.1
*Odd's Ratio with 95% Confidence Interval, [#]P-value derived from Cochrane Mantel Haenszel test

For the main secondary endpoints: there were similar numbers of responders in both groups for abdominal pain intensity, stool consistency, weekly abdominal pain response (i.e. pain decrease from baseline of ≥30%, ≥40% and ≥50%, respectively), weekly stool consistency response (decrease from baseline of ≥50%) and weekly response for overall IBS signs and symptoms. The number of responders and the responder rates (%) of the main secondary efficacy variables over the 24-week double-blind treatment period (mITT Population, N=474) are summarised in Table 1 above.

There were no consistent significant results in the subgroup analyses, with the exception of:

- the subgroup of patients with baseline IBS-SSS Score > moderate < (N=115), where
  - the response rate of sustained efficacy (*with at least 2 weeks between week 21 and 24*) was higher in the ibodutant group (18, 30.5%) compared to the placebo group (7, 12.5%). The OR (95% CI) was 3.073 (1.17, 8.08); the difference between treatment groups was statistically significant (p=0.020).
  - the response rate for stool consistency (*over 24 weeks*) was higher in the ibodutant group (24, 40.7%) compared to the placebo group (13, 23.2%). The OR (95% CI) was 2.268 (1.01, 5.09); the difference between treatment groups was statistically significant (p=0.046).
  - the weekly response rate for stool consistency by week (i.e. decrease versus baseline of at least 50%) *at week 11* was higher in the ibodutant group (26, 44.1%) compared to the placebo group (14, 25.0%). The OR (95% CI) was 2.363 (1.07, 5.23); the difference between treatment groups was statistically significant (p=0.033).
- the subgroup of patients with BMI ≥30 (N=197), where
  - the weekly response rate for stool consistency by week (i.e. decrease versus baseline of at least 50%) *at week 21* was higher in the ibodutant group (40, 39.6%) compared to the placebo group (25, 26.0%). The OR (95% CI) was 1.862 (1.02, 3.41); the difference between treatment groups was statistically significant (p=0.043).

No differences between groups in the change of IBS-SSS score were observed from baseline to the end of the 24-week double-blind treatment period (p=0.965).

Similar improvements from baseline in IBS-D symptoms were observed in both treatment groups over the 24 week treatment period without clinically relevant changes in patient subgroups.

The combined weekly response for abdominal pain intensity and stool consistency over 12 weeks of treatment in ≥50% of patients of the weeks of treatment (6 out of 12 weeks) did not discriminate from placebo (p=0.701).

For the endpoints related to the second 28-week double-blind treatment period: there were similar numbers of responders in the three treatment sequences for abdominal pain and stool consistency responders (see Table 2):

Table 2. Number of responders (responder rate %) over the 28-week double-blind treatment period (mITT Population – only re-randomised patients, N=300)

Efficacy Variable	Ibodutant - Ibodutant (N=152)	Placebo - Ibodutant (N=73)	Placebo - Placebo (N=75)
Response for abdominal pain	55 (36.2%)	28 (38.4%)	27 (36.0%)
Response for stool consistency	52 (34.2%)	24 (32.9%)	23 (30.7%)

Source: Final SAR Tables 14.2.2.10.10, 14.2.2.10.11.

Similar improvements from baseline to the end of the second double-blind treatment period in IBS-SSS score were observed in the treatment sequences 'Ibodutant – Ibodutant' (mean [SD]: -125.2 [134.49]) and 'Placebo – Placebo' (mean [SD]: -120.0 [129.44]), although a slightly higher improvement was observed in the treatment sequence 'Placebo– Ibodutant' (mean [SD]: -139.6 [125.83]).

The consumption of rescue medication (RM use by week and patient reported days of RM use) was similar in both treatment groups over the first 24-week treatment period and no differences were found between the treatment sequences in the second 28-week double-blind treatment period.

Pharmacokinetic Results:

Not done.

Safety and Tolerability Results:

In the first 24 weeks of double-blind treatment 383 TESS were reported in 163 (29.3%) patients of the Safety Population. Slightly less TESS were reported in the ibodutant group (187 TESS in 81 [29.2%] patients) compared with the placebo group (196 TESS in 82 [29.4%] patients).

Of these, 5 (0.9%) patients experienced 6 serious TESS (ibodutant, 3 TESS in 3 [1.1%] patients; placebo, 3 TESS in 2 (0.7%) patients); none of them related to the study drug. Forty three (7.7%) patients experienced 63 treatment-related TESS (ibodutant, 24 TESS in 20 [7.2%] patients; placebo, 39 TESS in 23 [8.2%] patients).

A total of 9 [1.6%] patients experienced 9 TESS which led to study discontinuation (ibodutant, 6 TESS in 6 [2.2%] patients; placebo, 3 TESS in 3 [1.1%] patients). Two of them were SAEs: patient 001047009 (allocated to ibodutant group) suffered a worsening of cervical spinal stenosis and she was withdrawn at week 5 during the first 24 weeks of double-blind study treatment. Patient 049067010 (allocated to placebo group) suffered a whiplash of the cervical spine at week 10 and she was withdrawn from the study at week 17. There was no death in the first 24 weeks of double-blind study treatment and the majority of TESS was mild.

By System Organ Class (SOC), the most commonly reported TESS were infections and infestations (122 TESS in 90 [16.2%] patients overall) and gastrointestinal disorders (72 TESS in 44 [7.9%] patients overall). By preferred term (PT), no TESS was reported in ≥ 5% of patients overall, with no notable differences between treatment groups in the safety and tolerability profile.

In the following 30 weeks (28-week double-blind treatment period and 2-week follow-up) 153 TESS were reported in 69 (21.5%) patients who received at least one treatment period dose (24 [30.0%] patients randomised to placebo-ibodutant, 33 [20.5%] patients randomised to ibodutant-ibodutant; 12 [15.0%] patients randomised to placebo-placebo sequences).

Of these, 5 (1.6%) patients experienced at least 1 serious TESS (1 [1.3%] patients randomised to placebo-ibodutant and 4 [2.5%] patients randomised to ibodutant-ibodutant) none of them related to the study drug. Three (0.9%) patients experienced at least 1 related TESS (2 [2.5%] patients in placebo-ibodutant and 1 [0.6%] patient in ibodutant-ibodutant treatment sequences).

Severe TESS were reported in 6 patients randomised to the following sequences: ibodutant–ibodutant (4 [2.5%] patients); placebo-ibodutant and placebo-placebo (1 [1.3%] patient each) but none of them was leading to study discontinuation. One patient (001567001) in the ibodutant-ibodutant group died due to a suicide that was judged by the investigator as not related to study treatment.

By System Organ Class (SOC), the most commonly reported TESS were infections and infestations (39 TESS in 33 [10.3%] patients overall) and gastrointestinal disorders (20 TESS in 10 [3.1%] patients overall). By preferred term (PT), no TESS was reported in ≥ 3% of patients overall. There were no notable differences between treatment sequences.

There were no notable changes over time of significant differences between treatment groups in haematology, biochemistry, urinalysis, physical examination, vital signs and ECG.

Conclusions:

- Ibodutant 10 mg QD PO did not demonstrate efficacy over placebo in the treatment of IBS-D in female patients with at least moderate abdominal pain over the 24-week double-blind treatment period.
- Ibodutant 10 mg QD PO was safe and well tolerated.

Date of Final Synopsis: 02 NOV 2016