ORIGINAL ARTICLE

The neurokinin-2 receptor antagonist ibodutant improves overall symptoms, abdominal pain and stool pattern in female patients in a phase II study of diarrhoea-predominant IBS

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ABSTRACT

Background Tachykinins have been implicated in the pathophysiology of IBS with diarrhoea (IBS-D). Our aim was to study the efficacy and safety of ibodutant, a selective neurokinin-2 (NK2) receptor antagonist, in patients with IBS-D.

Methods This multinational double-blind, placebo-controlled study recruited 559 patients with IBS-D according to Rome III criteria. After a 2-week treatment-free run-in, patients were randomised to ibodutant 1 mg, 3 mg, 10 mg or placebo once daily for eight consecutive weeks. Responders were those with a combined response of satisfactory relief (weekly binary question yes/no) of overall IBS symptoms and abdominal pain/discomfort on ≥75% weeks (primary end point). Secondary end points included abdominal pain and stool pattern. Data were also analysed according to US Food and Drug Administration (FDA)-approved interim end points (improvement of pain and stool consistency). Safety was assessed by monitoring adverse events and laboratory tests. Prespecified statistical analysis involved the whole group as well as gender subgroups.

Results Demographics and baseline characteristics were comparable for all treatment arms. In the overall population, responsiveness tended to increase with escalating ibodutant doses. In the prespecified analysis by gender, ibodutant 10 mg demonstrated significant superiority over placebo in females (p=0.003), while no significant effect occurred in males. This was confirmed for secondary end points and for the responder analysis according to FDA-approved end points. The tolerability and safety of ibodutant was excellent at all doses.

Conclusions Ibodutant showed dose-dependent efficacy response in IBS-D, reaching statistical significance at the 10 mg dose in female patients. The safety and tolerability profile of ibodutant was similar to placebo.

Trial registration number NCT01303224.

Significance of this study

What is already known on this subject?

- Hypercontractility and hypersensitivity of the bowel have been implicated in the pathophysiology of IBS with diarrhoea (IBS-D).
- Neurokinins and neurokinin-2 receptors are candidate mediators of hypercontractility and hypersensitivity.
- Ibodutant is a highly selective neurokinin-2 receptor antagonist with high oral bioavailability.

What are the new findings?

- In a controlled phase 2 trial, ibodutant tended to dose-dependently improve symptoms in IBS-D.
- A statistically significant dose–response effect over placebo occurred in female patients, with the best efficacy see at the 10 mg dose of ibodutant.
- Ibodutant showed a tolerance profile similar to placebo.

How might it impact on clinical practice in the foreseeable future?

- The findings confirm involvement of neurokinin-2 receptors in the pathophysiology of IBS-D, at least in female patients.
- As ibodutant does not cross the blood–brain barrier, the findings demonstrate the relevance of peripheral neural changes in neurotransmitter signalling in (women with) IBS-D.
- The results warrant further evaluation of the 10 mg dose of ibodutant in female patients with IBS-D.

INTRODUCTION

The IBS (IBS) is a functional bowel disorder in which abdominal pain or discomfort is associated with defecation or a change in bowel habits, and with features of disordered defecation.[1] It is a chronic, relapsing condition that affects 7–14% of adults in the Western world.[2–4] In the absence of organic abnormalities and specific biological markers, IBS is diagnosed by symptom-based criteria. The Rome working party has established standard diagnostic criteria (Rome criteria) that are based on the most prominent feature of IBS, namely the clear link between abdominal pain or discomfort and bowel function, being either relieved by defecation (suggesting a colonic origin) or associated with change in stool frequency or

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consistency (suggesting changes in intestinal transit).[1 5] IBS is subclassified according to the predominant bowel habits and, according to the most recent Rome III criteria, this subclassification is solely based on stool consistency: patients with loose stools >25% of the time and hard stools <25% of the time are defined as patients with 'IBS with diarrhoea' (IBS-D).[6 7]

Pharmacological treatment of IBS remains challenging with drugs only showing limited effects on single symptoms rather than the whole syndrome.[8–10] Tachykinin (NK) receptor antagonists are a promising class of candidate drugs that have been investigated in several clinical trials during the last decades for their possible use in therapy of a variety of different human diseases.[11 12] This promise has gone largely unfulfilled, however, considering the fact that to date only a few NK1 receptor antagonists were fully developed to registration for the treatment of chemotherapy-induced emesis.[13 14] The tachykinin neurokinin-2 (NK2) receptor (with neurokinin A as the preferred endogenous ligand) is widely and abundantly expressed in the gut, airways and genitourinary tract.[15 16] Its activation, by neurokinin A (NKA) or NK2 receptor-selective ligands, induces prominent biological responses, including a robust and long-lasting contraction of smooth muscle.[17 18] NK2 receptor activation has also been shown to be involved in producing sensory nerve stimulation and activation of visceral reflexes.[19–21] Based on these preclinical findings, it has been speculated that NK2 receptor antagonists could be useful in the treatment of symptoms of IBS.[22 23] Furthermore, in a phase II dose-finding study, the selective tachykinin NK2 receptor antagonist, ibodutant, showed benefit over placebo in patients with diarrhoea-predominant IBS and a baseline pain severity score >1.[24] Supporting evidence for this hypothesis was obtained when administration of exogenous NKA to healthy human volunteers induced powerful intestinal contractions and pain, mimicking spontaneous symptoms of IBS.[25 26]

In this study, we present the results of a phase II study with ibodutant, a potent and selective NK2 receptor antagonist from Menarini Ricerche S.p.A.,[27] showing its ability to alleviate the main symptoms in female patients with IBS-D.

METHODS

Study design

The study was designed as a double-blind, randomised, placebo-controlled, parallel-group study, which was conducted in eight European countries involving a total of 71 sites from October 2010 through May 2012 (clinicaltrials.gov identifier NCT01303224). The trial was designed, conducted and reported in accordance with the principles of the Good Clinical Practice guidelines. The study enrolled patients with a clinical diagnosis of IBS-D according to the Rome III diagnostic criterion.[1] During the experimental clinical phase, patients fulfilled a 2-week screening/run-in period, followed by an 8-week double-blind treatment period and a 2-week treatment withdrawal period, for a total study duration of 12 weeks and an overall five site visits. Patients who met the inclusion criteria entered the screening/run-in period in which demographic data, medical history and concomitant medication were recorded and physical examination, 12-lead ECG, safety blood testing and pregnancy tests were conducted. During the run-in period, patients were instructed to use an Interactive Voice/Web Response System completion to provide daily and weekly assessment of symptoms, to be continued until the end of study. The 2-week screening/run-in period served also as a treatment-free, prospective baseline observation period to characterise the patient's baseline IBS symptoms in the absence of any IBS pharmacological and/or non-pharmacological therapy. At the end of the 2-week screening/run-in period, the patients were randomly allocated in equal proportions in a 1:1:1:1 ratio to one of the following four treatment arms: ibodutant 1 mg, 3 mg or 10 mg, or to placebo. The dose range of 1–10 mg and the study duration of 8 weeks were chosen based on a post hoc analysis of the IRIS-1 dose-finding study, which showed the best response with the 10 mg dose compared with 30 and 60 mg, and which showed therapeutic benefit in the first four weeks.[24]

Randomisation was performed centrally by a computer-generated schedule in blocks of 8 and was balanced within each site. Patients, trial centre personnel and sponsor staff were not aware of the group assignments until the database was locked. Treatments had to be taken in the morning, in fasting conditions once daily and to be continued along the entire 8-week double-blind treatment period. A 2-week post-treatment withdrawal period completed the study in order to assess drug withdrawal/rebound effects. During the double-blind 8-week treatment phase and the 2-week withdrawal phase, the restricted use of loperamide was allowed as rescue medication for severe diarrhoea.

The study was designed by Menarini Pharmaceuticals, conducted by contract research organisation INC Research (legacy: Kendle International S.r.l.) under the supervision of Menarini Ricerche S.p.A., and the data were analysed by personnel at Menarini Ricerche S.p.A. All authors have read and contributed to review the initial draft of the manuscript and approved to submit for publication the final manuscript.

Eligibility criteria

The study population consisted of male and female patients aged 18–70 years, with normal physical examination, able to give written informed consent prior to study entry and compliant to undergo all visits and procedures scheduled in the study. The patients with a clinical diagnosis of IBS-D were eligible if they met the symptom-based criteria as determined by the Rome III modular questionnaire, reporting that they had recurrent abdominal pain or discomfort for at least 3 days per month in the last 3 months associated with at least two of the following characteristics: improvement with defecation; onset associated with a change in the frequency of stool; onset associated with a change in form (appearance) of stool. In addition, patients had to report symptom onset at least 6 months prior to diagnosis, loose or watery stools at least 25% of the time in the last 3 months, hard or lumpy stools <25% of the time in the last 3 months and more than three bowel movements per day at least 25% of the time in the last 3 months. The study population was also confined to patients with abdominal pain of at least moderate intensity on at least 3 days per week (based on daily diaries, see below) and a weekly average of at least three bowel movements per day during both weeks of the 2-week run-in period. Patients older than 50 years or patients with a positive family history of colorectal cancer required a normal colonoscopy or flexible sigmoidoscopy performed within the last 5 years and after the onset of IBS symptoms, and completed before screening visit. During the study, women of childbearing potential were required the use of a highly effective contraceptive method throughout the entire study period and up to 30 days post treatment. Patients were not eligible to participate in the study if they met any of the following key exclusion criteria: organic abnormalities of the GI tract, including history of colonic or major abdominal surgery, current or previous diagnosis of neoplasia (except non-GI neoplasia in complete remission ≥5 years), IBSs, symptomatic gallbladder stone disease,

complicated diverticulosis (ie, diverticulitis) and ectopic endometriosis. Patients with alarm signs (eg, fever, rectal bleeding, unintentional weight loss, anaemia) required additional examinations in order to exclude any organic GI diseases. From the study were also excluded patients with history of gluten enteropathy; lactose intolerance as assessed by response to diet; history of positive tests for ova or parasites, or occult blood in the stool in the previous 6 months; a diagnosis of diabetes mellitus (either type 1 or 2); unstable medical conditions; and major psychiatric, neurological, cardiovascular disorders or uncontrolled metabolic disease. In accordance with guidelines,[19] drugs with specific effects on bowel function and or pain such as antimuscarinic drugs, drugs enhancing intestinal motility (eg, laxatives and prokinetic drugs) and analgesics were prohibited. Antidepressants (and benzodiazepines) were allowed as single agents provided patients were on stable dose 6 months prior to study entry and were maintained at stable dose during the study. Patients were asked to refrain from relevant changes in dietary habits, lifestyle or exercise regimen starting from 2 months prior to study entry until the end of the trial.

Study end points

In agreement with guidance from the European Medicines Agency (EMA),[28] the dual primary end point was the response of satisfactory relief of overall IBS symptoms and the response of satisfactory relief of abdominal pain/discomfort response at the end of 8 weeks of treatment. For each primary end point separately, the response was defined as at least 6 weeks with satisfactory relief during 8 weeks of treatment (75% rule) (weekly interactive voice response system (IVRS)/interactive web response system (IWR) diary records). The chosen primary end point was in accordance with the EMA guidelines that were accepted and available at the time of the start of the study, requesting end points that allow demonstration of significant changes in both overall IBS symptoms and abdominal pain, and advocate a response definition requiring improvement for at least 50% of the time.[28] The release of the US Food and Drug Administration (FDA) guidelines regarding the IBS efficacy criteria that new drugs have to satisfy for IBS-D,[29] published only at the end of the clinical trial, gave new indications for inclusion criteria of patients with IBS-D as well as response criteria for the evaluation of efficacy of new drugs and offered the opportunity to evaluate ibodutant also according to different efficacy criteria versus placebo. A number of secondary clinical efficacy end points were considered to further outline the efficacy of ibodutant and to evaluate the dose–effect relationship as follows: response for relief of overall IBS symptoms and of abdominal pain/discomfort over 8 weeks of treatment, where response was defined as at least 4 weeks with satisfactory relief during 8 weeks of treatment (50% rule) and as at least two consecutive weeks of satisfactory relief during week 5 to week 8; assessment of health-related quality of life. Exploratory efficacy end points were also assessed in order to better characterise the efficacy profile of ibodutant on individual symptoms that characterise IBS-D, that is, stool frequency, stool consistency, abdominal pain, bloating and urgency, its impact on the use of loperamide, as well as to evaluate the time course of the effects of ibodutant, namely its effect after the first four weeks of treatment and the effect of 2-week treatment withdrawal.

Assessments

Through the daily IVRS/IWRS diary, the following assessments were recorded: IBS symptoms (abdominal pain, abdominal bloating and urgency) using a balanced five-point scale with 0=no symptoms, 1=mild, 2=moderate, 3=severe, 4=very severe; stool frequency (number of bowel movements per day); stool consistency (for every bowel movement on that day) using the seven-point Bristol Stool Scale with 1='separate hard lumps, like nuts, hard to pass', 2='sausage shaped, but lumpy', 3='like sausages, but with cracks on surface', 4='like sausage or snake, smooth and soft', 5='soft blobs with clear cut edges (passed easily)', 6='fluffy pieces with ragged edges, a mushy stool', 7='watery, no solid pieces, entirely liquid'.[30]

Through the weekly IVRS/IWRS diary, the IBS symptom relief was evaluated for the primary and secondary end point using the answers to the single-item binary (yes/no) questions: *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?* IBS symptom severity rate was also assessed based on the answers to the following question: *how would you rate your IBS symptoms abdominal discomfort/pain, bowel habits, and other IBS symptoms during the last week?* using a five-point scale ranging from 0='no symptoms' to 5='very severe symptoms'. According to the end points endorsed by FDA guideline for IBS-D,[29] due to the thorough daily diary data collection during the run-in phase, it was possible to apply the new proposed FDA entry criteria. Therefore, data were analysed according to the following response definitions based on the weekly response for abdominal pain and stool consistency (combined and separately): a weekly responder should be defined as a patient who achieves a decrease in the weekly average of worst daily abdominal pain in the past 24 h score of at least 30% compared with baseline and a ≥50% reduction in the number of days per week with at least one stool that has the consistency of Bristol Stool Scale (BSS) type 6 or 7 compared with baseline. This response definition had to be met for at least 50% of the weeks of treatment. Health-related quality of life was evaluated using the European Quality of Life Questionnaire 5D (EQ-5D) assessing the change in EQ-5D score at the end of 8 weeks of treatment versus baseline. It comprised a visual analogue scale ranges from '0'=worst imaginable health state to '100'=best imaginable health state and the five subdomains 'mobility', 'self-care', 'usual activities', 'pain/discomfort' and 'anxiety/depression'. Exploratory efficacy end points included mean changes between 8 weeks of treatment and baseline in stool frequency, stool consistency (BSS), abdominal pain, abdominal bloating, urgency (five-point scales) and IBS-symptom severity score (IBS-SSS). Moreover, exploratory end points comprised the mean use of rescue medication (loperamide 2 mg) and the response in terms of IBS-SSS improvement (≥50 score point reduction in IBS-SSS). According to the statistical analysis plan, primary, secondary, exploratory and FDA-endorsed end points were separately analysed by gender, age (<50 vs >50 years) and IBS severity at baseline (mild/moderate/severe IBS-SSS). The site investigators assessed also patient-reported adverse events (AEs), serious AEs and other safety evaluations including physical examination, vital signs, safety laboratory tests and 12-lead ECG.

Statistical analysis

We calculated that a sample size of 560 evaluable patients was needed in order to provide approximately 80% power in rejecting the null hypothesis of equality between any dose of ibodutant and placebo on the basis of the following assumptions: primary end point rate for placebo=40%; expected mean therapeutic gain over placebo=15% for at least one out of three tested doses of ibodutant; significance level=5% two-sided. The lead author had access to detailed numerical data; statistical

analysis was conducted by the sponsor. All efficacy analyses were run on the intention-to-treat (ITT) population except for the FDA-endorsed end points,[29] for whom a modified ITT (mITT) population was applied (see below). All variables were presented using appropriate descriptive statistics according to the variable nature; continuous variables: number of non-missing observations, mean, SD, minimum, median, and maximum; categorical variables: number of non-missing observations and relevant percentages. The primary efficacy end point was analysed using a Mantel–Haenszel test in a 2×2 contingency table to compare separately each of the three active treatment groups with placebo. A two-sided overall significance level of 5% was used. The following pairs of hypotheses were to be tested:

H_{01}: $p_{Placebo}=p_{1\ mg}$ against H_{A1}: $p_{Placebo} \neq p_{1\ mg}$,
H_{02}: $p_{Placebo}=p_{3\ mg}$ against H_{A2}: $p_{Placebo} \neq p_{3\ mg}$,
H_{03}: $p_{Placebo}=p_{10\ mg}$ against H_{A3}: $p_{Placebo} \neq p_{10\ mg}$,

where p was defined as the proportion of responders at the 75% rule of satisfactory relief of IBS symptoms and abdominal pain/discomfort in a particular treatment arm. Multiplicity was adjusted by using the Hochberg procedure. Secondary end points with binary outcome were analysed in the same way as the primary end point. Secondary end points with continuous outcome were non-normally distributed and, hence, analysed by applying the non-parametric Wilcoxon rank-sum test, comparing the placebo and each treatment group, and applying the Hochberg procedure to avoid an accumulation of type I error. Exploratory variables and safety variables were analysed by means of descriptive statistics only. IBS-D response criteria according to the FDA guidelines[29] were analysed using a Mantel–Haenszel and adjustment for multiplicity by using the Hochberg procedure analogously to the primary efficacy analysis. All safety analyses were performed on the safety population, that is, all patients who took at least one dose of study medication.

RESULTS

Patients

A total of 1054 patients were recruited and started a 2-week run-in period for confirmation of IBS-D severity and baseline assessment. Of these, 565 patients were eligible for randomisation, indicating a screening failure rate of 53.6%. Details of the patient disposition are available in figure 1. A total of 559 patients took at least one dose of study medication and provided at least one primary end point assessment, forming the ITT population (ibodutant 1 mg: n=140; ibodutant 3 mg: n=138;

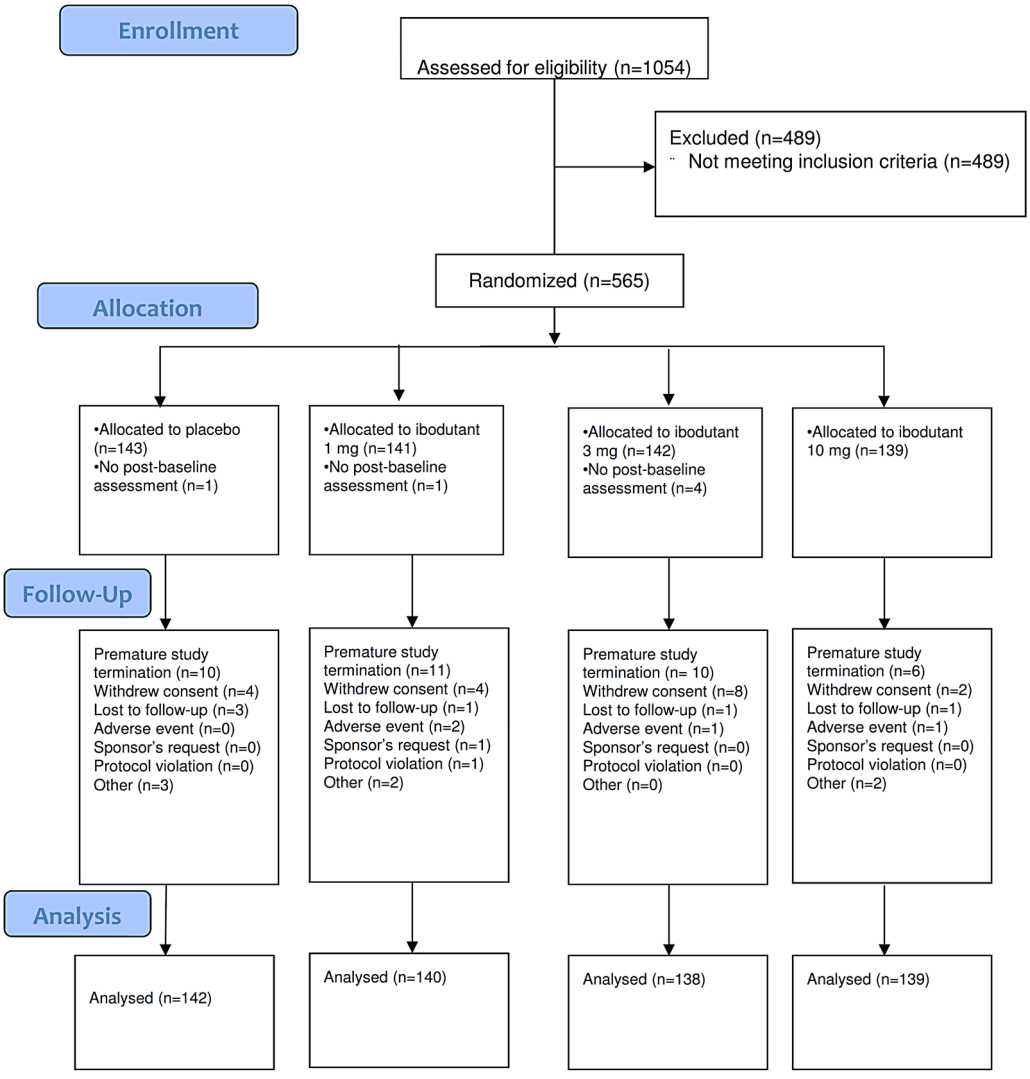

Figure 1 Consort flow diagram.

ibodutant 10 mg: n=139; and placebo: n=142). In order to comply with the FDA entry criteria for patients with IBS-D, seven patients from the overall ITT population were excluded because of insufficient baseline severity, leading to a mITT population of 552 patients (ibodutant 1 mg: n=139; ibodutant 3 mg: n=138; ibodutant 10 mg: n=136 patients; placebo: n=139) on which it was possible to analyse the efficacy of ibodutant according to FDA-endorsed end points. Patient groups were well comparable with respect to baseline demographics and baseline characteristics (tables 1 and 2). On average, study patients were predominantly females (n=333 (59.6%)), on average 46.0±13.5 years of age, without any noteworthy differences between the treatment groups.

Primary efficacy end point and FDA-endorsed end points

In terms of satisfactory relief of overall IBS symptoms and abdominal pain/discomfort (75% rule; combined primary end point), an incremental response with increasing doses of ibodutant (1, 3 and 10 mg) could be shown in the overall ITT population of patients with IBS-D, although none of the ibodutant doses achieved statistically significant superiority over placebo following 8 weeks of treatment after correcting for multiple testing (figure 2). In this regard, it is noteworthy that the definition of combined satisfactory relief of overall IBS symptoms and abdominal pain/discomfort was particularly stringent because relief of both, overall IBS symptoms and abdominal pain/discomfort, had to be reported in the same week in order to satisfy this combined end point.

In the statistical analysis plan, responses in each gender were analysed separately. Female patients, which accounted for the majority of the study participants, showed a clear dose-dependent response in terms of satisfactory relief of overall IBS symptoms and abdominal pain/discomfort to ibodutant according to the 75% rule. While only 24.4% of the women responded to placebo, the response rate rose to 36.0% under ibodutant 1 mg, 40.2% under ibodutant 3 mg and reached 46.8% of response in the ibodutant 10 mg group. The latter, almost doubled response rate, observed with ibodutant 10 mg achieved statistical significance over placebo (p=0.003; figure 2). No such effect was observed in male study participants where 31.2% responded to placebo, 25.5% to ibodutant 1 mg, 21.6% to ibodutant 3 mg and 30.0% to ibodutant 10 mg.

When the study data were analysed according to the abdominal pain and stool consistency response definitions endorsed by the FDA, ibodutant 10 mg once daily provided a superior response in terms of stool consistency compared with placebo in the overall study population. The analysis according to gender confirmed a particularly striking response in female patients (n=220) when the FDA criteria for response were applied. In terms of combined weekly response for abdominal pain and stool consistency, the responder rate in females treated with ibodutant 10 mg was 54.5% compared with 31.2% with placebo (p = 0.003). The weekly response for stool consistency showed a statistically significant superiority of ibodutant 10 mg in both the subpopulation of female patients (p=0.017) and in the overall population (p=0.014; table 3). Similar to the analysis according to the binary satisfactory relief end point, no corresponding benefit could be demonstrated in male patients with IBS-D using the FDA-endorsed end points.

Secondary efficacy end points

In terms of satisfactory relief of overall IBS symptoms and abdominal pain/discomfort (50% rule; combined primary end point, with at least two consecutive weeks of satisfactory relief during week 5 to week 8), a statistically significant superiority of ibodutant 10 mg over placebo was shown in the entire population (p=0.015) and in female patients only (p=0.014). The percentage of responders in female patients in the 10 mg group was 60.8% vs 41.0% in placebo group (p=0.014).

Table 1 Demographic and baseline characteristics of the patients (intention-to-treat population)*

Characteristic	Placebo N=142	Ibodutant 1 mg N=140	Ibodutant 3 mg N=138	Ibodutant 10 mg N=139	p Value†
Mean age (range)—years	44 (20–70)	46 (18–70)	47 (18–69)	47 (18–69)	0.27
Age ≥65 years—no. of patients (%)	10 (7.0%)	11 (7.8%)	15 (10.8%)	10 (7.2%)	0.68
Sex—no. of patients (%)					
Female	78 (54.5)	89 (63.3)	87 (61.3)	79 (56.8)	0.75
Male	64 (44.4)	51 (36.2)	51 (35.9)	60 (43.2)	0.67
Race—no. of patients (%)‡					
White	142 (100.0)	140 (100.0)	138 (100.0)	138 (99.3)	0.99
Asian	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	–
Body mass index§	26.9±4.62	26.2±5.04	25.8±4.28	26.1±4.46	0.77
Stool frequency—mean/day	4.4±1.2	4.6±1.5	4.4±1.3	4.4±1.5	0.28
Stool consistency score¶	5.7±0.6	5.7±0.6	5.7±0.5	5.7±0.6	0.70
Abdominal pain score**	2.3±0.5	2.5±0.6	2.3±0.5	2.3±0.5	0.051
Bloating score**	2.2±0.6	2.4±0.8	2.2±0.7	2.2±0.7	0.086
Urgency score**	2.4±0.6	2.5±0.7	2.5±0.6	2.4±0.6	0.094
IBS-symptom severity score (IBS-SSS)††	355±69	343±68	333±78	332±74	0.38

*Plus-minus values are means±SD.
†p Values were calculated with the use of analysis of variance for continuous data and the Cochran–Mantel–Haenszel test for categorical data.
‡Race was self-reported.
§The body mass index is the weight in kilograms divided by the square of the height in metres.
¶Stool consistency was assessed with the use of the seven-point Bristol Stool Form Scale, where 1 indicates separate, hard lumps, like nuts (hard to pass); 2 sausage-shaped but lumpy; 3 like a sausage but with cracks on the surface; 4 like a sausage or snake, smooth and soft; 5 soft blobs with clear-cut edges (passed easily); 6 fluffy pieces with ragged edges or a mushy stool; and 7 watery, no solid pieces (entirely liquid).
**Abdominal pain, bloating and urgency were all assessed with the use of a five-point ordinal scale: 0 indicates none, 1 mild, 3 severe and 4 very severe.
††The IBS-SSS is a five-item questionnaire to assess IBS symptom severity including that includes four visual analogue scales. Each item can range between 0 and 100 so that the overall sum of scores ranges between 0 (best) and 500 (worst) score points.

Table 2 IBS symptom severity at baseline (visit 2)—intention-to-treat population (n=559)

	Ibodutant 1 mg N=140 n (%)	Ibodutant 3 mg N=138 n (%)	Ibodutant 10 mg N=139 n (%)	Placebo N=142 n (%)	Total N=559 n (%)
Abdominal pain score*					
n	140	138	139	142	559
Mean (SD)	2.5 (±0.6)	2.3 (±0.5)	2.3 (±0.5)	2.3 (±0.6)	2.3 (±0.5)
Median (min; max)	2.4 (1.4; 4.0)	2.2 (1.5; 3.5)	2.2 (1.4; 3.9)	2.2 (1.4; 4.0)	2.3 (1.4; 4.0)
Bloating score*					
n	140	138	139	142	559
Mean (SD)	2.4 (±0.8)	2.2 (±0.7)	2.2 (±0.7)	2.2 (±0.6)	2.3 (±0.7)
Median (min; max)	2.4 (0.0, 4.0)	2.2 (0.0; 3.9)	2.2 (0.0; 3.9)	2.3 (0.5; 3.8)	2.3 (0.0; 4.0)
Urgency score*					
n	140	138	139	142	559
Mean (SD)	2.5 (±0.7)	2.5 (±0.6)	2.4 (±0.6)	2.4 (±0.6)	2.4 (±0.7)
Median (min; max)	2.5 (0.8; 4.0)	2.5 (1.1; 4.0)	2.4 (1.0; 4.0)	2.4 (0.4; 4.0)	2.4 (0.4; 4.0)
Stool frequency/day					
n	140	138	139	142	559
Mean (SD)	4.6 (±1.5)	4.4 (±1.3)	4.4 (±1.5)	4.4 (±1.2)	4.5 (±1.4)
Median (min; max)	4.3 (2.7; 10.4)	4.4 (2.8; 10.6)	4.1 (2.6; 11.9)	4.2 (2.8; 8.9)	4.2 (2.6; 11.9)
Stool consistency†					
n	140	138	139	142	559
Mean (SD)	5.7 (±0.6)	5.7 (±0.5)	5.7 (±0.6)	5.7 (±0.6)	5.7 (±0.6)
Median (min; max)	5.7 (4.4; 7.0)	5.6 (4.3; 7.0)	5.6 (4.1; 7.0)	5.7 (4.0; 7.0)	5.7 (4.0; 7.0)
IBS-SSS score‡					
n	140	138	139	142	559
Mean (SD)	343.4 (±68.8)	333.3 (±78.3)	332.6 (±74.3)	335.7 (±69.4)	336.3 (±72.7)
Median (min; max)	345.5 (134; 495)	347 (70; 460)	329 (147; 500)	330.5 (130; 48)	336.3 (70; 500)
IBS symptom severity rate*					
n	140	138	139	142	559
Mean (SD)	2.7 (±0.7)	2.6 (±0.6)	2.6 (±0.6)	2.6 (±0.6)	2.7 (±0.6)
Median (min; max)	3.0 (1.0; 4.0)	3.0 (1.0; 4.0)	3.0 (1.0; 4.0)	3.0 (1.0; 4.0)	3.0 (1.0; 4.0)
EQ-5D QoL VAS score§					
n	140	138	139	142	559
Mean (SD)	54.5 (±22.9)	55.5 (±21.9)	58.1 (±22.9)	55.3 (±22.3)	55.8 (±22.5)
Median (min; max)	60.0 (5.0; 100)	55.0 (2.0; 96.0)	61.0 (5.0; 100)	56.5 (0.0; 95)	60 (0.0; 100)

*Five-point scale ranging from '0'= no symptoms to '5'=very severe.
†Seven-point BSS ranging from '1'=hard lumpy stool to '7'=watery, liquid stool.
‡IBS-SSS, ranging from '0' to '500'.
§EQ-5D QoL VAS ranging from '0'=worst imaginable health state to '100'=best imaginable health state.
EQ-5D QoL VAS, European Quality of Life Questionnaire 5D Visual Analogue Scale; IBS-SSS, IBS-symptom severity score.

Additionally analysed secondary end points assessed the separate components of the primary end point, that is, the response of satisfactory relief of overall IBS symptoms and of abdominal pain. Results on the relief of abdominal pain showed a statistically significant superiority of ibodutant 10 mg in both the overall population and the subpopulation of female patients (p values respectively 0.009 and 0.025).

Satisfactory relief of overall IBS symptoms over the 8-week double-blind treatment phase showed a higher response rate in the ibodutant 10 mg group, especially in the subpopulation of female patients (48.2% and 53.2%, respectively) over placebo (38.7% and 45.1%, respectively); however, this numerical difference did not reach statistical significance after correction for multiple testing (table 4).

Exploratory efficacy end points and related quality-of-life end points

In female patients, ibodutant 10 mg also elicited a marked improvement of stool consistency (figure 3) (tendency towards less loose/water stools), and in the average of the daily reported stool frequency (figure 4) and urgency (figure 5). These exploratory end points were only descriptively analysed.

Quality of life according to the EQ-5D questionnaire improved similarly in all treatment groups including placebo, with no demonstrable significant advantage of any ibodutant dose over placebo. The use of rescue medication and the response in terms of IBS-SSS improvement (≥50 score point reduction in IBS-SSS) also did not show any statistically significant difference among treatment groups.

Treatment-free withdrawal phase

During the 2-week treatment-free withdrawal phase, patients continued to report their IBS symptoms and the response rates for the primary end point of satisfactory relief of overall IBS symptom and abdominal pain/discomfort declined markedly in all treatment groups. This decline was higher in the ibodutant treatment groups (approximately 10–15%) than in the placebo group (approximately 4%), but there were no signs of rebound worsening after cessation of active therapy.

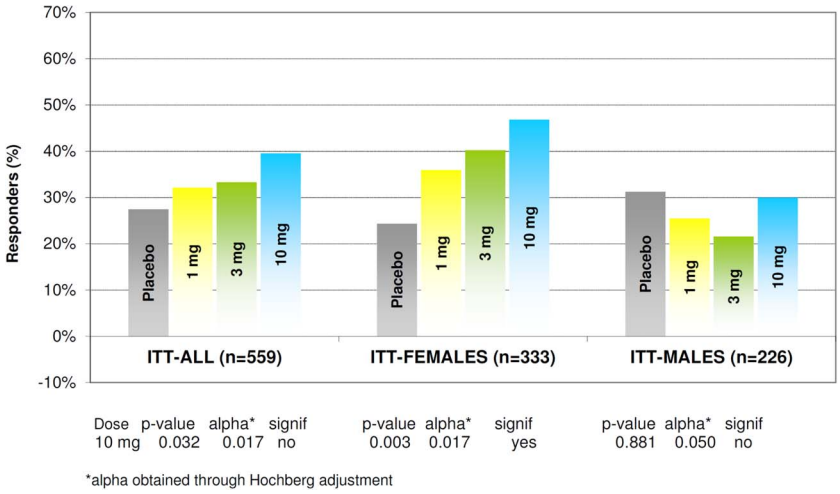

Figure 2 Primary end point: response to different doses in the entire population, female patients and male patients. ITT, intention-to-treat.

Safety results

The incidence of treatment-related treatment-emergent signs and symptoms (TESSs) and serious TESS was extremely low: along the entire study duration with 8 weeks of repeated treatment in 565 patients with IBS-D (safety population), 45 patients (8.0%) reported a total of 73 TESSs, which were considered at least possibly treatment-related—most commonly non-specific events like headache and nausea—without any overt difference among treatments. Table 5 summarises TESS type and incidence across the study arms.

Only five serious TESS occurred (three in the placebo group (mydriasis, abdominal pain, uterine leiomyoma), one in the ibodutant 3 mg group (appendicitis) and one in the ibodutant 10 mg group (type 2 diabetes mellitus))—all of them considered not related to study medication. Moreover, neither dose of ibodutant elicited any relevant changes in safety laboratory tests, ECG parameters or vital signs so that it can be stated that ibodutant has shown a good safety profile. The very low incidence of patients who withdrew from the treatment/study confirms the good tolerability of ibodutant.

DISCUSSION

In the present study, we evaluated the efficacy and safety of three different doses of ibodutant, a highly selective NK2 antagonist, in patients with IBS-D. The prespecified analysis evaluated satisfactory relief of abdominal pain and of overall IBS-D symptoms in the entire population as a group and in each gender separately. In addition, the data were analysed using the more recently published FDA-recommended end points for IBS-D.[29] The data consistently show significant improvement of overall symptoms and of abdominal pain severity with the 10 mg dose in female patients with IBS-D.

Currently, treatment options for patients with IBS-D are limited. Musculotropic agents and loperamide are the first-line agents of choice, but both do not address the full symptom spectrum of IBS-D.[31] Alosetron, a 5-HT3 receptor antagonist, was shown to be efficacious for the treatment of IBS-D in women only, but is only available in a restricted user programme in the USA due to an associated risk of ischaemic colitis.[8 32] In 2015, the FDA also approved rifaximin and eluxadoline for the treatment of IBS-D,[33] but to date no approval by the EMA has occurred.

The 2003 EMA guidance for the evaluation of treatment trials in IBS recommended to assess change in overall symptoms and in severity of abdominal pain/discomfort co-primary end points.[28] In line with previous trials[34–36] and with the published EMA guidance, we used the weekly assessment of the binary end point of satisfactory relief of either overall symptoms or

Table 3 US Food and Drug Administration end point

	1 mg	3 mg	10 mg	Placebo
Weekly response for abdominal pain and stool consistency (% and 95% CI)				
Overall (n=552)	42.5% (34.2% to 50.7%) (p=0.39)	38.4% (30.3% to 46.5%) (p=0.86)	49.3% (40.9% to 57.7%) (p=0.050)	37.4% (29.4% to 45.5%)
Female (n=330)	44.9% (34.6% to 55.3%) (p=0.70)	44.8% (34.4% to 55.3%) (p=0.074)	54.6% (43.4% to 65.7%) (p=0.0035)*	31.2% (20.8% to 41.5%)
Male	38.0% (24.6% to 51.5%) (p=0.45)	27.5% (15.2% to 39.7%) (p=0.054)	42.4% (29.8% to 55.0%) (p=0.76)	45.2% (32.8% to 57.6%)
Weekly response for stool consistency (% and 95% CI)				
Overall (n=552)	58.3% (50.1% to 66.5%) (p=0.40)	54.4% (46.0% to 62.7%) (p=0.85)	67.7% (59.8% to 75.5%) (p=0.014)*	53.2% (44.9% to 61.5%)
Female (n=330)	58.4% (48.2% to 68.7%) (p=0.24)	59.8% (49.5% to 70.1%) (p=0.18)	74.0% (64.2% to 83.8%) (p=0.0017)*	49.4% (38.2% to 60.5%)
Male	58.0% (44.3% to 71.7%) (p=0.99)	45.1% (31.4% to 58.8%) (p=0.17)	59.3% (46.8% to 71.9%) (p=0.025)	58.1% (45.8% to 70.4%)

Table 4 Secondary end point

	1 mg	3 mg	10 mg	Placebo
Response for relief of overall symptoms and abdominal pain—50% rule (% and 95% CI)				
Overall (n=559)	51.4% (43.2% to 59.7%) (p=0.35)	44.2% (35.9% to 52.5%) (p=0.032)	53.2% (44.9% to 61.5%) (p=0.015)*	38.7% (30.7% to 46.7%)
Female (n=333)	56.2% (45.9% to 66.5%) (p=0.051)	51.7% (41.2% to 62.2%) (p=0.17)	60.8% (50.0% to 71.5%) (p=0.014)*	41.0% (30.1% to 51.9%)
Male	43.1% (29.5% to 56.7%) (p=0.43)	31.4% (18.6% to 44.1%) (p=0.61)	43.3% (30.8% to 55.9%) (p=0.40)	35.9% (24.2% to 47.7%)
Relief of overall symptoms—75% rule (% and 95% CI)				
Overall (n=559)	41.4% (33.3% to 49.6%) (p=0.48)	39.1% (31.0% to 47.3%) (p=0.75)	48.2% (39.9% to 56.5%) (p=0.066)	37.3% (29.4% to 45.3%)
Female (n=333)	44.9% (34.6% to 55.3%) (p =0.40)	46.0% (35.5% to 56.5%) (p=0.33)	53.2% (42.2% to 64.2%) (p=0.065)	38.5% (27.7% to 49.3%)
Male	35.3% (22.2% to 48.4%) (p=0.94)	27.5% (15.2% to 39.7%) (p=0.33)	41.7% (29.2% to 54.1%) (p=0.51)	35.9% (24.2% to 47.7%)
Relief of abdominal pain—75% rule (% and 95% CI)				
Overall (n=559)	37.9% (29.8% to 45.9%) (p=0.34)	42.0% (33.8% to 50.3%) (p=0.096)	47.5% (39.2% to 55.8%) (p=0.009)	32.4% (24.7% to 40.1%)
Female (n=333)	41.6% (31.3% to 51.8%) (p=0.072)	49.4% (38.9% to 59.9%) (p=0.0055)*	51.9% (40.9% to 62.9%) (p=0.0025)*	28.2% (18.2% to 38.2%)
Male	31.4% (18.6% to 44.1%) (p=0.49)	29.4% (16.9% to 41.9%) (p=0.36)	41.7% (29.2% to 54.1%) (p=0.64)	37.5% (25.6% to 49.4%)

severity of abdominal pain/discomfort as a primary outcome variable. The binary end points have been used in a large number of IBS trials and have shown ability to detect clinically relevant improvement in symptom severity.[34–36] We set a particularly high threshold for response by requesting satisfactory relief of both variables in the same week, for 75% of the weeks. Through this approach, response really requires improvement of the IBS-D symptom pattern in all its aspects, and placebo response rates are potentially lower. A dose-dependent response was observed for the overall responder rate and for each co-primary end point separately in female patients. The 10 mg dose showed the largest response in females, with a margin over placebo of 23%. Similar results were obtained in secondary outcome variables, including analyses where 50% of the weeks were considered sufficient for response, or separate analysis of the effects on abdominal pain. The observed beneficial effects were also confirmed when the FDA-defined end points for IBS-D trials were used. Both the FDA-endorsed and EMA-endorsed end points are well established and accepted to reflect clinically meaningful changes, indicating that ibodutant provides important benefits in a condition for which only a few therapeutic options are currently available.

A previous study evaluated dose ranges between 10 and 60 mg daily in the overall IBS population, showing a statistically

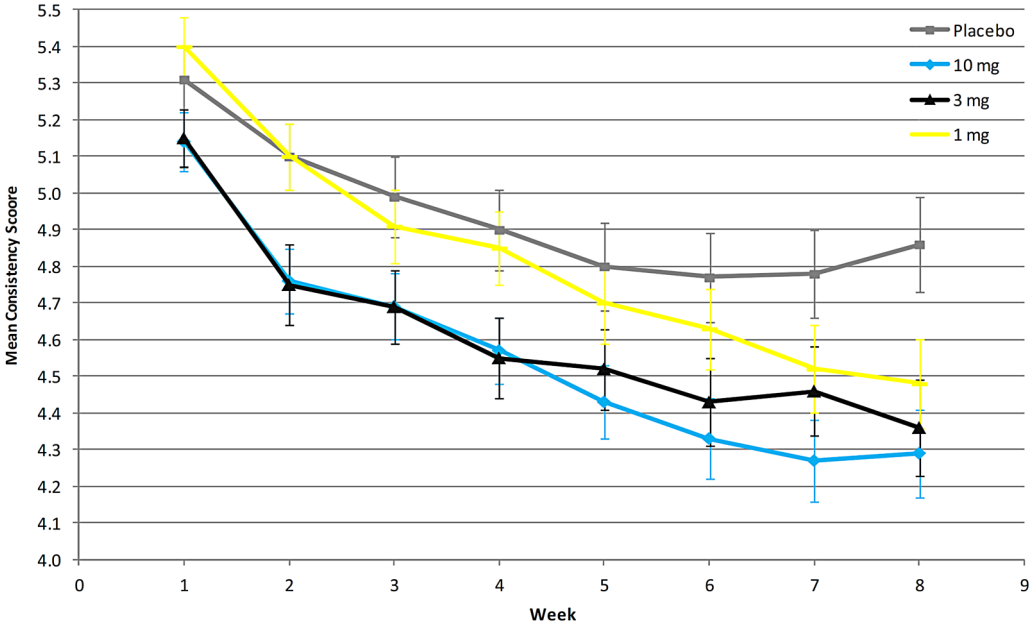

Figure 3 Mean stool consistency by week for female patients (n=333).

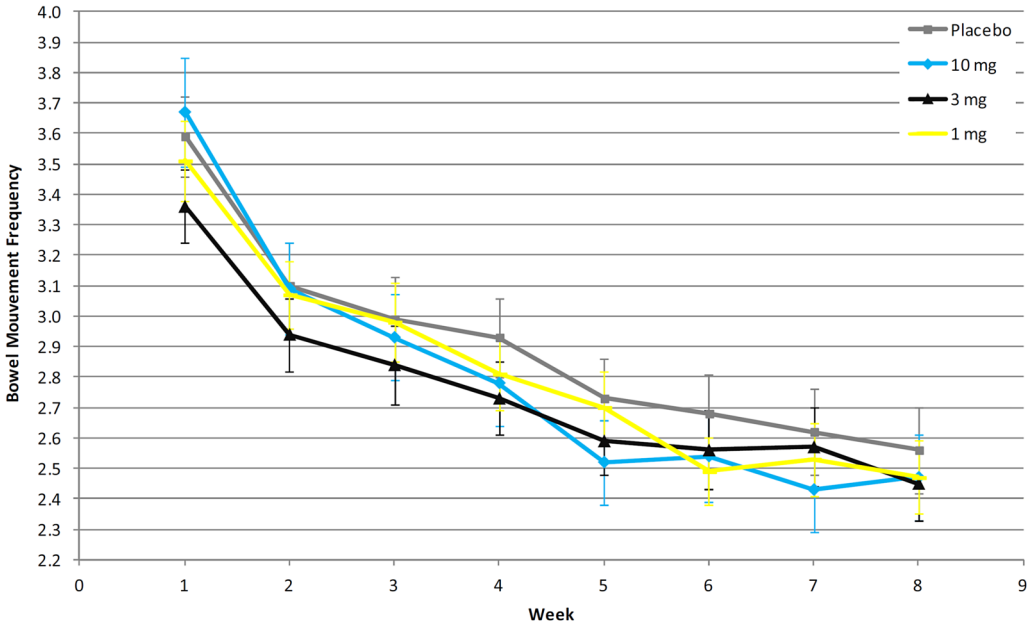

Figure 4 Mean stool frequency by week for female patients (n=333).

non-significant but consistent trend towards a higher response with the 10 mg dose in the IBS-D subgroup of patients, with no particular differences by gender, suggesting that males could not be completely unresponsive to ibodutant.[24] In the present study, nevertheless, no significant effects were obtained in the male population, either using the EMA-specified or FDA-specified end points. The reason for this gender-based discrepancy is currently under further investigation, but may reflect differences in pathophysiology of IBS-D, or differences in expression or sensitivity of NK2 receptors in males compared with females.[37] In favour of a different pathophysiological mechanism in IBS-D in females versus males, initial studies with alosetron also found efficacy mainly in females, and the drug was only approved for females in the USA.[9] Pharmacokinetic analyses from previous studies with ibodutant did not show differences in plasma levels or distribution volume as explanation of the gender difference.[24]

In addition to the efficacy findings, ibodutant displayed an excellent safety and tolerance profile in the current and in previous studies.[24] These trials showed no differences between treatments in the incidence rates for individual AEs, and SAEs were rare. The fact that a previous study evaluating higher doses of ibodutant also failed to show any drug-related AEs is particularly reassuring.[24] The fact that ibodutant does not cross the blood–brain barrier well is also reassuring in terms of tolerance and safety.[24]

The lack of central nervous system penetration of the drug also establishes a peripheral site of action underlying the

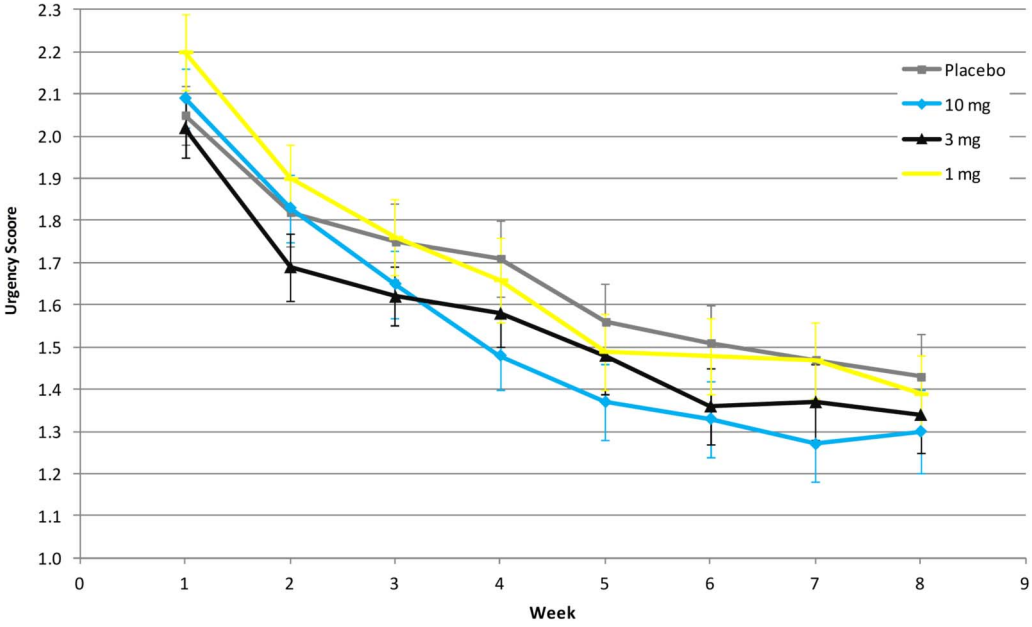

Figure 5 Mean stool urgency by week for female patients (n=333).

Table 5 Incidence of treatment-emergent signs and symptoms (TESS) and type TESS occurring in ≥2% of patients in either treatment group

	Ibodutant 1 mg N=141 n (%)	Ibodutant 3 mg N=142 n (%)	Ibodutant 10 mg N=139 n (%)	Placebo N=143 n (%)	Total N=565 n (%)
Number of TESSs	57	73	71	56	257
Number of patients reporting at least one TESS	42 (29.8)	41 (28.9)	43 (30.9)	32 (22.4)	158 (28.0)
Number of patients reporting at least one treatment-related* TESS	13 (9.2)	8 (5.6)	10 (7.2)	12 (8.4)	43 (7.7)
Number of patients reporting at least one severe TESS†	1 (2.4)	2 (4.9)	1 (2.3)	3 (9.4)	7 (4.4)
Number of patients reporting at least one TESS leading to study discontinuation†	3 (7.1)	4 (9.8)	1 (2.3)	0 (0.0)	8 (5.1)
Number of patients reporting at least one SAE (serious TESS)	0 (0.0)	1 (0.7)	1 (0.7)	3 (2.1)	5 (0.9)
Number of patients reporting at least one AE that resulted in death	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

System organ class preferred term	#—n (%)	#—n (%)	#—n (%)	#—n (%)	#—n (%)
GI disorders	13—13 (9.2)	11—11 (7.7)	8—8 (5.8)	12—11 (7.7)	44—43 (7.6)
Abdominal pain	1—1 (0.7)	2—2 (1.4)	0—0 (0.0)	4—3 (2.1)	7—6 (1.1)
Nausea	1—1 (0.7)	4—4 (2.8)	5—5 (3.6)	3—3 (2.1)	16—16 (2.8)
Infections and infestations	10—8 (5.7)	22—22 (15.5)	21—21 (15.1)	14—14 (9.8)	67—65 (11.5)
Gastroenteritis	0—0 (0.0)	2—2 (1.4)	3—3 (2.2)	0—0 (0.0)	5—5 (0.9)
Influenza	0—0 (0.0)	2—2 (1.4)	3—3 (2.2)	5—5 (3.5)	10—10 (1.8)
Nasopharyngitis	6—5 (3.5)	4—4 (2.8)	5—5 (3.6)	3—3 (2.1)	18—17 (3.0)
Upper respiratory tract infection	0—0 (0.0)	0—0 (0.0)	3—3 (2.2)	1—1 (0.7)	4—4 (0.7)
Investigations	5—5 (3.5)	4—3 (2.1)	7—7 (5.0)	2—2 (1.4)	18—17 (3.0)
Blood creatine phosphokinase increased	3—3 (2.1)	0—0 (0.0)	1—1 (0.7)	1—1 (0.7)	5—5 (0.9)
Nervous system disorders	11—11 (7.8)	6—6 (4.2)	12—9 (6.5)	8—7 (4.9)	37—33 (5.8)
Dizziness	3—3 (2.1)	2—2 (1.4)	1—1 (0.7)	0—0 (0.0)	6—6 (1.1)
Headache	7—7 (5.0)	3—3 (2.1)	11—8 (5.8)	4—4 (2.8)	25—22 (3.9)

*Treatment-related TESSs are those with a relationship to study treatment of 'certain', 'probable', 'possible' or 'unassessable/unclassifiable' on the adverse event page.
†Percentage calculated on the number of patients with at least one TESS.
#, number of events; n, number of patients; SAE, serious adverse event.

observed symptomatic benefit. Extensive studies in animal models, as well as observations in healthy humans (NKA infusion study), indicate that tachykinins are not involved in the control of normal visceral sensorimotor function, but play a role in exaggerated contractility and hypersensitivity under pathological conditions. The improvements in overall symptoms, abdominal pain and stool pattern support a similar role for NK2 receptor activation in the GI tract as a key pathophysiological mechanism in women with IBS-D. Moreover, in a preclinical study,[16] it was established that the site of action of NK2 receptor antagonists in relieving visceral hyperalgesia is a peripheral, inside the gut wall.

A number of exploratory end points were also evaluated in the current study. Both the IBS-SSS and the EQ5 questionnaire did not show a significant difference between placebo and ibodutant doses. Presumably, these questionnaires are more subject to placebo responses than the primary and secondary end points, and demonstrating quality of life benefits in IBS may require the use of disease-specific questionnaires, such as the IBS-QOL.[38]

The present study shows efficacy for the 10 mg dose of ibodutant in female patients with IBS-D, with an attractive tolerance and safety profile. In males with IBS-D, in contrast, no efficacy was shown with the current dose range (1–10 mg daily). The efficacy and safety profile of the NK2 receptor antagonist ibodutant observed in the present study support its further evaluation for the treatment of women with IBS-D.

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Patient consent Obtained.

Ethics approval Each participating centre's board approved the study.

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The neurokinin-2 receptor antagonist ibodutant improves overall symptoms, abdominal pain and stool pattern in female patients in a phase II study of diarrhoea-predominant IBS

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