Evaluation of Efficacy Variables in Clinical Study of Irritable Bowel Syndrome with Diarrhea

January 2018

Motoko IDA

Evaluation of Efficacy Variables in Clinical Study of Irritable Bowel Syndrome with Diarrhea

A Dissertation Submitted to
the Graduate School of Life and Environmental Sciences,
the University of Tsukuba
in Partial Fulfillment of the Requirements
for the Degree of Doctor of Philosophy in Biotechnology
(Doctoral Program in Bioindustrial Sciences)

Motoko IDA

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Abbreviations

At least a 50% reduction from baseline	≥50% reduction
Bristol Stool Form Scale	BSFS
95% confidence intervals	95% CIs
Corticotropin-releasing hormone	CRH
Full analysis set	FAS
Food and Drug Administration	FDA
Good Clinical Practice	GCP
Good Post-marketing Study Practice	GPSP
5-Hydroxytryptamine, serotonin	5-HT
5-Hydroxytryptamine 3	5-HT_3
Irritable bowel syndrome	IBS
IBS with diarrhea	IBS-D
IBS with constipation	IBS-C
IBS Severity Index	IBSSI
Japanese versions of the IBS severity index	IBSSI-J
Patient reported outcome	PRO
Quality of life	QOL
Ramosetron hydrochloride	Ramosetron

Introduction

The choice of primary endpoint for a clinical trial is one of the most important determinants of the ability of a clinical trial to demonstrate the efficacy of therapeutic agents. Physiological outcomes such as clinical laboratory values and doctor's assessment are often used with high reliability in clinical trials, since objectivity and doctor's judgment are regarded as important for drug development. However, among diseases, there are functional diseases in which no abnormality is observed in clinical laboratory values or diagnostic imaging. In these diseases, the development of evidence-based drugs is delayed due to lack of appropriate primary endpoints in clinical trials. Irritable bowel syndrome (IBS) is one such disease; patients are reported to be less satisfied with existing treatments and to repeatedly shop for doctors [1]. Finding variables that can properly evaluate drug efficacy and developing new drugs will increase the options for new treatments for patients who are struggling with IBS treatment and can fulfill the needs of the medical industry. The purpose of this study was to evaluate and examine clinically meaningful variables in clinical studies of ramosetron hydrochloride (ramosetron) for patients with IBS with diarrhea (IBS-D).

Pathophysiology of IBS

IBS is a functional disease characterized by prolonged persistence or recurrence of abnormal bowel habits and abdominal pain and discomfort without organic diseases or biochemical abnormalities [2]. IBS is not a life-threatening disease, but has been shown to limit the activity of patients and to

negatively impact social functioning, with substantial economic loss [3]. It is also reported that IBS can severely compromise the patient's quality of life (QOL), even to a greater extent than in patients with end-stage renal disease or patients with diabetes [4]. Surveys conducted outside Japan have reported that the estimated prevalence of IBS in the general population is from 5% to 20%, with about 200 new patients per 100,000 population per year [5, 6]. In Japan, a large population-based internet survey by Kanazawa et al. revealed that about 16.5% of the survey population met the Rome III criteria for IBS, which is established by Rome committee, the international working group on Functional Bowel Disorders and Functional Abdominal Pain [7]. A web-based survey by Miwa that used Rome III showed that 13% of the respondents had IBS [8].

IBS as defined by the Rome III criteria [9] is classified into four subtypes: IBS-D, IBS with constipation (IBS-C), mixed-type IBS, and unsubtyped IBS. A variety of factors are considered to be involved in the etiology of IBS, including abnormal gastrointestinal motility, visceral hypersensitivity, abnormal brain–gut interactions, gastrointestinal infection and sociopsychological strain [10]. Stress-related disturbance of brain–gut interactions is a particularly important factor in functional gastrointestinal disorders including IBS [11]. IBS patients reported significantly more stress than controls without bowel dysfunction and the slope of the regression equation relating bowel symptoms to stress was significantly steeper for the IBS group [12].

Psychosocial stress causes stimulation of the hypothalamus, releasing corticotropin-releasing hormone (CRH), and causes abnormalities in gastrointestinal motility and lowering of the sensory threshold in the

gastrointestinal tract via neurotransmitters, such as 5-hydroxytryptamine, serotonin (5-HT) released from enteric nerves or enterochromaffin cells. Some evidence suggests that 5-HT has a crucial role in IBS-D pathophysiology. Patients with IBS-D show exaggerated colonic motility in response to colonic distention [13] and secretion of 5-HT [14]. Moreover, in animal studies and clinical pharmacological tests, 5-hydroxytryptamine 3 (5-HT_3) receptor antagonists have been reported to suppress abnormalities of gastrointestinal motility (abnormal bowel movements) and a decrease in the sensory threshold in the gastrointestinal tract caused by CRH and stresses [15-17], which suggests involvement of the 5-HT_3 receptor in the occurrence of IBS-D symptoms.

Development of ramosetron

Ramosetron, a potent and selective 5-HT_3 receptor antagonist was developed at Astellas pharmaceutical company in Japan [15, 18-20] (Figure 1). In rats, ramosetron clearly reduces stress-induced diarrhea and defecation caused by CRH [15, 19]. In addition, ramosetron increases the threshold of abdominal pain responses induced by colonic distension in rats [21]. Thus, ramosetron is expected to improve IBS symptoms via reducing the vicious cycle for stress-related disturbance of brain–gut interactions. Figure 2 summarized pathophysiology of IBS and mode of action of ramosetron [21].

The efficacy of ramosetron for patients with IBS-D was demonstrated based on the results of improvement of overall IBS symptoms in a previous phase II and III study [22, 23]. However, stratified analysis by sex using the chi-

square test (two-sided significance level of 0.05) in the phase III study revealed that ramosetron did not show significant improvement compared to placebo in the global assessments of relief of the overall IBS symptoms of female patients [23]. Based on the above results, marketing approval was granted for the indication of “IBS-D in male patients” in Japan in July 2008. Subsequently, additional clinical studies were conducted to evaluate the efficacy and safety of ramosetron for female patients with IBS-D [24-26]. These studies indicated that 2.5 μg/day of ramosetron was an effective treatment for female patients with IBS-D, in contrast to the optimal dose of ramosetron at 5 μg/day for male patients. Ramosetron was approved for use by women in May 2015.

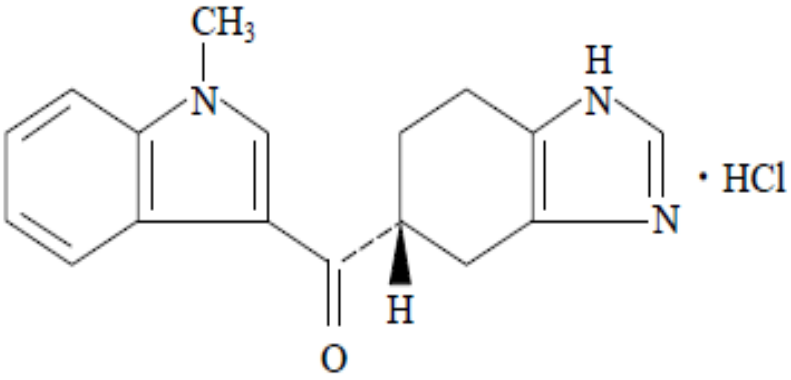
Efficacy variables in clinical trials

Rome committee discussed primary variables in clinical studies for functional gastrointestinal tract disturbances including IBS. It was concluded that, since IBS is a syndrome, instead of evaluating individual symptoms the improvement of overall symptoms of the syndrome should be assessed and subjects should evaluate the effects of therapeutics because improvement of subjective symptoms is clinically important for IBS [27]. Consequently, IBS clinical trials commonly used patient-reported rating of change in overall IBS symptoms as the primary endpoint, which have included “Adequate relief” or “Satisfactory relief” and “Subject global assessment of relief” of IBS symptoms. Those endpoints required patients to average either specific symptoms or all signs and symptoms of IBS in a 1-week and then compare the weekly average to past period like before trial entry. Table 1 summarized primary variables used

in the clinical trials for the same class drug as ramosetron.

As well, “global assessment of relief of overall IBS symptoms” was chosen to be the primary variables for previous clinical trials of ramosetron [22, 23], and its efficacy was demonstrated. Abdominal pain and discomfort, which were the main subjective symptoms of patients with IBS-D, would be assessed by subjects as “global assessment of relief of abdominal pain/discomfort” and that symptoms of diarrhea, such as abnormal stool form, frequent bowel movement and defecation urgency, would be evaluated by patients as “global assessment of improvement in abnormal bowel habits”. These two global assessments focused on the main subjective symptoms in the patients with IBS-D and individual IBS symptoms were assessed as secondary valuables. Table 2 showed global assessments used in clinical trials of ramosetron. Global assessment allows patients to assess improvement of multiple IBS symptoms, however, global assessment cannot show how ramosetron is effective for individual IBS symptoms. Therefore, it was deemed beneficial to assess “clinically meaningful improvements, focusing on the patient’s chief complaint and the severity of major IBS symptoms” in addition to the global assessment.

I firstly explored and examined those variables and I found the “improvement in stool consistency” can be a valuable to show how ramosetron is effective for individual IBS symptoms. Secondary, I show the results of clinical studies used the newly developed variable, “improvement in stool consistency” as primary endpoint to evaluate the prospective effect of ramosetron. Finally, I discuss and conclude the efficacy variables in clinical study for patients with IBS-D. This manuscript referred to List of Published Articles 1 and 2.



Chemical name：(-)-(*R*)-5-[(1-Methyl-1*H*-indol-3-yl)carbonyl]-4, 5, 6, 7-tetrahydro-1*H*-benzimidazole monohydrochloride

Molecular formula：$C_{17}H_{17}N_3O$・HCl

Molecular weight：315.80

General name：Ramosetron hydrochloride

Figure 1. Structure of ramosetron.

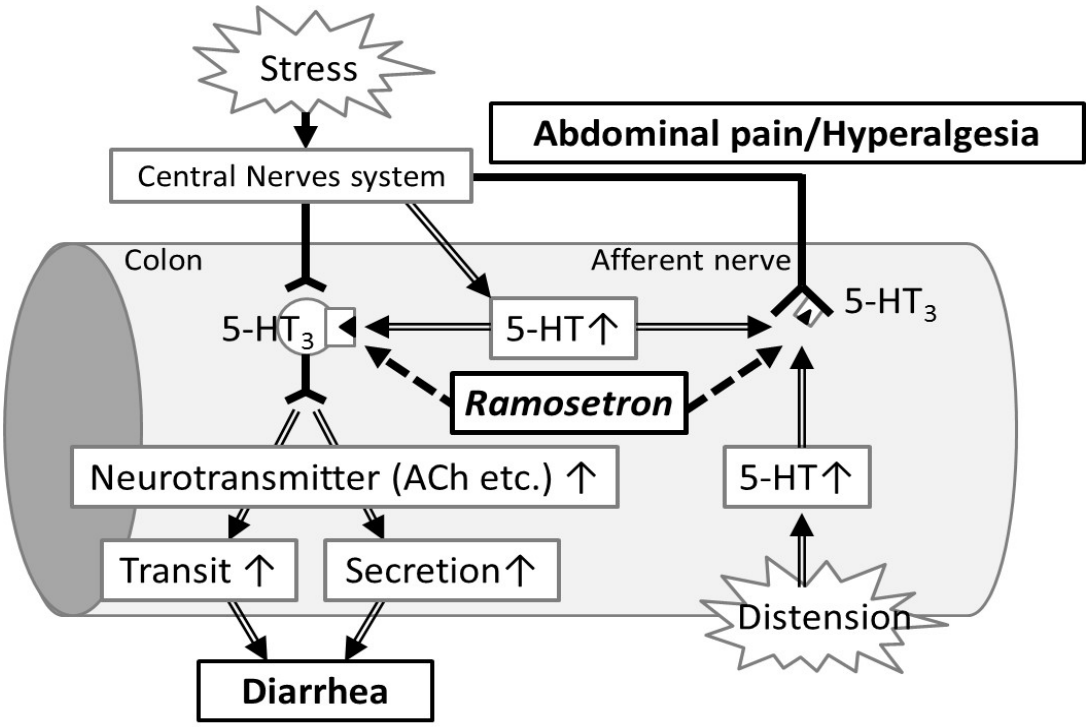


Figure 2. Pathophysiology of IBS and mode of action of ramosetron [Modified Figure 7 in reference 21].

Table 1. Primary variables used in IBS clinical trials for the same class drug as ramosetron

Primary Endpoint	Question and Answer	Drug and Indication
Adequate relief	Q. In the past 7 days, have you had adequate relief of your IBS pain or discomfort? A. Binary (Yes/No)	Alosetron ($5HT_3$ antagonist) IBS-D [28-30]
Satisfactory relief	Q. Did you have satisfactory relief of your overall IBS symptoms / your abdominal discomfort or pain during the last week? A. Binary (Yes/No)	Tegaserod ($5HT_4$ partial agonist) IBS-C [31-34]
Subject global assessment of relief	Q. Please consider how you felt during the past treatment period in regard to your IBS, in particular your overall well-being, and symptoms of abdominal pain/discomfort and altered bowel habit. Compared to the way you usually felt before entering the trial, how would you rate your relief of symptoms during the past week? A. 5-Point Likert scale	

Table 2. Global assessments used in clinical trials of ramosetron

Endpoints	Question and Answer
<Primary> Global assessment of relief of overall IBS symptoms	Q. How would you rate your relief of overall IBS symptoms during the past week compared to the way you usually felt before entering the trial? A. 0, completely relieved; 1, considerably relieved; 2, somewhat relieved; 3, unchanged; and 4, worsened
<Secondary> Global assessment of relief of abdominal pain/discomfort	Q. How would you rate your relief of abdominal pain/discomfort during the past week compared to the way you usually felt before entering the trial? A. 0, completely relieved; 1, considerably relieved; 2, somewhat relieved; 3, unchanged; and 4, worsened
<Secondary> Global assessment of improvement in abnormal bowel habits	Q. How would you rate your relief of abnormal bowel habits during the past week compared to the way you usually felt before entering the trial? A. 0, nearly normalized; 1, considerably relieved; 2, somewhat relieved; 3, unchanged; and 4, worsened

Definition of responder	
Weekly responders	Patients with scores of 0 or 1 at each weekly evaluation point.
Monthly responders	Patients who were weekly responders for at least 2 of the 4 weeks.

Chapter 1 Evaluation of Efficacy Variables Focusing on the Patient's Chief Complaint and the Severity of Major IBS Symptoms

A randomized, placebo-controlled, phase IV pilot study was conducted to explore and examine efficacy variables focusing on the patient's chief complaint and the severity of major IBS symptoms in male patients with IBS-D (Clinicaltrials.gov ID: NCT00918411). The study protocol was designed in accordance with the Declaration of Helsinki, Good Clinical Practice (GCP), Good Post-marketing Study Practice (GPSP), the applicable laws and regulations and was approved by the institutional review board at each site. All patients provided written informed consent prior to participating in study-related procedures.

This chapter is divided into 3 parts. First part shows the general methods and results in the previously used variables including global assessments in this phase IV pilot study, second and third parts concentrate on the results focusing on the severity of major IBS symptoms and the patient's chief complaint, respectively [List of Published Articles 1 and 2].

1.1 Synopsis of Phase IV Pilot Study (General Results Including Global Assessments)

1.1.1 Background

This study was conducted from June 2009 to December 2009 at 25 Japanese centers that have departments of gastroenterology as post marketing study, where clinical study was conducted within the approved indication of ramosetron. This part showed general methods and results in the previously used variables including global assessments in this phase IV pilot study.

1.1.2 Methods

1) Patient Population

Male outpatients aged 20–64 years were diagnosed with IBS-D based on the Rome III criteria. In the Rome III criteria [9], IBS-D is defined as recurrent abdominal pain/discomfort for at least 3 days per month in the preceding 3 months, in association with two or more of the following: improvement with defecation, onset associated with a change in the frequency of stools, and/or onset associated with a change in the form (appearance) of stools. Furthermore, patients have loose (mushy) or watery stools at least 25% of the time and hard or lumpy stools for less than 25% of bowel movements.

Patients were eligible if they fulfilled the criteria for the last 3 months, with symptom onset at least 6 months prior to diagnosis. Organic diseases were excluded by colonoscopy or double-contrast barium enema if these examinations had not been performed within 5 years. Based on a medical interview conducted by the attending physician before provisional registration,

patients were excluded if any of the following were evident: a history of resection of the stomach, small intestine, or large intestine (excluding appendicitis or resection of benign polyps); history or current evidence of inflammatory bowel disease; history or current evidence of ischemic colitis, concurrent infectious enteritis, hyperthyroidism, hypothyroidism, or other diseases that may affect gastrointestinal transit or colonic function; history or current evidence of abuse of drugs or alcohol within the previous year; malignant tumors; current evidence of severe depression or a severe anxiety disorder that could potentially affect the evaluation of study drug efficacy; concurrent serious cardiovascular, respiratory, renal, hepatic, gastrointestinal (excluding IBS), hematological, or neurological/psychiatric diseases; or a history of drug allergies. In addition, patients were excluded if they were using drugs or undergoing examinations that could affect the evaluation of study drug efficacy; if they had been enrolled in previous clinical studies of ramosetron or had taken ramosetron; and if they were participating or had participated in other clinical studies within the 12 weeks prior to study initiation.

Patients satisfying the inclusion and exclusion criteria for typical IBS-D symptoms during a 1-week baseline period were enrolled. To avoid enrolling patients with extremely mild IBS, severity of abdominal pain/discomfort had to exceed mean scores of 0.7 or more assessed daily on a 5-point ordinate (numerical rating) scale (0, none; 1, mild; 2, moderate; 3, severe; and 4, intolerable). The number of bowel movements had to exceed three times or more per week. Stool consistency was assessed with using the Bristol Stool Form Scale (BSFS) [9, 10] as follows; type 1, separate hard lumps, like nuts (hard to pass); type 2, sausage shaped but lumpy; type 3, like a sausage but

with cracks on its surface; type 4, like a sausage or snake, smooth and soft; type 5, soft blobs with clear-cut edges (passed easily); type 6, fluffy pieces with ragged edges (mushy stool); or type 7, watery, no solid pieces, and entirely liquid (Figure 3). Following this classification of stool consistency using the BSFS, patients who had either type 1 or type 2 stools were excluded to enroll patients who are showing symptoms of IBS-D. Patients who had not used drugs or undergone examinations that could affect the evaluation of study drug efficacy within 10 days prior to randomization; who recorded all items in the patient diary for 5 days or more during the baseline period; and who were not judged ineligible for the study according to the clinical laboratory test results obtained before the baseline period were randomized and then given treatment.

2) Study Design

This randomized, placebo-controlled clinical study comprised a provisional registration period, a 1-week baseline period, and a 12-week treatment period, similar to previous studies [22, 23]. Following the baseline period, eligible patients were randomly assigned to 12-week oral treatments with placebo or ramosetron 5 μg once daily before breakfast. Visits were scheduled at Weeks 2, 4, 8, and 12 (or at discontinuation) to assess treatment efficacy, drug compliance, and occurrence of adverse events. Randomization was performed in a 1:1 ratio using a block size of four based on a randomization list developed by a third-party contract research organization. Placebo tablets were externally distinguishable from ramosetron tablets, however, they were indistinguishable when packaged in press through pack sheets. Patients were prohibited to use drugs or undergo examinations, such as other IBS therapeutic

drugs, antidiarrheal drugs, and colonoscopy, that could affect the evaluation of study drug efficacy during the treatment period. All patients, investigators, and sponsors were blinded until all observations and evaluations were completed, the statistical analysis plan was finalized, and all data had been locked.

3) Data Collection

During the baseline and treatment periods, patients recorded their IBS symptoms daily on paper diary cards at bedtime. In the diary, patients recorded the BSFS for every bowel movement throughout the study period. Patients scored severity on a 5-point ordinate (numerical rating) scale and the duration of all continuous abdominal pain/discomfort from Week 1 to Week 4, Week 8 and Week 12 they had experienced. Urgency and feeling of incomplete evacuation were assessed on a binary scale. Every 7 days during the treatment period, patients also graded summarized IBS symptoms compared with the baseline period on a 5-point ordinate scale as follows: relief of overall IBS symptoms and abdominal pain/discomfort (0, completely relieved; 1, considerably relieved; 2, somewhat relieved; 3, unchanged; and 4, worsened) and improvement in abnormal bowel habits (0, nearly normalized; 1, considerably relieved; 2, somewhat relieved; 3, unchanged; and 4, worsened) (Table 2). Patients assessed IBS severity using the Japanese version of the IBS Severity Index (IBSSI-J) every 4 weeks [35, 36]. Symptoms related to the chief complaint were assessed by an investigator at an interview.

4) Efficacy Endpoints

In the monthly responder rates for global assessment of relief of overall IBS symptoms, relief of abdominal pain/discomfort and improvement in abnormal bowel habits, patients with scores of 0 or 1 at each weekly evaluation point were defined as weekly responders, and patients who were weekly responders for at least 2 of the 4 weeks were defined as monthly responders (Table 2). All adverse events were recorded during the intervention period.

5) Statistical Analysis

Sample sizes of 60 patients or more (30 patients/group or more) were set based on the feasibility of a post marketing study to explore and examine the endpoints of the patient's chief complaint or IBS severity. Statistical analysis was performed using SAS Drug Development (ver. 3.4) and PC-SAS (ver. 8.2) (SAS Institute Inc., Cary, NC, USA).

Efficacy analyses included the full analysis set (FAS), which included all patients who received at least one dose of the study drug during the treatment period and for whom at least one endpoint could be evaluated. Safety analyses were performed for all patients who received at least one dose of the study drug during the treatment period.

Monthly responder rates for global assessment are expressed as a percentage of responders, and 95% confidence intervals (95% CIs) are presented. The treatment groups were compared using the chi-square test with a two-sided significance level of 0.05.

1.1.3 Results

1) Overall Study Population

Figure 4 showed flowchart showing patient progress throughout the study. Written informed consent was provided by 115 patients. Of these, 17 patients dropped out and 98 patients were randomly allocated to the ramosetron 5 μg group (n = 47), or the placebo group (n = 51). Ultimately 44 patients in the ramosetron 5 μg group and 45 patients in the placebo group completed the study. The reasons for discontinuation are shown in Figure 4. In the placebo group, one patient discontinued by withdrawing consent after randomization, with no data, and was excluded from the FAS used in the efficacy analyses. The decision to exclude this patient from FAS was taken before unblinding, according to the predefined procedure stipulated in the study protocol. Demographic and baseline characteristics were similar among patients allocated to each group (Table 3). The medication adherence rates were 97.6% in the ramosetron 5 μg group and 97.9% in the placebo group.

2) Global Assessment

The monthly responder rate for global assessment of relief of overall IBS symptoms at the last evaluation point was 46.8% (95% CI, 32.1-61.9) in the ramosetron 5 μg group and 34.0% (95% CI, 21.2-48.8, *P* = 0.281) in the placebo group (Figure 5). Even though the number of patients enrolled in this study is limited, a statistically significant difference between ramosetron and placebo was shown in the Month 2 (*P* = 0.012). Monthly responder rates for improvement in abnormal bowel habits in the ramosetron 5 μg group were significantly higher than those in the placebo group in the Month 1 (*P* = 0.015)

and the Month 3 (P = 0.048) (Figure 6A). On the other hand, monthly responder rates for relief of abdominal pain/discomfort in the ramosetron 5 μg group did not show a statistically significant difference between ramosetron and placebo at any evaluation point (Figure 6B).

3) Safety

Safety was evaluated for all 98 patients. Adverse events were experienced by 27 patients (57.4%) in the ramosetron 5 μg group and by 20 patients (39.2%) in the placebo group (Table 4). The incidence of hard stool was higher in the ramosetron 5 μg group than in the placebo group, which was considered to be caused by the pharmacological action of ramosetron. All the events including constipation and hard stool observed in this study were mild and improved quickly. There was no occurrence of ischemic colitis or serious adverse events.

1.1.4 Discussion

Despite the limited patient number in this study, statistically significant differences between ramosetron and placebo were shown in the monthly responder rate for global assessment of relief of overall IBS symptoms in the Month 2 and in the monthly responder rates for improvement in abnormal bowel habits in the Month 1 and the Month 3. Improvement in bowel habits was shown to contribute to improvement of global assessment of relief of overall IBS symptoms, as in previous studies [23]. On the other hand, the difference between the ramosetron 5 μg and the placebo groups was not evident in the monthly responder rate for relief of abdominal pain/discomfort. In the other

study with the larger patient number, the ramosetron group showed a statistically significant improvement compared to the placebo group in the monthly responder rates for relief of abdominal pain/discomfort [23, 25, 37]. It is considered that ramosetron can show the effect more clearly on abnormal bowel habits than abdominal pain/discomfort.

1		Separate hard lumps, like nuts (hard to pass)
2		Sausage-shaped but lumpy
3		Like a sausage but with cracks in its 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 (a mushy stool)
7	Entirely liquid	Watery, no solid pieces

Figure 3. Bristol Stool Form Scale (BSFS) [9, 10].

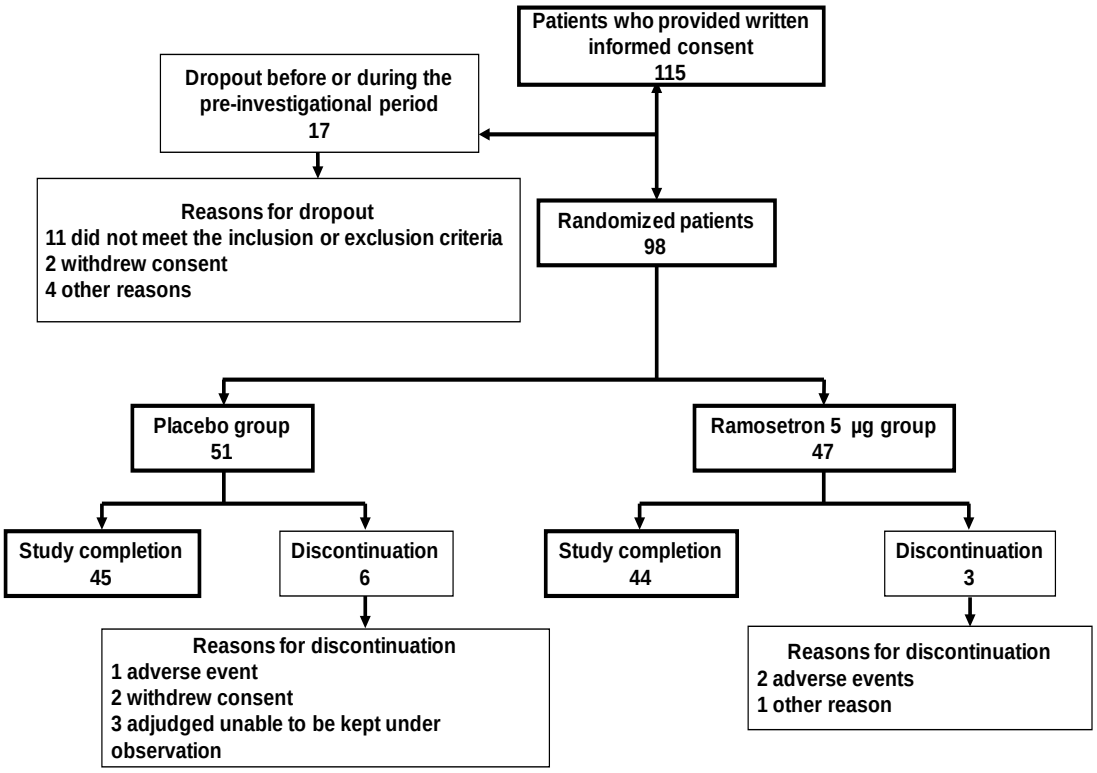


Figure 4. Flowchart showing patient progress throughout the study. Reasons for dropping out of the study are shown.

Table 3. Demographics and baseline characteristics

Patient background	Placebo (n = 50)	Ramosetron 5 μg (n = 47)	*P* value
Age (years)	40.9 ± 11.11	41.0 ± 9.31	0.97
Duration of disease (months)	103.9 ± 90.27	111.5 ± 129.10	0.738
Severity of abdominal pain/discomfort (0-4)	1.43 ± 0.58	1.52 ± 0.61	0.481
Bristol Stool Form Scale (1-7)	5.55 ± 0.66	5.52 ± 0.43	0.764
Stool frequency (times/day)	2.77 ± 1.33	2.44 ± 1.09	0.181

Data are expressed as mean ± standard deviation. *P* values were calculated using analysis of variance.

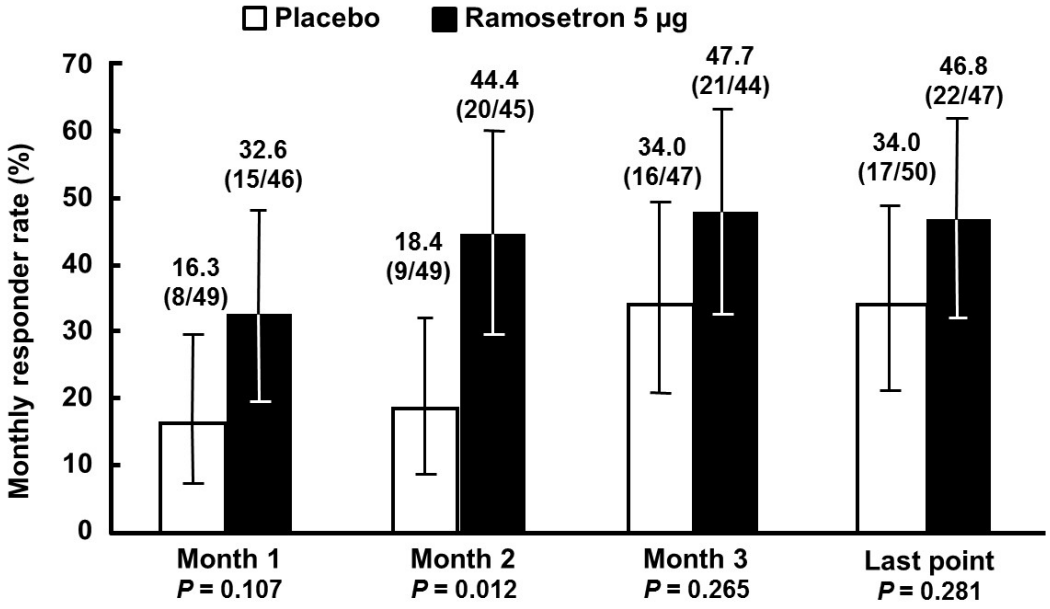
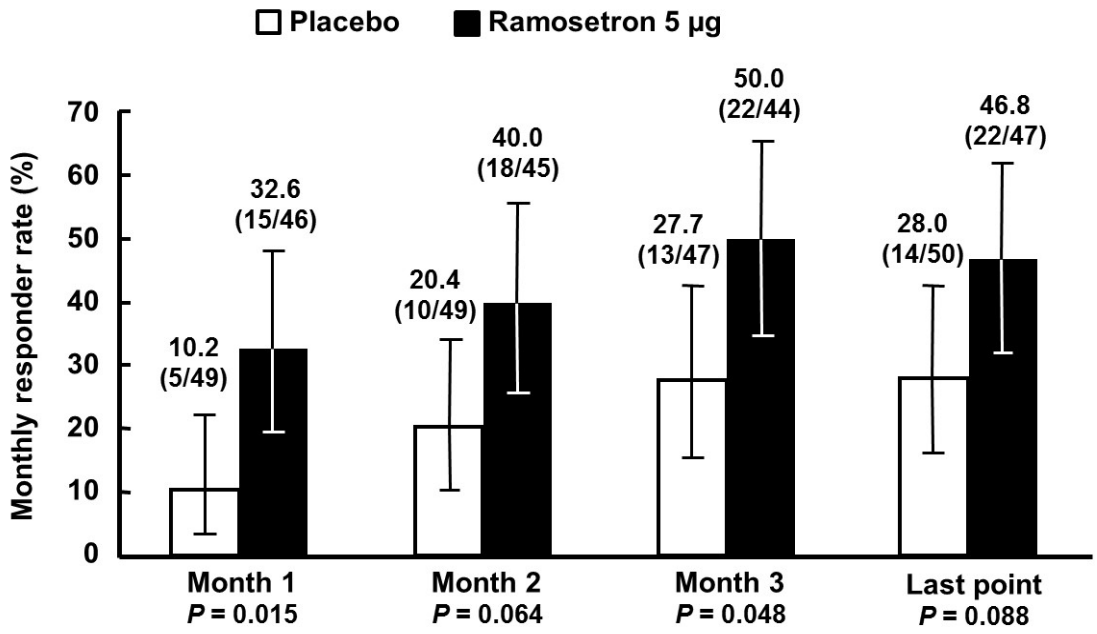


Figure 5. Monthly responder rates for relief of overall IBS symptoms. Column height: responder rate (%). Error bar: 95% CI. *P* values were calculated using the chi-square test.

A)



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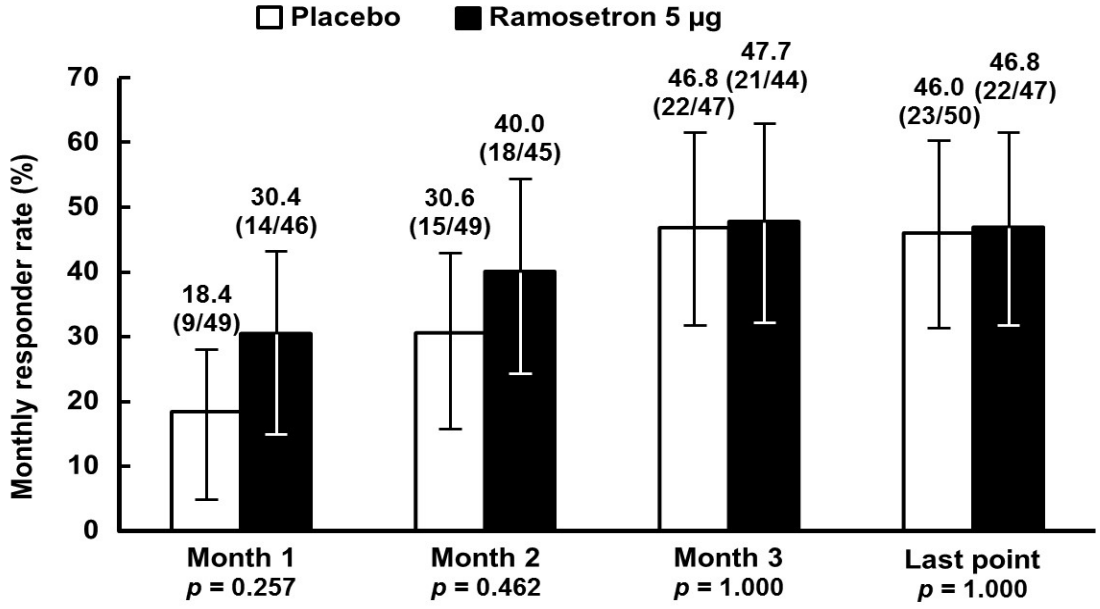


Figure 6. Global assessments. A) Monthly responder rates for improvement in abnormal bowel habits. B) Monthly responder rates for relief of abdominal pain/discomfort. Column height: responder rate (%). Error bar: 95% CI. *P* values were calculated using the chi-square test.

Table 4. Incidence of adverse events

Event	Placebo (n = 51)	Ramosetron 5 μg (n = 47)
All adverse events	20 (39.2%)	27 (57.4%)
Gastrointestinal disorders	8 (15.7%)	13 (27.7%)
Abdominal discomfort	0 (0.0%)	2 (4.3%)
Constipation	2 (3.9%)	0 (0.0%)
Hard stool	3 (5.9%)	9 (19.1%)
Nausea	2 (3.9%)	0 (0.0%)
Infections and infestations	4 (7.8%)	5 (10.6%)
Nasopharyngitis	4 (7.8%)	3 (6.4%)
Gastroenteritis	0 (0.0%)	2 (4.3%)
Hepatobiliary disorders	2 (3.9%)	2 (4.3%)
Hepatic function abnormal	2 (3.9%)	1 (2.1%)
Skin and subcutaneous tissue disorders	2 (3.9%)	3 (6.4%)
Dermatitis contact	1 (2.0%)	2 (4.3%)

Data are expressed as number (%). Events with an incidence of ≥ 3% in any of the groups are listed.

1.2 Evaluation of Efficacy Variables Focusing on the Severity of Major IBS Symptoms

1.2.1 Background

To explore and examine variables that allow evaluation of “clinically meaningful improvements, focusing on the severity of major IBS symptoms” achieved by this drug, the IBS severity index (IBSSI) was assessed as a new measure in this study. The IBSSI is a reliable and well-validated instrument for measuring the presence and severity of specific IBS symptoms [35]. Japanese versions of the IBS severity index (IBSSI-J) developed and validated by Shinozaki et al. are available in Japan [36]. Most studies confirming responsiveness of IBSSI were trials aiming at evaluating behavioral interventions, and these effects were not compared to placebo. Preliminary evaluation was thought to be needed to assess responsiveness of IBSSI-J in clinical trials using pharmacological agents.

1.2.2 Methods

IBSSI-J contains five questions that measure, on a 100-point scale, the severity of abdominal pain, the frequency of abdominal pain, the intensity of abdominal distention, dissatisfaction with bowel habits, and interference with QOL. All five components contribute to the score equally, yielding overall scores ranging from 0 to 500. IBS severity is graded as mild (75–174), moderate (175–299), or severe (300–500) on the basis of overall scores [35]. Whitehead et al. have proposed that at least a 50% reduction from the baseline score (≥50% reduction) in IBSSI overall score was considered to constitute

clinically meaningful improvement of symptoms [38]. Based on this report, patients who had ≥50% reduction in IBSSI-J overall score were defined as responders at each evaluation point (*ad hoc* analysis). Change from baseline and percent change from baseline in IBSSI-J score were summarized at each evaluation point by treatment group. Treatment comparison used a *t*-test with a two-sided significance level of 0.05. IBSSI score was categorized and summarized by whether the subject was a monthly responder on global assessment of relief of overall IBS symptoms.

1.2.3 Results

1) Baseline

The baseline IBSSI-J overall scores in the ramosetron 5 μg and placebo groups were 267.1 ± 98.75 and 246.6 ± 80.52, respectively (Table 5). Severity of IBS can be graded as mild (75–174), moderate (175–299), or severe (300–500) on the basis of overall IBSSI scores. The proportions of patients with moderate severity at baseline were 29.8% in the ramosetron 5 μg group and 64.0% in the placebo group, with severe grading 46.8% and 22.0%, respectively. The respective first-quartile point and third-quartile points were 180.0 and 355.0 in the ramosetron 5 μg group and 200.0 and 290.0 in the placebo group (Table 6). Most patients enrolled in this study were classified as moderate to severe.

Table 6 also showed the baseline score for each of the five components included in the IBSSI-J. The highest score was dissatisfaction with bowel habits, 68.6 ± 25.55 and 66.8 ± 22.78 in the ramosetron 5 μg and placebo groups, respectively. Second was interference with QOL (60.0 ± 27.59 and 54.3± 27.39,

respectively), followed by frequency of abdominal pain (55.1± 33.87 and 57.4 ± 33.61, respectively). Intensity of abdominal distention showed the lowest scores, 35.6 ± 32.25 and 23.8 ± 25.65, respectively. Abdominal pain was assessed from the aspects of severity and frequency in the IBSSI-J. Frequency of abdominal pain was worse than severity of abdominal pain.

2) Assessment of Treatment Efficacy

Change in IBSSI-J overall score from baseline (Table 7) was -133.5 ± 110.72 in the ramosetron 5 μg group and -108.2 ± 94.44 in the placebo group (*P* = 0.228) at the last evaluation point. Differences between the ramosetron 5 μg and placebo groups adjusted by baseline scores were -11.51 (95% CI, -43.13-20.11, *P* = 0.471) at Week 4, -14.39 (95% CI, -47.70-18.93, *P* = 0.393) at Week 8, -16.90 (95% CI, -54.80-21.01, *P* = 0. 378) at Week 12 and -13.60 (95% CI, -49.89-22.68, *P* = 0.459) at the last evaluation point (Figure 7). Differences in responder rates for ≥50% reduction in IBSSI-J between in the ramosetron 5 μg group and the placebo group were over 10%, except Month 1 (Figure 8).

Changes from baseline and percent change from baseline for each five component of the IBSSI-J are shown in Tables 7 and 8, respectively. All of each five components showed numerically greater change in the ramosetron 5 μg group than in the placebo group at all evaluation points (Table 7). Percent change from baseline had greater change in the ramosetron 5 μg group than in placebo group in all components except intensity of abdominal distention (Table 8).

3) Relationship between IBSSI-J and Global Assessment

To evaluate clinically meaningful improvement of IBSSI-J, change from baseline and percent change from baseline in IBSSI-J score were compared by responder/non-responder for global assessment of relief of overall IBS symptoms. Mean changes in IBSSI-J overall scores from baseline are categorized into ≤ -200, -200 < and ≤ -80, -80 < and ≤ -50, -50 < and ≤ 0, 0 < and compared by responder/non-responder for global assessment of relief of overall IBS symptoms in Figure 9. Patients who had mean changes in IBSSI-J overall scores from baseline exceeding 200 points were more numerous in the responder group on global assessment compared to the non-responder group (45.9% vs. 11.1% at Week 12). Patients with a change of over 80 points or over 50 points were also more numerous in the responder group on global assessment than in the non-responder group at all evaluation points.

Similarly, the percent change in IBSSI-J from baseline was categorized into ≤ -75%, -75% < and ≤ -50%, -50% < and ≤ -30%, -30% < and ≤ 0% and 0% < and compared by responder/non-responder for global assessment of relief of overall IBS symptoms (Figure 10). The number of patients who had a ≥ 75% reduction in IBSSI-J overall score was higher in the responder group on global assessment than in the non-responder group (35.1% vs. 11.1% at Week 12). The rate of patients who had a ≥ 50% reduction or ≥ 30% reduction in IBSSI-J overall score was also higher in the responder group on global assessment than in the non-responder group at all evaluation points.

1.2.4 Discussion

This study showed that most patients enrolled had moderate to severe IBS symptoms in the baseline period. The highest score among each component was for dissatisfaction with bowel habits. Second was for interference with QOL and frequency of abdominal pain. It is well known that IBS significantly impairs health related QOL [4]. The patients in this study were considered to have impaired QOL. The lowest score of the five components was for intensity of abdominal distention. Patients with abdominal distention and/or bloating were reported to be more numerous with IBS-C than with IBS-D [39]. The lowest score of intensity of abdominal distention in IBSSI-J in this study might be related to a lower contribution of abdominal distention to IBS symptom severity in IBS-D.

The proportion of patients who had a ≥ 50% reduction in IBSSI-J overall score was more than 10% higher in the ramosetron 5 μg group than in the placebo group, except Month 1. Although significant results were lacking, changes in IBSSI-J score at all evaluation points in the ramosetron 5 μg group seems to be superior to that of the placebo group. Francis et al. suggested that a decrease of 50 points in IBSSI overall score correlated with improvement in clinical symptoms [35]. On the other hand, Whitehead et al. have proposed that ≥ 50% reduction in IBSSI overall score from the baseline score was considered to constitute clinically meaningful improvement of symptoms [38]. In this study, other categorization was evaluated to find “clinically meaningful improvements” by pharmacological agents, and compared responder/non-responder for global assessment of relief of overall IBS symptoms. In Francis’s report, mean change of IBSSI from baseline to 3 months later was significantly greater in the patients

who became clinically considerably better than little changed (change in score: 83 vs. 6) [35]. Based on their reports, -50 and -80 points reductions were selected. The baseline IBSSI-J overall scores in our ramosetron 5 μg and placebo groups were 267.1 ± 98.75 and 246.6 ± 80.52, respectively (Table 5). Because IBS severity is rated as No symptoms (0-74), a -200 points reduction was set as the score at which the symptoms were eliminated. Similarly, in addition to 50% reduction, 3/4 and 1/3 reduction categories were examined to explore the clinical meaningful change. This study showed patients who had changes in their overall IBSSI-J scores from baseline of over 50 points were more numerous in the monthly responder group based on global assessment of relief of overall IBS symptoms than in the non-responder group. This finding is in accordance with the results of Francis et al. [35]. The proportion of patients who had a ≥ 50% reduction in IBSSI-J overall score was also higher in the responder group on global assessment (24/37, 64.9%) than in the non-responder group (18/54, 33.3%) at Week 12. The studies by Francis et al. and Whitehead et al. were trials aiming to evaluate behavioral interventions, and these effects were not compared to placebo. In patients with IBS-C, it was recently reported that linaclotide, guanylate cyclase-C agonist, showed a statistically significantly higher change in IBSSI overall score from baseline as well as in the percentage of patients with ≥ 50% reduction in IBSSI overall score compared to placebo [40]. Nevertheless, those data suggest that the IBSSI could be used for measuring response to pharmacological agents for patients with IBS-C; there are little data used for measuring the response of patients with IBS-D. Differences between ramosetron and placebo in this study were not evident. This study was the first trial to use the IBSSI-J to measure the response

to pharmacological agents in patients with IBS-D. Further investigation will be needed to use this questionnaire as a primary endpoint in clinical studies related to the development of pharmacological agents for IBS-D patients.

In this study, the monthly responder group with respect of global assessment of relief of overall IBS symptoms showed a greater change in the IBSSI-J overall score and percent change from baseline than did the non-responder group. This study thus revealed that responses on global assessment were correlated with improvement in IBSSI-J, suggesting that global assessment reflects improvement of the symptom severity of patients with IBS-D.

Table 5. Baseline characteristics classified by IBSSI-J severity

Baseline	Placebo (n = 50)	Ramosetron 5 μg (n = 47)	*P* value
IBSSI-J overall score	246.6 ± 80.52	267.1 ± 98.75	0.264
No symptoms (0-74)	0 (0.0%)	1 (2.1%)	-
Mild (75-174)	7 (14.0%)	10 (21.3%)	-
Moderate (175-299)	32 (64.0%)	14 (29.8%)	-
Severe (300-500)	11 (22.0%)	22 (46.8%)	-

Data are expressed as mean ± standard deviation. *P* values were calculated using analysis of variance.

Table 6. Baseline IBSSI-J score

		N	Mean ± SD	Min	Max	Median	First-quartile	Third-quartile	*t*-test
Overall score	Placebo	50	246.6 ± 80.52	80	410	245	200	290	t = -1.123, df = 95, *P* = 0.264
	Ramosetron 5 μg	47	267.1 ± 98.75	60	440	275	180	355	
Severity of abdominal pain	Placebo	50	44.3 ± 26.71	0	100	47.5	20	70	t = -0.647, df = 95, *P* = 0.519
	Ramosetron 5 μg	47	47.8 ± 26.70	0	90	50	30	70	
Frequency of abdominal pain	Placebo	50	57.4 ± 33.61	0	100	60	30	90	t = 0.335, df = 95, *P* = 0.739
	Ramosetron 5 μg	47	55.1 ± 33.87	0	100	60	30	90	
Intensity of abdominal distention	Placebo	50	23.8 ± 25.65	0	80	17.5	0	50	t = -2.007, df = 95, *P* = 0.048
	Ramosetron 5 μg	47	35.6 ± 32.25	0	100	30	0	60	
Dissatisfaction with bowel habits	Placebo	50	66.8 ± 22.78	20	100	60	50	90	t = -0.361, df = 95, *P* = 0.719
	Ramosetron 5 μg	47	68.6 ± 25.55	0	100	70	50	90	
Interference with QOL	Placebo	50	54.3 ± 27.39	0	100	55	30	80	t = -1.013, df = 95, *P* = 0.314
	Ramosetron 5 μg	47	60.0 ± 27.59	0	100	60	40	80	

Data are expressed as mean ± standard deviation (SD). *P* values were calculated using analysis of variance.

Table 7. Change in each IBSSI-J component score from baseline at each evaluation point

	Week 4		Week 8		Week 12		Last point	
	Placebo	Ramosetron 5 μg	Placebo	Ramosetron 5 μg	Placebo	Ramosetron 5 μg	Placebo	Ramosetron 5 μg
	Mean ± SD *P* value	Mean ± SD *P* value	Mean ± SD *P* value	Mean ± SD *P* value	Mean ± SD *P* value	Mean ± SD *P* value	Mean ± SD *P* value	Mean ± SD *P* value
N	48	46	49	44	47	44	50	47
Overall scores	-75.0 ± 81.52	-95.9 ± 105.12 (*P* = 0.283)	-103.0 ± 81.81	-130.6 ± 114.27 (*P* = 0.181)	-110.3 ± 97.04	-137.0 ± 113.18 (*P* = 0.231)	-108.2 ± 94.44	-133.5± 110.72 (*P* = 0.228)
Severity of abdominal pain	-15.3 ± 25.18	-17.0 ± 25.15 (*P* = 0.743)	-21.4 ± 28.46	-24.3 ± 27.41 (*P* = 0.625)	-21.9 ± 30.42	-26.6 ± 27.01 (*P* = 0.439)	-21.9 ± 29.76	-26.1 ± 26.41 (*P* = 0.467)
Frequency of abdominal pain	-16.5 ± 25.89	-20.0 ± 32.52 (*P* = 0.560)	-24.7 ± 29.38	-26.6 ± 35.04 (*P* = 0.777)	-25.1 ± 32.56	-28.2 ± 35.13 (*P* = 0.666)	-24.6 ± 31.77	-28.1 ± 33.98 (*P* = 0.603)
Intensity of abdominal distension	-9.7 ± 23.13	-16.3 ± 27.68 (*P* = 0.214)	-12.2 ± 24.54	-17.8 ± 26.66 (*P* = 0.295)	-11.5 ± 25.83	-16.6 ± 29.88 (*P* = 0.385)	-10.8 ± 25.26	-16.3 ± 29.22 (*P* = 0.325)
Dissatisfaction with bowel habits	-16.2 ± 31.23	-20.8 ± 28.18 (*P* = 0.454)	-19.2 ± 33.55	-31.4 ± 29.88 (*P* = 0.067)	-25.1 ± 33.57	-33.4 ± 31.50 (*P* = 0.230)	-24.8 ± 33.84	-32.5 ± 30.63 (*P* = 0.243)
Interference with QOL	-17.3 ± 27.76	-21.8 ± 29.94 (*P* = 0.454)	-25.5 ± 27.75	-30.5 ± 34.84 (*P* = 0.445)	-26.7 ± 28.67	-32.2 ± 32.53 (*P* = 0.396)	-26.1 ± 28.04	-30.6 ± 32.44 (*P* = 0.470)

Data are expressed as mean ± standard deviation (SD). *P* values were calculated using analysis of variance.

Table 8. Percent change in each IBSSI-J component score from baseline at each evaluation point

	Week 4		Week 8		Week 12		Last point	
	Placebo	Ramosetron 5 μg	Placebo	Ramosetron 5 μg	Placebo	Ramosetron 5 μg	Placebo	Ramosetron 5 μg
	Mean ± SD *P* value	Mean ± SD *P* value	Mean ± SD *P* value	Mean ± SD *P* value	Mean ± SD *P* value	Mean ± SD *P* value	Mean ± SD *P* value	Mean ± SD *P* value
N	48	46	49	44	47	44	50	47
Overall scores	-27.2 ± 29.72	-31.2 ± 40.08 (*P* = 0.589)	-40.7 ± 26.73	-43.8 ± 35.33 (*P* = 0.639)	-42.7 ± 32.71	-48.9 ±34.51 (*P* = 0.379)	-42.6 ± 31.98	-47.8± 33.94 (*P* = 0.432)
Severity of abdominal pain	-20.6 ± 62.3	-40.5 ± 33.55 (*P* = 0.070)	-36.7 ± 53.26	-54.2 ± 42.23 (*P* = 0.102)	-32.9 ± 91.13	-58.3 ± 35.56 (*P* = 0.103)	-34.4 ± 88.82	-57.5 ± 36.13 (*P* = 0.117)
Frequency of abdominal pain	-27.2 ± 43.33	-36.0 ± 44.90 (*P* = 0.361)	-44.5 ± 46.43	-49.1 ± 50.54 (*P* = 0.666)	-46.3 ± 50.08	-51.2 ± 49.21 (*P* = 0.653)	-46.8 ± 49.55	-51.5 ± 48.2 (*P* = 0.653)
Intensity of abdominal distension	-44.6 ± 55.51	-27.4 ± 91.19 (*P* = 0.368)	-56.3 ± 51.91	-44.5 ± 76.81 (*P* = 0.479)	-47.5 ± 61.58	-40.9 ± 62.39 (*P* = 0.679)	-44.5 ± 65.79	-40.1 ± 60.93 (*P* = 0.779)
Dissatisfaction with bowel habits	-11.9 ± 65.32	-25.1 ± 41.22 (*P* = 0.252)	-15.7 ± 77.16	-39.0 ± 39.47 (*P* = 0.078)	-29.3 ± 52.81	-43.4 ± 48.44 (*P* = 0.190)	-28.7 ± 52.17	-42.4 ± 47.01 (*P* = 0.183)
Interference with QOL	-11.1 ± 115.81	-31.3 ± 45.69 (*P* = 0.277)	-28.6 ± 116.7	-44.5 ± 51.7 (*P* = 0.411)	-22.2 ± 174.64	-49.0 ± 43.65 (*P* = 0.330)	-24.0 ± 169.49	-47.1 ± 46.31 (*P* = 0.374)

Data are expressed as mean ± standard deviation (SD). *P* values were calculated using analysis of variance.

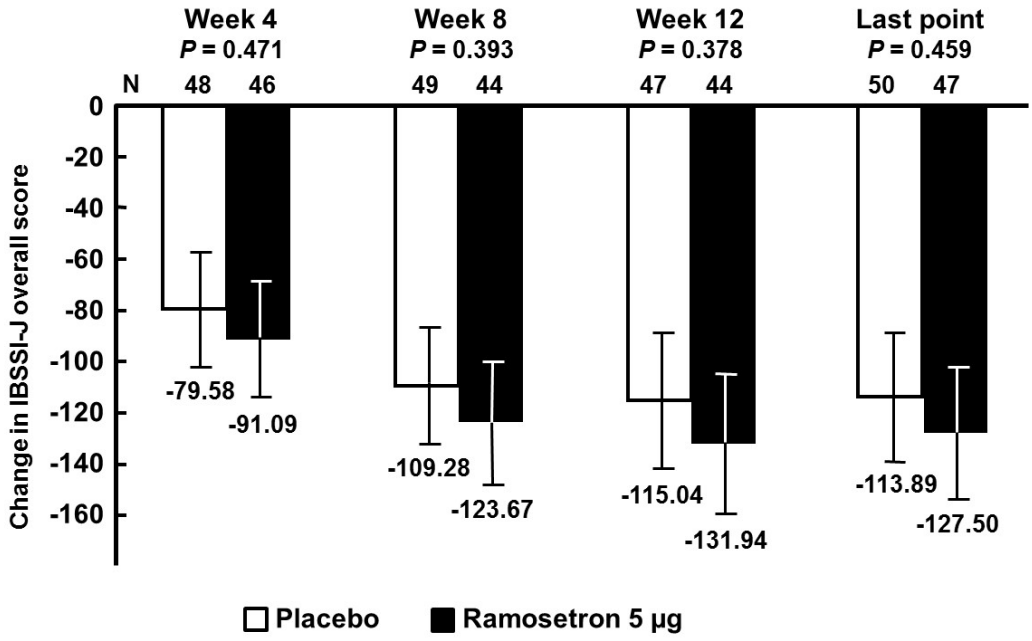


Figure 7. Change in IBSSI-J overall scores from baseline, adjusted by baseline score. Column height: the values adjusted using the baseline score as a covariate. Error bar: 95% CI. *P* values were calculated using analysis of covariance with the treatment group as a factor and baseline score as a covariate.

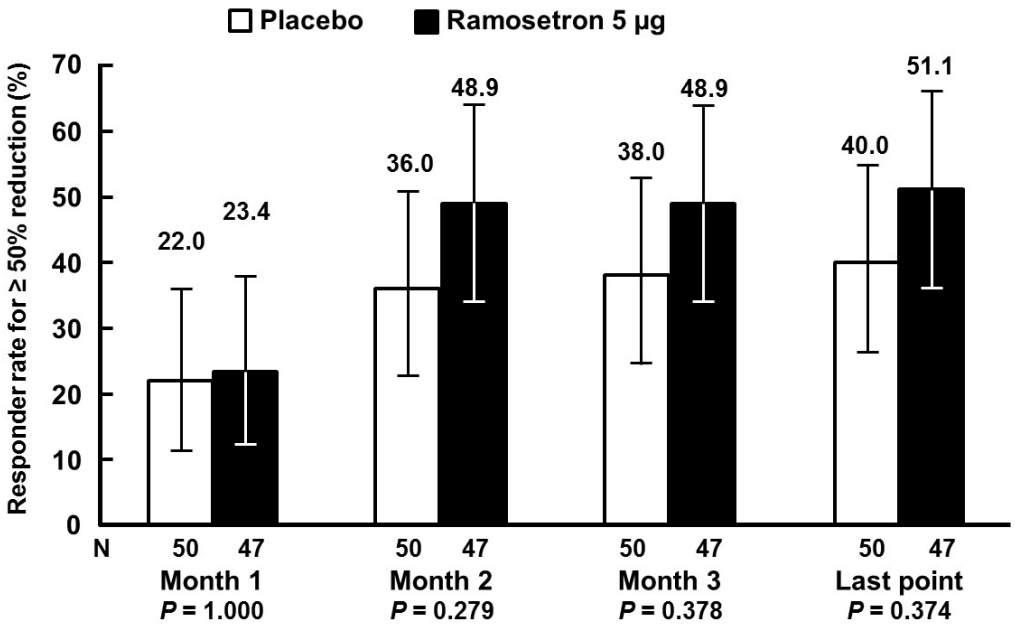


Figure 8. Responder rates for at least a 50% reduction from baseline in IBSSI-J overall score. Column height: responder rates (%). Error bar: 95% CI. *P* values were calculated using the chi-square test.

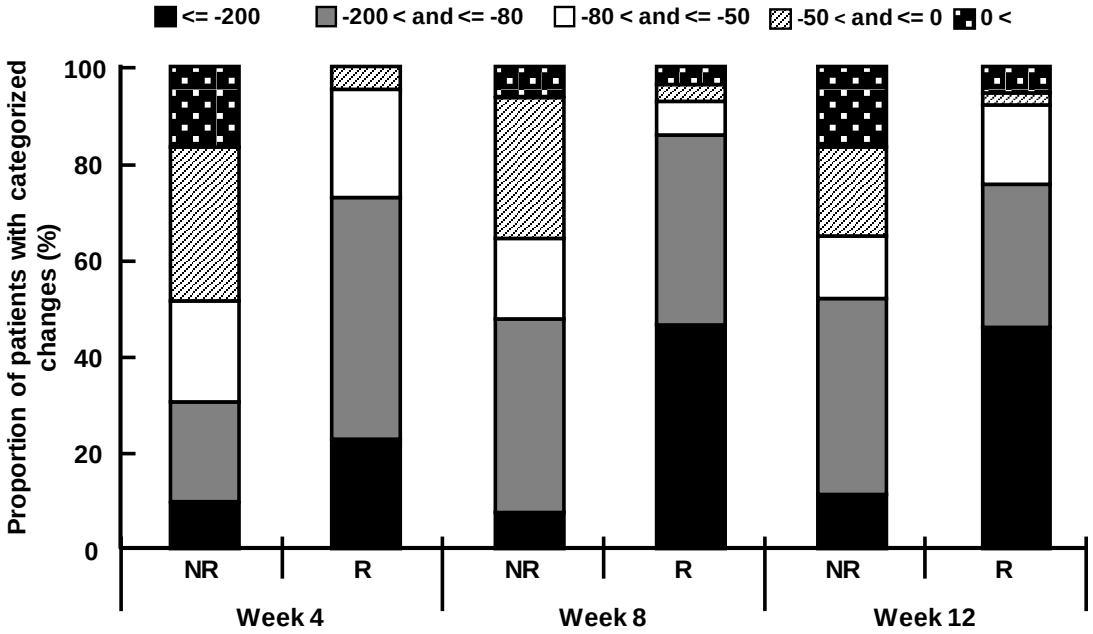


Figure 9. Relationship between changes in IBSSI-J overall scores and global assessment. Changes in IBSSI-J overall scores from baseline were compared by responder (R) /non-responder (NR) for global assessment of relief of overall IBS symptoms. Mean changes in IBSSI-J overall scores from baseline were categorized into the following groups: ≤ -200, -200 < and ≤ -80, -80 < and ≤ -50, -50 < and ≤ 0, and 0 <.

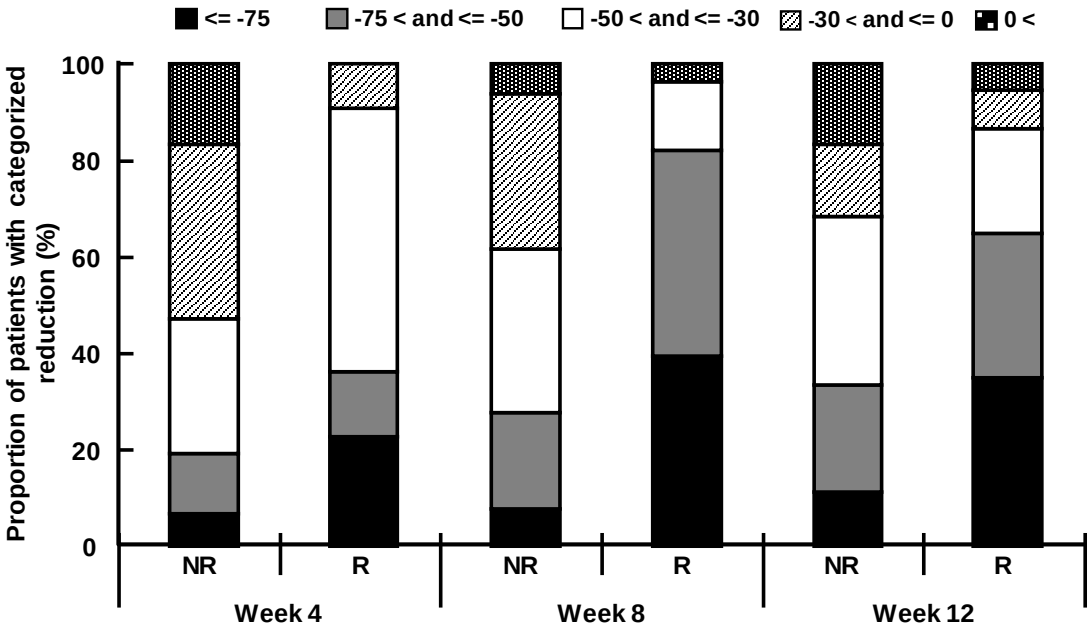


Figure 10. Relationship between percent change in IBSSI-J overall score and global assessment. Percent change in IBSSI-J overall score from baseline was compared by responder (R) /non-responder (NR) for global assessment of relief of overall IBS symptoms. Percent change in IBSSI-J from baseline was categorized into the following groups: ≤ -75%, -75% < and ≤ -50%, -50% < and ≤ -30%, -30% < and ≤ 0%, and 0% <.

1.3 Evaluation of Efficacy Variables Focusing on the Patient's Chief Complaint

1.3.1 Background

Because IBS is a syndrome, most previous studies to develop agents for IBS have used global assessments as primary endpoints [22-26, 37, 41]. Individual symptoms of IBS were assessed as secondary endpoints. The most bothersome IBS symptoms reported in clinical trials of alosetron, the same class drug as ramosetron, were abdominal pain and urgency [30, 42]. However, there were no data regarding the chief complaint in previous clinical trials of ramosetron. To explore and examine variables that allow evaluation of "clinically meaningful improvements, focusing on the patient's chief complaint," the chief complaint and its relief by this study drug were assessed in this study.

1.3.2 Methods

Symptoms related to the chief complaint were clarified by an investigator at an interview. The investigator scored the most bothersome IBS symptoms the patient had (none, abdominal pain/discomfort, stool form, stool frequency, urgency, feeling of incomplete evacuation, and others) as symptoms of the chief complaint at the Week 0, 4, 8, and 12 (or at discontinuation) visits. The investigator also scored any improvement in symptoms of the chief complaint the patients had before administration compared to the baseline period on a 5-point ordinate scale (0, completely relieved; 1, considerably relieved; 2, somewhat relieved; 3, unchanged; and 4, worsened) at the Week 4, 8, and 12 (or at discontinuation) visits. The treatment groups were compared

using the Wilcoxon rank sum test with a two-sided significance level of 0.05. As an *ad hoc* analysis, patients with scores of 0 (completely relieved) or 1 (considerably relieved) at each evaluation point were defined as responders, with relief of their chief complaint. Patients with missing data were regarded as non-responders. Chi-square test was used for treatment comparison. BSFS was evaluated using the *t*-test.

Improvement in stool consistency was analyzed for the patients with baseline BSFS scores over 5, in an *ad hoc* manner. Patients with weekly mean BSFS scores of 3 to 5 during a 1-week of the treatment period and a decrease of one or more points in mean BSFS scores from the baseline period were defined as weekly responders. Patients who were weekly responders for at least 2 of the 4 weeks in a 1-month were considered monthly responders. If more than 2 daily scores were missing during any week of the study period, the mean score for that week was defined as missing. Patients with missing mean BSFS scores were regarded as weekly non-responders. The treatment group were compared using a chi-square test.

1.3.3 Results

1) Baseline

Table 9 showed the symptoms of the chief complaint that patients had before administration. Abdominal pain/discomfort, stool form, and stool frequency were key symptoms for the patients enrolled in this study. The proportion of patients whose chief complaint was abdominal pain/discomfort was 34.0% in the ramosetron 5 μg group and 42.0% in the placebo group.

Regarding stool form and stool frequency, key symptoms among bowel habit abnormalities, the respective proportion of patients was 19.1% and 25.5% in the ramosetron 5 μg group and 18.0% and 20.0% in the placebo group.

2) Assessment of Treatment Efficacy

Improvement in the symptoms of the chief complaint that patients had before administration was assessed on a 5-point ordinate scale at every visit (Figure 11). Patients with scores of 0 (completely relieved) or 1 (considerably relieved) at each evaluation point were defined as responders (Figure 12). Responder rates for improvement in the symptoms of the chief complaint that patients had before administration were 53.2% (95% CI, 38.1–67.9 at the last point) in the ramosetron 5 μg group and 42.0% (95% CI, 28.2–56.8 at the last point, $P = 0.368$) in placebo. The difference between placebo and ramosetron was over 10% at all evaluation points. Figure 13 showed improvement in the symptoms of each chief complaint that patients had before administration. Regarding stool form, the number of patients who had completely relieved or considerably relieved symptoms in the ramosetron 5 μg group increased in a time-dependent manner. Almost all patients showed completely relieved (12.5%) or considerably relieved (75%) symptoms in relation to stool form in the ramosetron 5 μg group at Week 12. The difference between ramosetron and placebo was greatest with respect to stool form. Improvement in the ramosetron 5 μg group compared to placebo was also observed with respect to stool frequency at all evaluation points. Among patients who had abdominal pain/discomfort as a symptom of their chief complaint before administration, patients in the ramosetron 5 μg group showed numerous improvements at

Weeks 4 and 8 compared to patients in the placebo group with the same symptoms, however, the difference between ramosetron and placebo was not clear at Week 12 and at the last evaluation point.

3) Relationship between Improvement in Chief Complaint and Global Assessment

To evaluate clinical meaningful improvement of the chief complaint, improvement in the chief compliant that patients had before administration was compared by responder/non-responder for global assessment of relief of overall IBS symptoms (Figure 14). Regarding stool form, patients who reported that they were completely relieved or considerably relieved in the improvement of chief complaint were more numerous in the responder group on global assessment compared to the non-responder group (8/9, 88.9% vs. 3/9, 33.3% at the last point). The same results were observed for abdominal pain/discomfort (11/14, 78.6% vs. 8/23, 34.8% at the last point) and stool frequency (7/9, 77.8% vs. 1/13, 7.7% at the last point).

4) Weekly Changes in Stool Form

When compared to placebo, the greatest improvement in symptoms of the chief complaint that patients had before administration in the ramosetron 5 μg group was shown in stool form. Weekly change in BSFS scores were shown in Figure 15. BSFS scores were significantly lower in the ramosetron 5 μg group (4.36 ± 1.195 at the last point) than in the placebo group (4.85 ± 0.890 at the last point, P = 0.027) throughout the treatment period, except at Week 6. No significant difference was observed between the ramosetron 5 μg group and

the placebo group regarding changes in the severity of abdominal pain/discomfort and stool frequency from baseline per week.

5) *Ad hoc* Analysis for Newly Developed Variable “Improvement in Stool Consistency”

Because stool form was considered to be the most effective symptom for demonstrating if ramosetron brought about a clinically meaningful improvement, monthly responder rates for improvement in stool consistency were analyzed *ad hoc* for patients with baseline BSFS scores over 5 (Figure 16). Patients with weekly mean BSFS scores of 3 to 5 during a 1-week of the treatment period and a decrease of one or more points in mean BSFS scores from the baseline period were considered as clinically meaningful improvement in stool consistency. Responder rates for improvement in stool consistency were 40.5% (95% CI, 25.6–56.7 at the last point) in the ramosetron 5 μg group and 18.9% (95% CI, 8.0–35.2 at the last point, $P = 0.067$) in the placebo group. The difference between placebo and ramosetron was over 19% at all evaluation points.

1.3.4 Discussion

IBS is characterized by two major IBS symptoms, abdominal pain/discomfort and abnormal bowel habits. Regarding the chief complaint that patients had before administration, 34.0% of the patients in the ramosetron 5 μg group and 42.0% of the patients in the placebo group reported abdominal pain/discomfort. The remaining patients complained of abnormal bowel habits, including abnormal stool form, increased stool frequency, defecation urgency,

and a feeling of incomplete evacuation. Of these, the highest proportions were related to stool form (19.1% in the ramosetron 5 μg group and 18.0% in the placebo group) and stool frequency (25.5% in the ramosetron 5 μg and 20.0%, in the placebo group). Stool form and stool frequency were thus considered to be the most important chief complaints among the bowel habit abnormalities. When compared to placebo, the greatest improvement in symptoms of the chief complaint that patients had before administration in the ramosetron 5 μg group was shown in stool form. This result was consistent with the finding that BSFS scores were significantly lower in the ramosetron 5 μg group than in the placebo group.

This study, therefore, found that ramosetron acted most effectively on stool consistency. Stool consistency correlates with colonic transit time [43, 44] and can be a good indicator of bowel function. In rats, ramosetron also clearly reduced stress-induced diarrhea and accelerated defecation caused by CRH [15, 19]. To show how ramosetron is effective for individual IBS symptoms, focusing on stool consistency was considered to be acceptable in light of the drug's pharmacological mechanism.

Stool form is considered to be the most effective symptom for demonstrating if ramosetron brought about a clinically meaningful improvement. However, if the effect of ramosetron on stool consistency is excessive, it leads to constipation. In developing agents to treat IBS-D, it is insufficient to only compare the change in stool form from baseline between ramosetron and placebo. It is also considered important to define a clinically meaningful "improvement in stool consistency". BSFS scores of 3 to 5 are recognized as normal stool form in the Rome III criteria. Therefore, weekly mean BSFS scores

of 3 to 5 during a 1-week of the treatment period and a decrease of one or more points in mean BSFS scores from the baseline period are considered as clinically meaningful improvement in stool consistency. I thus defined monthly responder rates in respect to improvement in stool consistency (Table 10) and revealed greater responder rates in the ramosetron 5 μg group compared to the placebo group by *ad hoc* analysis.

In this study, improvement in the chief complaint the patient had before administration was more frequent in the responder group in global assessment of relief of overall IBS symptoms compared to the non-responder group. Improvement of each IBS symptom seems to be related to improvement of overall IBS symptoms. These relationships were obtained not only for stool form, but also for abdominal pain/discomfort and stool frequency.

Table 9. Chief complaint that patients had before administration of the study drug

Chief complaint: symptoms before administration	Placebo (n = 50)	Ramosetron 5 μg (n = 47)
None	0 (0.0%)	0 (0.0%)
Abdominal pain/discomfort	21 (42.0%)	16 (34.0%)
Stool form	9 (18.0%)	9 (19.1%)
Stool frequency	10 (20.0%)	12 (25.5%)
Urgency	6 (12.0%)	7 (14.9%)
Feelings of incomplete evacuation	4 (8.0%)	3 (6.4%)
Others	0 (0.0%)	0 (0.0%)

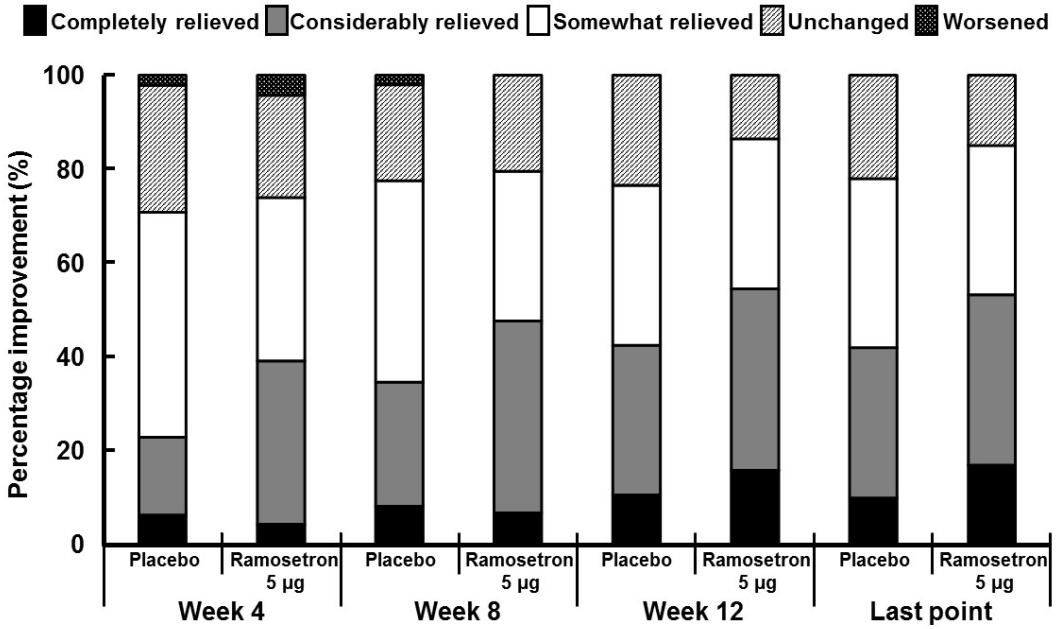


Figure 11. Improvement in symptoms of the chief complaint that patients had before administration of the study drug.

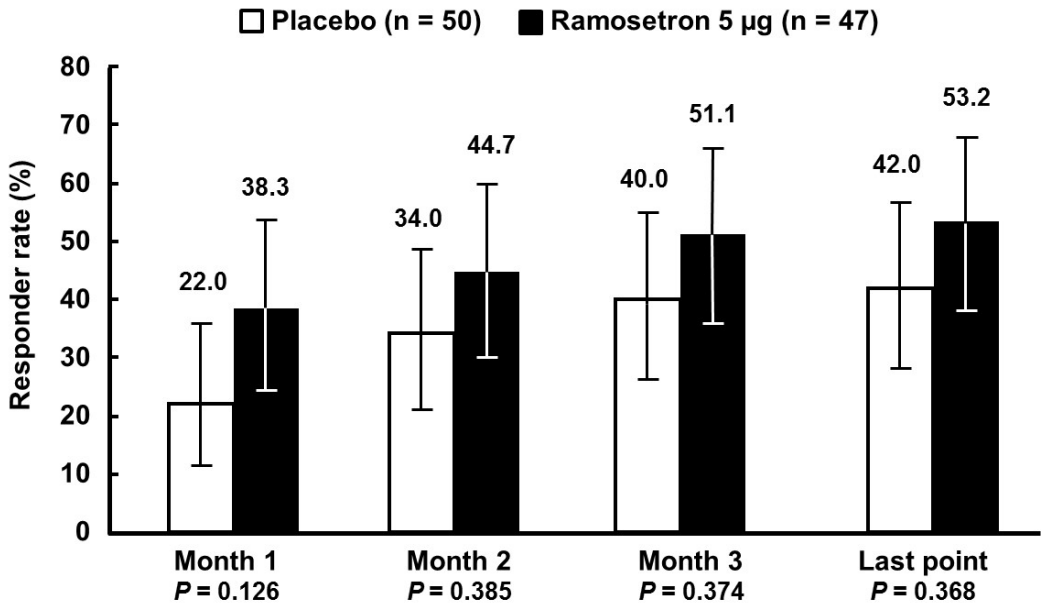


Figure 12. Responder rate for improvement in symptoms of the chief complaint that patients had before administration of the study drug. Height: responder rate (%). Error bar: 95% CI. *P* values were calculated using the chi-square test.

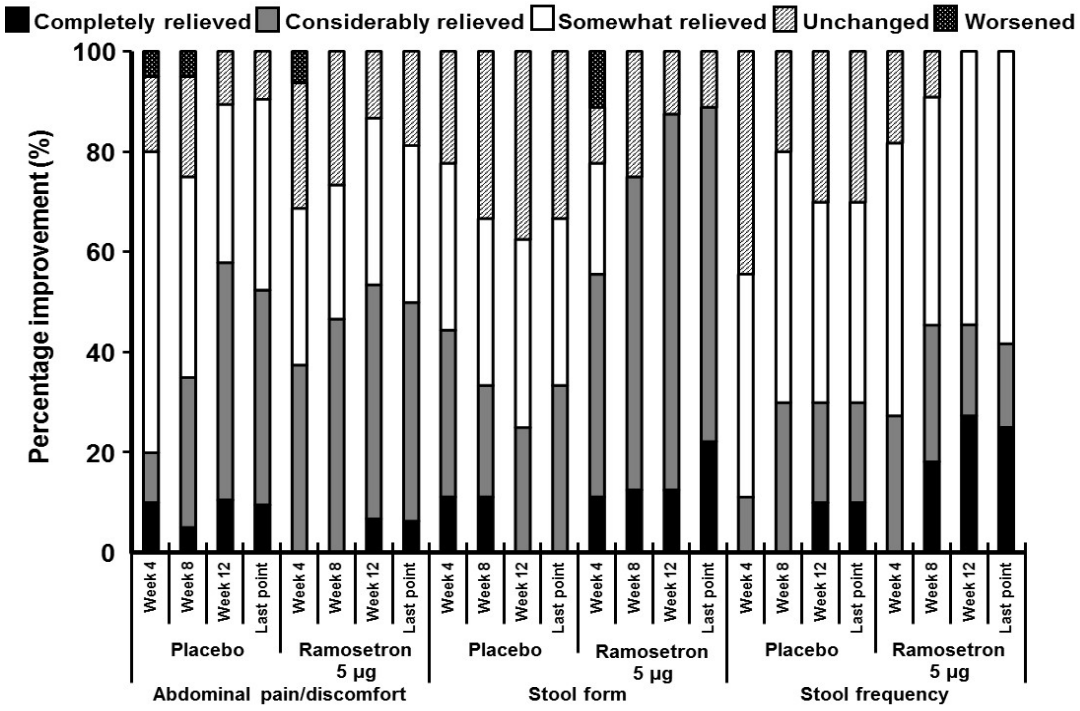


Figure 13. Improvement in symptoms of each chief complaint that patients had before administration of the study drug.

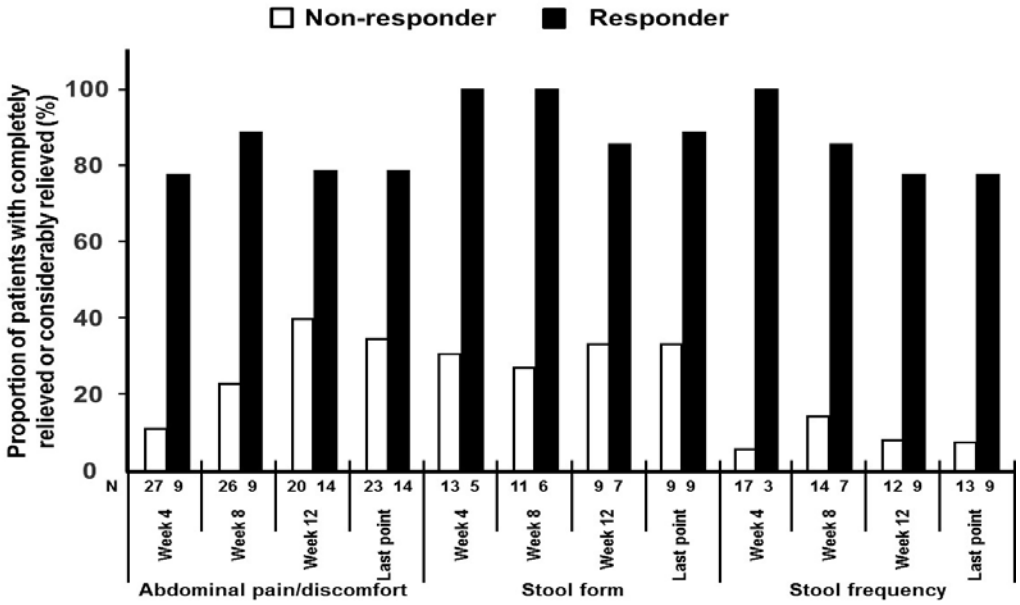


Figure 14. Relationship between improvement in chief compliant and global assessment. Improvement in chief compliant that patients had before administration was compared between responders and non-responders for global assessment of relief of overall IBS symptoms.

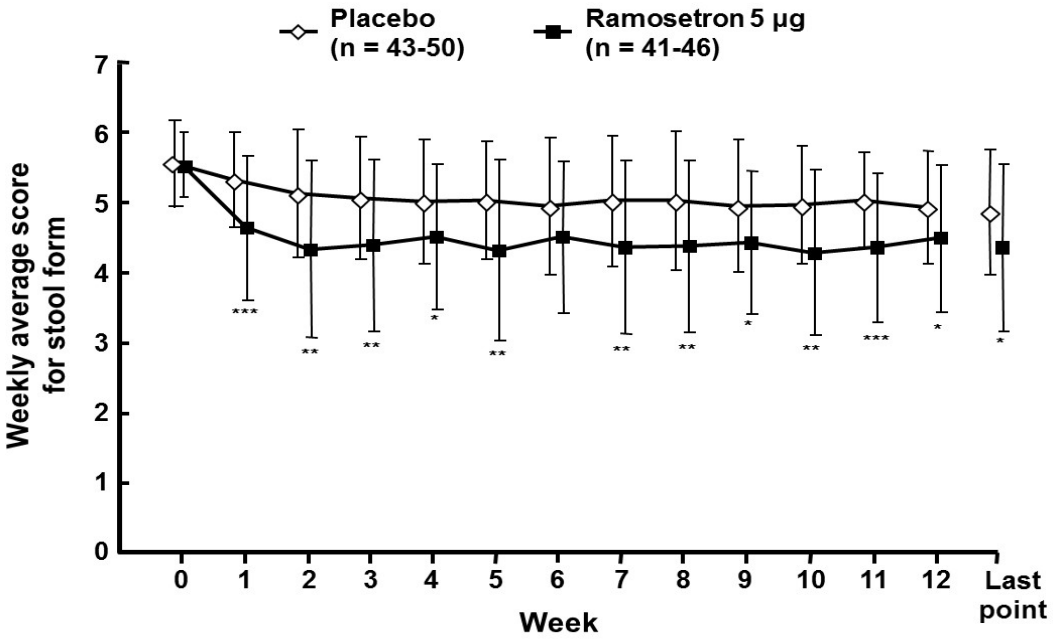


Figure 15. Weekly changes in BSFS scores. Line graph: means ± standard deviation. *P* values were calculated using the *t*-test, as follows: ****P* < 0.001, ***P* < 0.01 and **P* < 0.05.

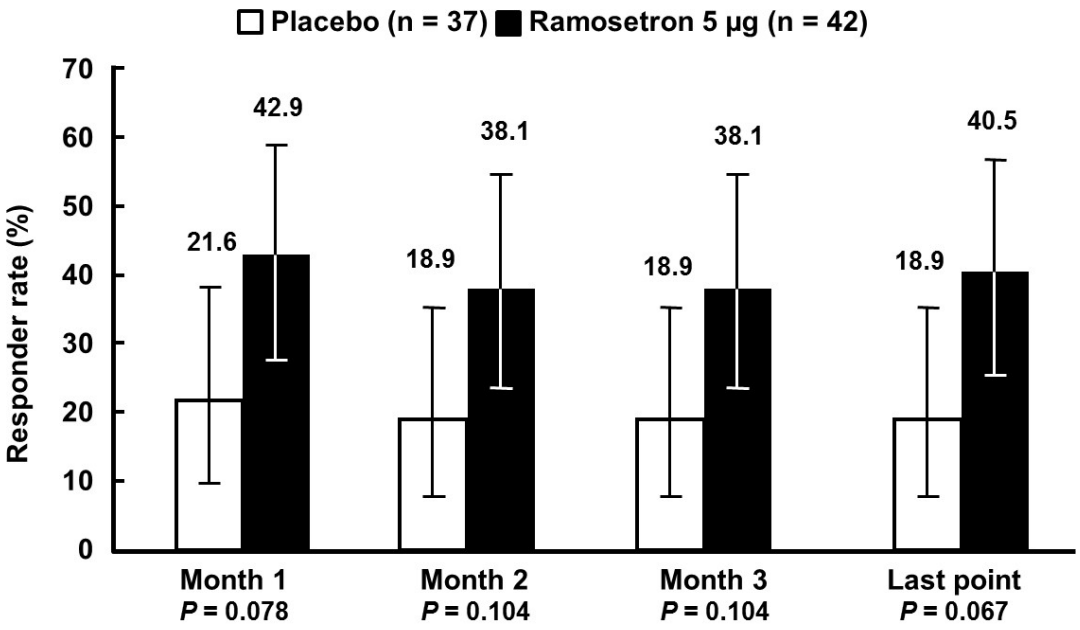


Figure 16. Monthly responder rates for improvement in stool consistency. Height: responder rate (%). Error bar: 95% CI. *P* values were calculated using the chi-square test.

Table 10. Definition of responder of “improvement in stool consistency”

Weekly responder	Weekly mean BSFS scores of 3 to 5 during a 1-week of the treatment period and a decrease of one or more points in mean BSFS scores from the baseline period.
Monthly responder	Patients who were weekly responders for at least 2 of the 4 weeks in a 1-month.

Chapter 2 Evaluation of Efficacy of Ramosetron Using Improvement in Stool Consistency

In this chapter, I summarized the results of clinical studies, which used the newly developed variable, “improvement in stool consistency” as the primary endpoint to evaluate the prospective effect of ramosetron [25, 37].

2.1 Phase IV Study of Ramosetron in Male Patients with IBS-D

2.1.1 Background

A randomized, placebo-controlled, phase IV study was conducted to evaluate the prospective effect of ramosetron with the improvement in stool consistency as the primary endpoint (Clinicaltrials.gov ID: NCT01225237) [37]. This study was conducted from October 2010 to August 2011 at 52 centers that have departments of gastroenterology. The study protocol was designed in accordance with the Declaration of Helsinki, GCP, GPSP, the applicable laws and regulations and was approved by the institutional review board at each site. All patients provided written informed consent prior to participating in study-related procedures.

2.1.2 Methods

1) Patient Population

This study comprised a provisional registration period, a 1-week baseline period, and a 12-week treatment period, similar to previous studies [22, 23]. Male outpatients aged 20–64 years were diagnosed according to the Rome III criteria. Patients satisfying the inclusion and exclusion criteria were monitored during a 1-week baseline period in which data on severity of abdominal pain/discomfort and stool consistency were collected to ensure that patients met the criteria. Patients who had not used drugs or undergone examinations that could affect the evaluation of study drug efficacy within 10 days prior to randomization; who recorded all items in the patient diary for ≥5 days during the baseline period; who had mean severity scores of abdominal

pain/discomfort of ≥0.7 during the baseline period (a 5-point ordinate scale); in whom no type 1 or 2 stool form, as scored by BSFS, was recorded during the baseline period; who had bowel movements for ≥5 days, with a mean score of >5 on BSFS during the baseline period; and who were not judged ineligible for the study according to the clinical laboratory test results received before the baseline period were randomized and successively administered treatment.

2) Study Design

Following the baseline period, eligible patients were randomly assigned to 12-week oral treatments with placebo or ramosetron 5 μg once daily before breakfast. Visits were scheduled at Weeks 2, 4, 8, and 12 (or at discontinuation) to assess treatment efficacy, drug compliance, and occurrence of adverse events. Randomization was performed in a 1:1 ratio using a block size of 4 with a web-based randomization system. All patients, investigators, and sponsors were blinded until all observations and evaluations were completed, statistical analysis plans were finalized, and all data had been entered.

3) Data Collection

During the baseline and treatment periods, patients recorded their IBS symptoms daily on paper diary cards at bedtime, and electronically entered data into a database daily using an interactive voice response system to support the completion of data entry in the paper diary cards. In the diary, patients recorded the BSFS types and stool frequencies and scored the severity of their abdominal pain/discomfort. Urgency and feeling of incomplete evacuation were assessed on a binary scale. Every 7 days during the treatment

period, patients also graded summarized IBS symptoms compared with the baseline period on a 5-point ordinate scale.

4) Efficacy Endpoints

The primary endpoint was monthly responder rates for improvement in stool consistency in the Month 1. Patients with weekly mean BSFS scores of 3 to 5 during a 1-week of the treatment period and a decrease of one or more points in mean BSFS scores from the baseline period were defined as weekly responders. Patients who were weekly responders for at least 2 of the 4 weeks in a 1-month were considered monthly responders (Table 10). If more than 2 daily scores were missing during any week of the study period, the mean score for that week was defined as missing. Patients with missing mean BSFS scores were regarded as weekly non responders.

Secondary endpoints included monthly responder rates for global assessment of relief of overall IBS symptoms, relief of abdominal pain/discomfort, and improvement in abnormal bowel habits. Patients with scores of 0 or 1 at each weekly evaluation point were defined as weekly responders, and patients who were weekly responders for at least 2 of the 4 weeks in a 1-month were considered to be monthly responders (Table 2). Scales measuring IBS symptoms, including severity of abdominal pain/discomfort, BSFS, stool frequency, urgency and feeling of incomplete evacuation and IBS-QOL were established for the secondary endpoints. All adverse events were recorded during the intervention period.

5) Statistical Analysis

Statistical analysis was performed using SAS Drug Development (ver. 3.4) and PC-SAS (ver. 9.1.3) (SAS Institute Inc., Cary, NC, USA). Sample sizes of 260 patients (130 patients/group) were calculated to provide 90% power to detect a 19.2% difference in monthly responder rates of improvement in stool consistency during the Month 2 between the 2 groups (18.9% and 38.1% for the placebo and ramosetron groups, respectively, Figure 16) based on the phase IV pilot study (Clinicaltrials.gov ID: NCT00918411), using the chi-square test with a two-sided significance level of 0.05.

Efficacy analyses included the FAS, which included all patients who received at least one dose of the study drug during the treatment period and for whom at least one endpoint could be evaluated. Safety analyses were performed for all patients who received at least 1 dose of the study drug during the treatment period.

Monthly responder rates for improvement in stool consistency and global assessments are expressed as a percentage of responders, and 95% CIs are presented. The treatment groups were compared using the chi-square test with a two-sided significance level of 0.05. Other monthly responder rate parameters were similarly analyzed. BSFS were evaluated by using the *t*-test. Adverse events were evaluated using Fisher's exact test.

2.1.3 Results

1) Improvement in Stool Consistency

The ramosetron 5 μg group showed significantly higher improvement in stool consistency compared to the placebo group at all evaluation points

(Figure 17). Monthly responder rates in the Month 1 (primary endpoint) were 50.3% (95% CI, 42.0–58.7) and 19.6% (95% CI, 13.5–26.9) in the ramosetron and placebo groups, respectively (difference, 30.7%; 95% CI, 20.4–41.1; $P < 0.001$). In the last evaluation points, responder rates were 44.2% (95% CI, 36.0–52.6) and 25.0% (95% CI, 18.3–32.8), respectively (difference, 19.2%; 95% CI, 8.6–29.9; $P < 0.001$)

2) Global Assessment

Monthly responder rates for global assessment of relief of overall IBS symptoms were significantly higher in the ramosetron 5 μg group than in the placebo group at all evaluation points (Figure 18). Monthly responder rates for improvement in abnormal bowel habits (Figure 19A) and relief of abdominal pain/discomfort (Figure 19B) were also significantly higher in the ramosetron 5 μg group than in the placebo group at all evaluation points.

3) Weekly Changes in Stool Form

Weekly BSFS scores were significantly lower in the ramosetron 5 μg group (4.9 ± 0.8 at Week 1 and 4.8 ± 1.0 at the last point) than those in the placebo group (5.4 ± 0.7 at Week 1 and 5.2 ± 0.8 at the last point, $P < 0.001$) throughout the treatment period (Figure 20).

4) Safety

The incidence of hard stools was significantly higher in the ramosetron 5 μg group (8.2%) than in the placebo group (1.3%, $P = 0.006$) (Table 11). The ramosetron 5 μg group also induced constipation in 3.4% patients. However,

the incidence was not significantly higher than that in the placebo group (0.7%). All episodes of constipation and hard stools in the ramosetron 5 μg group, assumed to be caused by the pharmacological actions of ramosetron, were classified as mild and resolved early without using rescue drugs.

2.1.4 Discussion

This study examined the effects of ramosetron on stool consistency in male IBS-D patients, testing the hypothesis that ramosetron 5 μg is superior to placebo in improving stool consistency. As a result, the ramonsetron 5 μg group showed significantly higher monthly responder rates for improvement in stool consistency compared to the placebo group in male patients with IBS-D. The ramosetron 5 μg group also showed significant improvement of global assessment and individual IBS symptoms including stool form. This study's results indicate that based on the pharmacologic profile of ramosetron, improvement in stool consistency is the best endpoint for studies of ramosetron in patients with IBS-D.

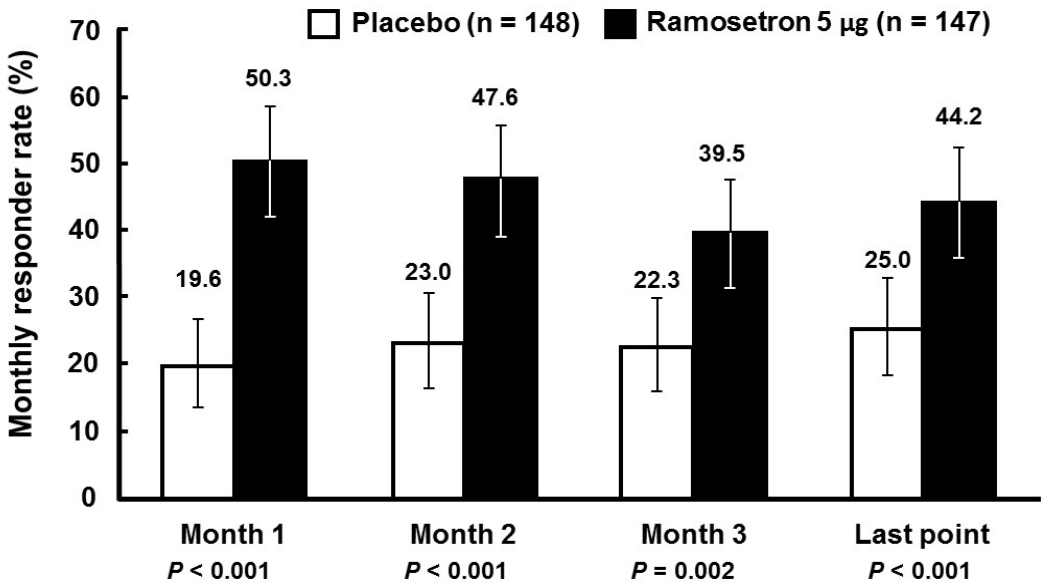


Figure 17. Monthly responder rates for improvement in stool consistency [Modified Figure 2 in reference 37]. Column height: responder rate (%). Error bar: 95% CI. *P* values were calculated using the chi-square test.

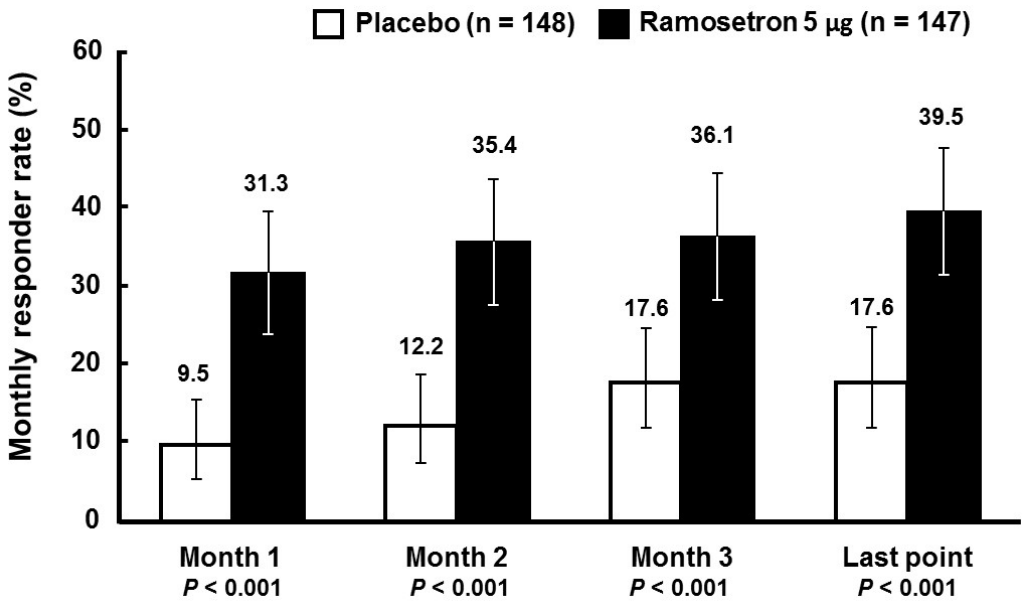
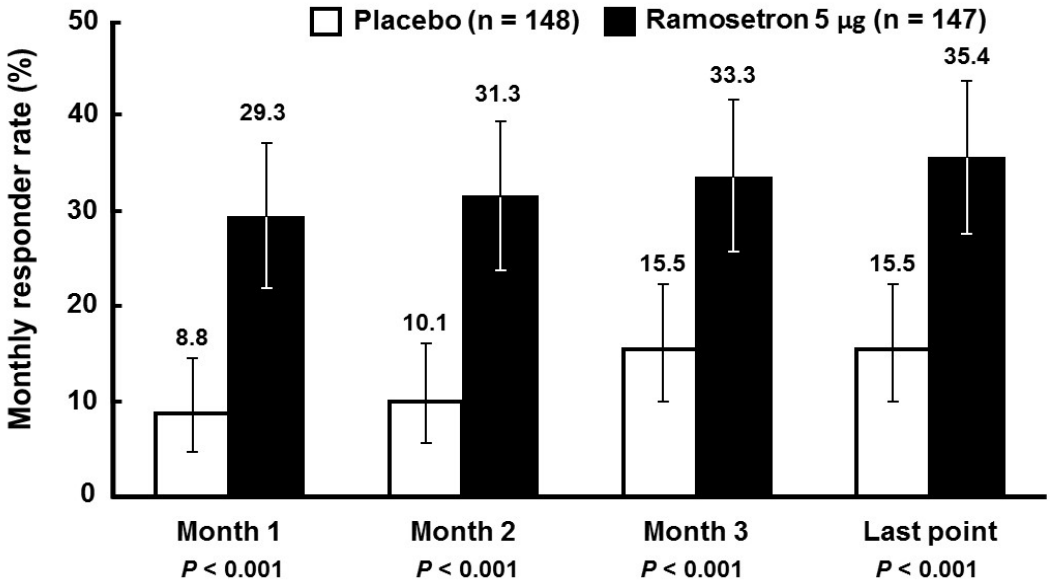


Figure 18. Monthly responder rates for relief of overall IBS symptoms [Modified Figure 3A in reference 37]. Column height: responder rate (%). *P* values were calculated using the chi-square test.

A)



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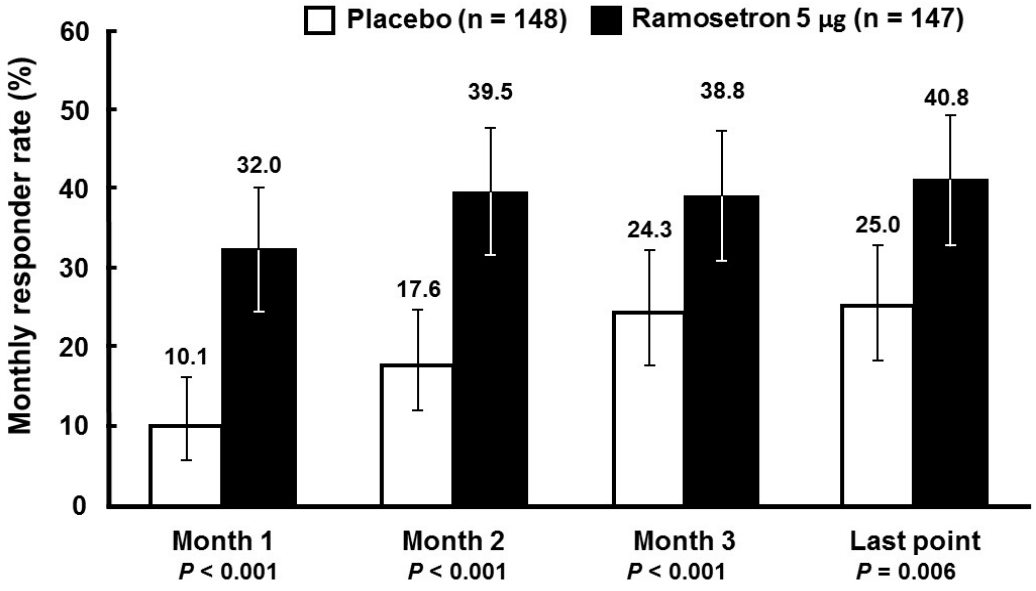


Figure 19. A) Monthly responder rate for improvement in abnormal bowel habits [Modified Supplementary Figure 2 in reference 37]. B) Monthly responder rates for relief of abdominal pain/discomfort [Modified Figure 3B in reference 37]. Column height: responder rate (%). *P* values were calculated using the chi-square test.

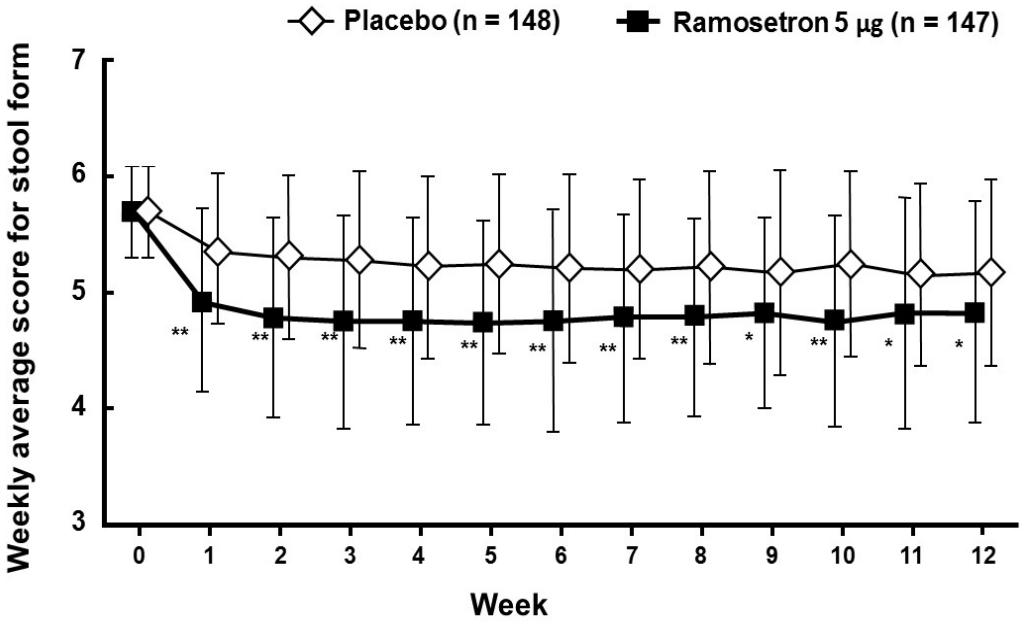


Figure 20. Weekly changes in BSFS scores [Modified Figure 3C in reference 37]. Line graph: means ± SD. *P* values were calculated using the *t*-test, as follows: ***P* < 0.001 and **P* < 0.01.

Table 11. Incidence of adverse events [Modified Table 2 in reference 37]

Event	Placebo (n = 149)	Ramosetron 5 μg (n = 147)	*P* value
All adverse events	77 (51.7%)	69 (46.9%)	0.48
Blood and lymphatic system disorders	1 (0.7%)	3 (2.0%)	0.37
Anemia	1 (0.7%)	3 (2.0%)	0.37
Gastrointestinal disorders	21 (14.1%)	21 (14.3%)	1.00
Constipation	1 (0.7%)	5 (3.4%)	0.12
Hard stool	2 (1.3%)	12 (8.2%)	0.01
Hepatobiliary disorders	5 (3.4%)	3 (2.0%)	0.72
Hepatic dysfunction	5 (3.4%)	3 (2.0%)	0.72
Infections and infestations	39 (26.2%)	29 (19.7%)	0.21
Gastroenteritis	2 (1.3%)	4 (2.7%)	0.45
Nasopharyngitis	25 (16.8%)	20 (13.6%)	0.52
Investigations	21 (14.1%)	13 (8.8%)	0.20
Increased serum alanine aminotransferase	7 (4.7%)	3 (2.0%)	0.34
Increased serum bilirubin	3 (2.0%)	3 (2.0%)	1.00
Nervous system disorders	4 (2.7%)	4 (2.7%)	1.00
Headache	1 (0.7%)	3 (2.0%)	0.37

Data are expressed as numbers (%). Events with an incidence of ≥2% in the ramosetron 5 μg group are listed. *P* values were calculated by using Fisher's exact test.

2.2 **Phase III Study of Ramosetron in Female Patients with IBS-D**

2.2.1 Background

A randomized, placebo-controlled, phase III study was conducted to determine whether ramosetron reduces symptoms of IBS-D in women (Clinicaltrials.gov ID: NCT01870895) [25]. It was deemed important to show how ramosetron is effective for individual IBS symptoms in addition to the improvement of overall symptoms of the syndrome. Monthly responder rates for improvement in stool consistency were assessed as co-primary endpoints with monthly responder rates for global assessment of relief of overall IBS symptoms. This study was conducted from February 2013 to February 2014 at 70 centers that have departments of gastroenterology. The study protocol was designed in accordance with the Declaration of Helsinki, GCP, the applicable laws and regulations and was approved by the institutional review board at each site. All patients provided written informed consent prior to participating in study-related procedures.

2.2.2 Methods

1) Patient Population

This study comprised a provisional registration period, a 1-week baseline period, and a 12-week treatment period, similar to previous studies [22, 23]. Female outpatients aged 20–64 years were diagnosed according to the Rome III criteria. Patients satisfying the inclusion and exclusion criteria were monitored during a 1-week baseline period in which data on severity of abdominal pain/discomfort and stool consistency were collected to ensure that

patients met the criteria. Patients who had not used drugs or undergone examinations that could affect the evaluation of study drug efficacy within 10 days prior to randomization; who recorded all items in the patient diary for ≥5 days during the baseline period; who had mean severity scores of abdominal pain/discomfort of ≥0.7 during the baseline period (a 5-point ordinate scale); in whom no type 1 or 2 stool form, as scored by BSFS, was recorded during the baseline period; who had bowel movements for ≥5 days during the baseline period; and who were not judged ineligible for the study according to the clinical laboratory test results received before the baseline period were randomized and successively administered treatment.

2) Study Design

Following the baseline period, eligible patients were randomly assigned to 12-week oral treatments with placebo or ramosetron 2.5 μg once daily before breakfast. Visits were scheduled at Weeks 2, 4, 8, and 12 (or at discontinuation) to assess treatment efficacy, drug compliance, and occurrence of adverse events. Randomization was performed in a 1:1 ratio using a block size of 4 with a web-based randomization system. All patients, investigators, and sponsors were blinded until all observations and evaluations were completed, statistical analysis plans were finalized, and all data had been entered.

3) Data Collection

During the baseline and treatment periods, patients recorded their IBS symptoms daily on paper diary cards at bedtime, and electronically entered data into a database daily using an interactive voice response system to

support the completion of data entry in the paper diary cards. In the diary, patients recorded the BSFS types and stool frequencies and scored the severity of their abdominal pain/discomfort. Urgency and feeling of incomplete evacuation were assessed on a binary scale. Every 7 days during the treatment period, patients also graded summarized IBS symptoms compared with the baseline period on a 5-point ordinate scale.

4) Efficacy Endpoints

The co-primary endpoints were monthly responder rate for improvement in stool consistency and monthly responder rates for global assessment of relief of overall IBS symptoms at last evaluation point. Patients with weekly mean BSFS scores of 3 to 5 during a 1-week of the treatment period and a decrease of one or more points in mean BSFS scores from the baseline period were defined as weekly responders in improvement in stool consistency (Table 10). If more than 2 daily scores were missing during any week of the study period, the mean score for that week was defined as missing. Patients with missing mean BSFS scores were regarded as weekly non responders. In global assessment of relief of overall IBS symptoms, patients with scores of 0 or 1 at each weekly evaluation point were defined as weekly responders (Table 2). Patients who were weekly responders for at least 2 of the 4 weeks in a 1- month were considered monthly responders in both primary endpoints. The last 4 weeks of the treatment phase constituted the assessment period for the primary endpoints.

Secondary endpoints included monthly responder rates for improvement in abnormal bowel habits and relief of abdominal pain/discomfort.

Scales measuring IBS symptoms, including severity of abdominal pain/discomfort, BSFS, stool frequency, urgency and feeling of incomplete evacuation and IBS-QOL were established for the secondary endpoints. All adverse events were recorded during the intervention period.

5) Statistical Analysis

Statistical analysis was performed using SAS Drug Development (ver. 3.4) and PC-SAS (ver. 9.1.3) (SAS Institute Inc., Cary, NC, USA). Sample sizes of 580 patients (290 patients/group) were calculated to provide 90% power to detect both a difference in monthly responder rates for global assessment of relief of overall IBS symptoms at the last point between the placebo group (38%) and the ramosetron 2.5 μg group (53%) and monthly responder rates for improvement in stool consistency at the last point between the placebo group (21%) and the ramosetron 2.5 μg group (40%) based on the phase II clinical study (Clinicaltrials.gov ID: NCT01274000) [24], using the chi-square test with a two-sided significance level of 0.05.

Efficacy analyses included the FAS, which included all patients who received at least one dose of the study drug during the treatment period and for whom at least one endpoint could be evaluated. Safety analyses were performed for all patients who received at least 1 dose of the study drug during the treatment period.

Monthly responder rates for global assessments and improvement in stool consistency are expressed as a percentage of responders, and 95% CIs are provided. The treatment groups were compared using the chi-square test test with a two-sided significance level of 0.05. The superiority of ramosetron

2.5 μg to placebo was defined with demonstrating statistically significance to placebo in both two co-primary endpoints. BSFS were evaluated using the *t*-test. Adverse events were evaluated using Fisher's exact test.

2.2.3 Results

1) Improvement in Stool Consistency

The monthly responder rate for improvement in stool consistency was 40.8% (95% CI, 35.1-46.6) in the ramosetron 2.5 μg group and 24.3% (95% CI,19.4-29.7) in the placebo group (difference, 16.5%; 95% CI,8.9-24.0; *P*<0.001; Figure 21).

2) Global Assessment

Ramosetron-treated patients showed significantly higher responder rates for global assessment of relief of overall IBS symptoms at the last point (50.7%; 95% CI, 44.8-56.6) than did placebo-treated patients (32.0%; 95% CI, 26.7–37.8; difference, 18.6%; 95% CI, 10.7-26.5; *P*<0.001; Figure 22). Monthly responder rates for improvement in abnormal bowel habits were significantly higher in the ramosetron 2.5 μg group than in the placebo group (Figure 23A). The monthly responder rates for relief of abdominal pain/discomfort in the ramosetron 2.5 μg group were also significantly higher than that in the placebo group (Figure 23B), except for Month 2.

3) Weekly Changes in Stool Form

Weekly BSFS scores were significantly lower in the ramosetron 2.5 μg group (4.32 ± 1.04) than those in the placebo group (4.80 ± 0.91 at last

evaluation point, $P < 0.001$) throughout treatment period (Figure 24) [25].

4) Safety

The incidences of constipation and hard stool considered to be caused by the pharmacological action of ramosetron were significantly higher in the ramosetron (11.0% and 22.6%, respectively) group than in the placebo group (4.6%, $P = 0.005$; 5.6%, $P < 0.001$, respectively) (Table 12). However, those adverse events observed were mild except that one patient in the ramosetron group showed a moderate level of hard stool which recovered immediately. Serious adverse events including anemia (one patient) and enterocolitis infectious (one patient) occurred only in the placebo group.

2.2.4 Discussion

This study aimed to verify the hypothesis that that remosetron could also be effective in female patients with IBS-D. The newly developed monthly responder rate of improvement in stool consistency (Table 10) was used as co-primary endpoints with monthly responder rates for global assessment of relief of overall IBS symptoms (Table 2). Both primary endpoints in the ramosetron 2.5 μg group showed significantly superior responses to the placebo group at all evaluation points. Based on these results, ramosetron was approved for use by women.

Monthly responder rates for improvement in abnormal bowel habits and weekly change in stool form showed significant improvement in the ramoseton group compared to the placebo group at all evaluation points. On the other hand, monthly responder rates for relief of abdominal pain/discomfort and

weekly change in the severity of abdominal pain/discomfort showed significant improvement at some evaluation points [25]. These results suggested stool form is superior to abdominal pain/discomfort to show how ramosetron is effective for individual IBS symptoms.

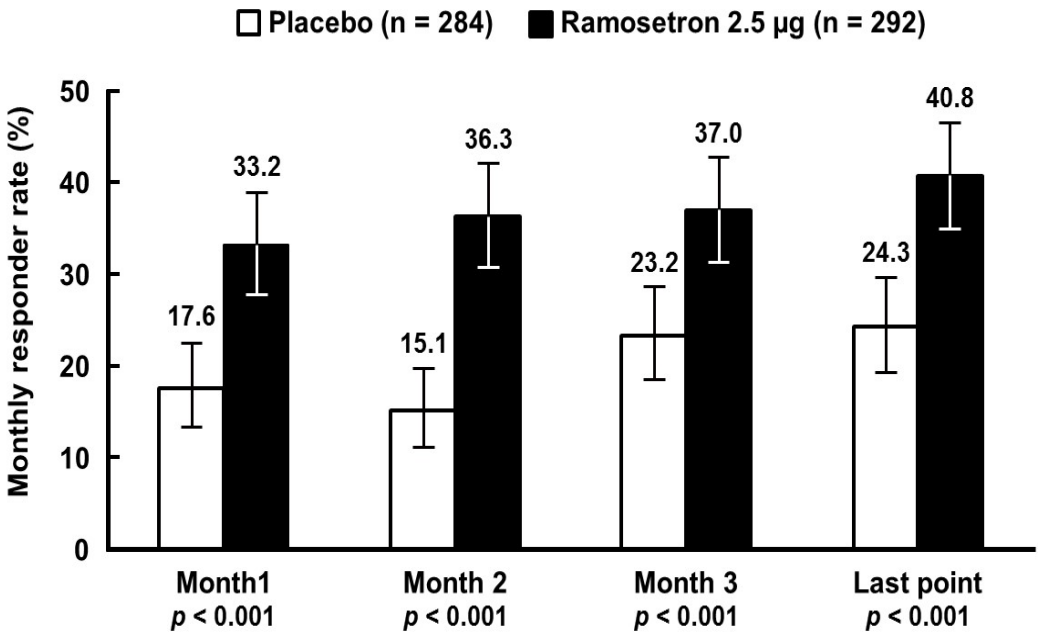


Figure 21. Monthly responder rates for improvement in stool consistency [Modified Figure 1B in reference 25]. Height: responder rate (%). Error bar: 95% CI. *P* values were calculated using the chi-square test.

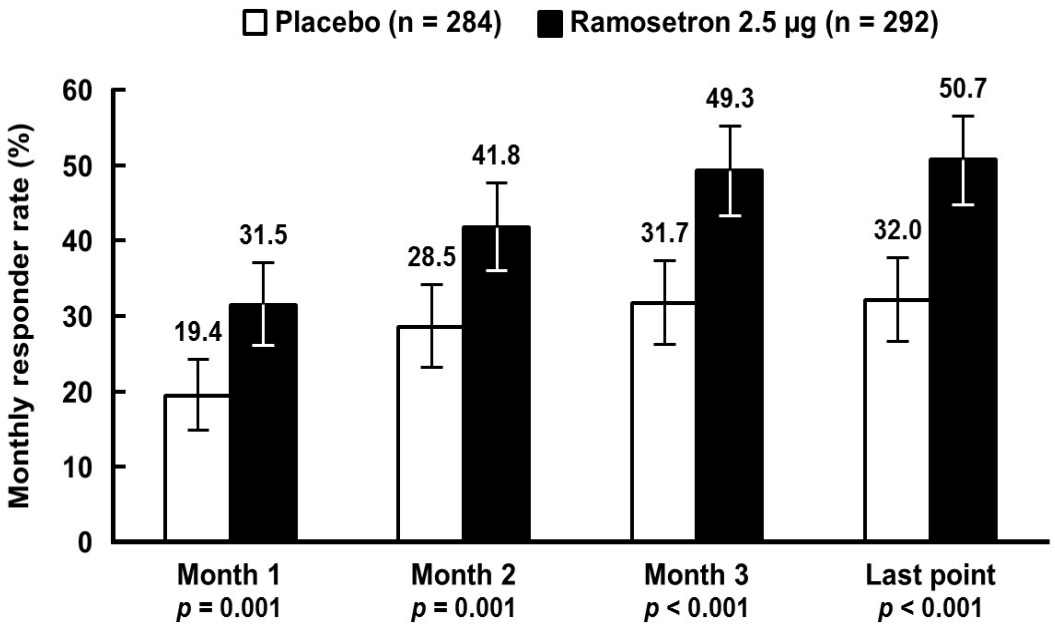
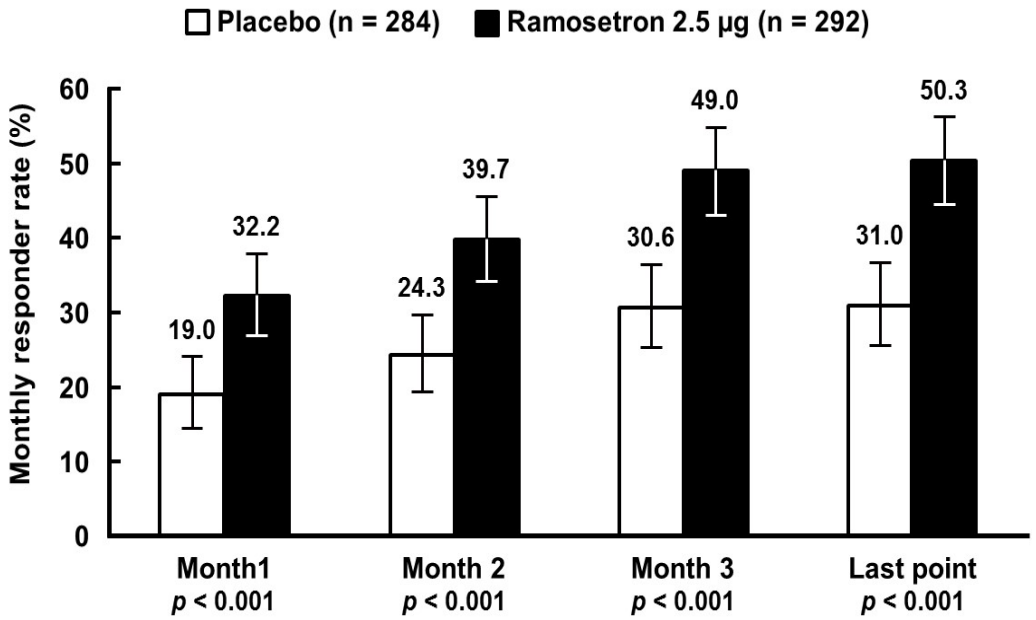


Figure 22. Monthly responder rates for relief of overall IBS symptoms [Modified Figure 1A in reference 25]. Height: responder rate (%). Error bar: 95% CI. *P* values were calculated using the chi-square test.

A)



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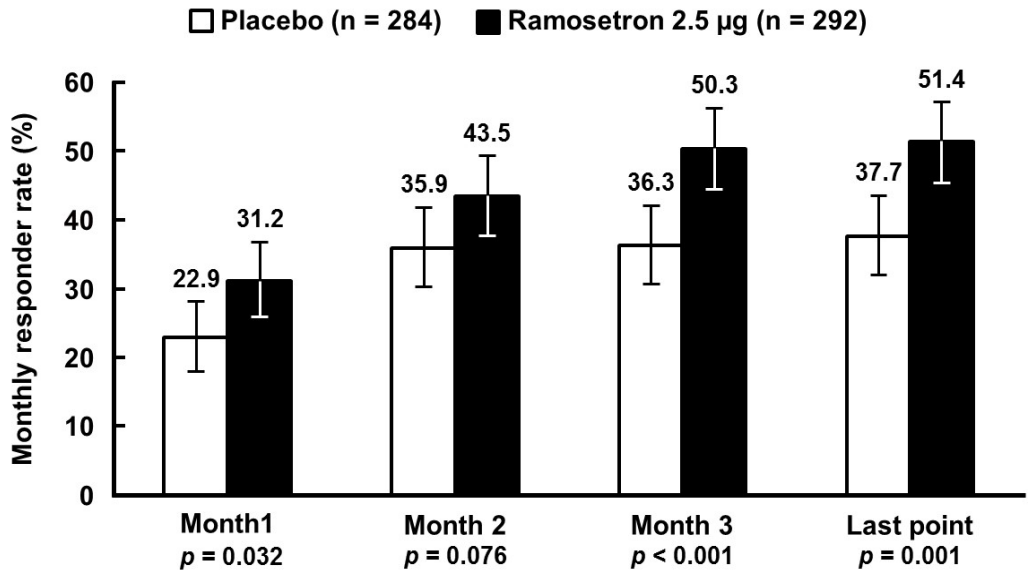

Figure 23. A) Monthly responder rates for improvement in abnormal bowel habits [Modified Figure 2B in reference 25]. B) Monthly responder rates for relief of abdominal pain/discomfort [Modified Figure 2A in reference 25]. Column height: responder rate (%). Error bar: 95% CI. *P* values were calculated using the chi-square test.

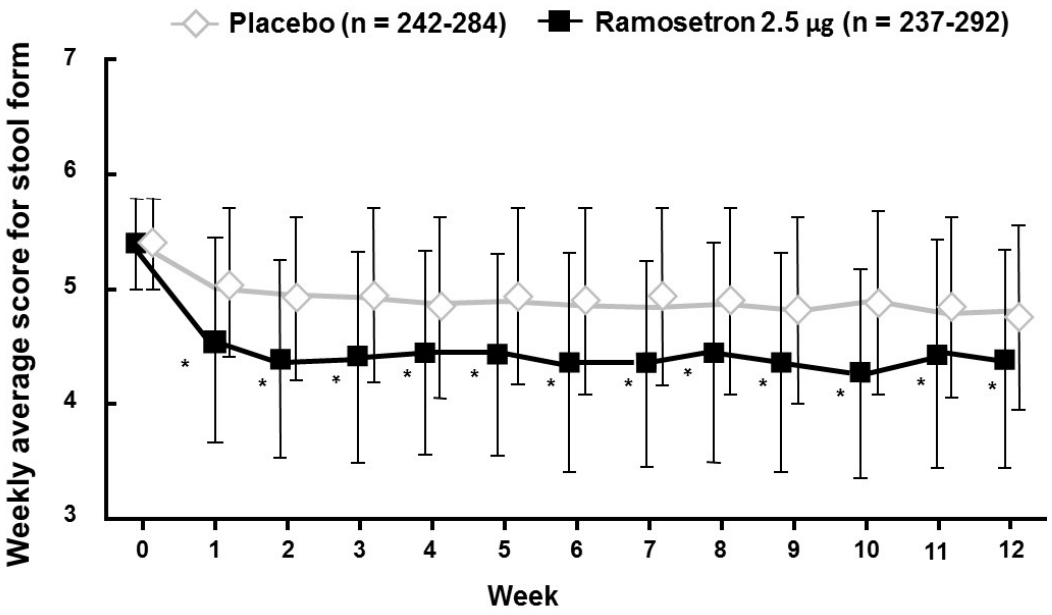

Figure 24. Weekly changes in BSFS scores. Line graph: mean ± 95% CI. *P* values were calculated using the *t*-test, as follows. **P* < 0.001.

Table 12. Incidence of adverse events [25]

Event	Placebo (n = 284)	Ramonsetron 2.5 μg (n = 292)	*P* value
All adverse events	118 (41.5%)	154 (52.7%)	0.009
Gastrointestinal disorders	46 (16.2%)	92 (31.5%)	< 0.001
Constipation	13 (4.6%)	32 (11.0%)	0.005
Hard stool	16 (5.6%)	66 (22.6%)	< 0.001
Infections and infestations	54 (19.0%)	56 (19.2%)	1.000
Nasopharyngitis	34 (12.0%)	34 (11.6%)	1.000
Pharyngitis	5 (1.8%)	6 (2.1%)	1.000

Data are expressed as numbers (%). Events with an incidence of ≥ 2% in the ramosetron 2.5 μg group are listed. *P* values were calculated using Fisher's exact test.

Chapter 3. Conclusions

The findings and discussion obtained by this research and future prospects are summarized below.

Chapter 1 showed the results of the phase IV pilot study to explore and examine efficacy variables to assess “clinically meaningful improvements, focusing on the patient’s chief complaint and the severity of major IBS symptoms” in addition to the global assessment. IBSSI-J showed that most patients enrolled had moderate to severe IBS symptoms in the baseline period. The highest severity score among each component was for dissatisfaction with bowel habits. Second was for interference with QOL and frequency of abdominal pain. The patients in this study were considered to have impaired QOL. The lowest score of the five components was for intensity of abdominal distention, which might be related to a lower contribution of abdominal distention in IBS-D. Changes in IBSSI-J score in the ramosetron 5 μg group seems to be superior to that of the placebo group numerically at all evaluation points, however, differences between ramosetron and placebo were not evident. Further investigation will be needed to use this questionnaire as a primary endpoint in clinical studies related to the development of pharmacological agents for IBS-D patients.

IBS is characterized by two major IBS symptoms, abdominal pain/discomfort and abnormal bowel habits. Regarding the chief complaint that patients had before administration, 34.0% of the patients in the ramosetron 5 μg group and 42.0% of the patients in the placebo group reported abdominal

pain/discomfort. Higher proportions of chief complaint in bowel habits were also observed in stool form (19.1% in the ramosetron 5 μg group and 18.0% in the placebo group) and stool frequency (25.5% in the ramosetron 5 μg group and 20.0% in the placebo group). When compared to placebo, the greatest improvement in symptoms of the chief complaint that patients had before administration in the ramosetron 5 μg group was shown in stool consistency. Stool consistency correlates with colonic transit time [43, 44] and can be a good indicator of bowel function. In rats, ramosetron also clearly reduced stress-induced diarrhea and accelerated defecation caused by corticotropin-releasing hormone [15, 19]. To show how ramosetron is effective for individual IBS symptoms, focusing on stool consistency was considered to be acceptable in light of the drug's pharmacological mechanism. If the effect of ramosetron on stool consistency is excessive, it leads to constipation. Therefore, it was also considered important to define a clinically meaningful "improvement in stool consistency". Patients with weekly mean BSFS scores of 3 to 5 during a 1-week of the treatment period and a decrease of one or more points in mean BSFS scores from the baseline period were defined as weekly responders. Patients who were weekly responders for at least 2 of the 4 weeks in a 1-month were defined as monthly responders.

In chapter 2, results of clinical studies were shown, and used the newly developed variable, "improvement in stool consistency" as the primary endpoint to evaluate the prospective effect of ramosetron. The ramonsetron 5 μg group showed significantly higher monthly responder rates in improvement in stool consistency compared to the placebo group at all evaluation points in male

patients with IBS-D [37]. In the phase III study for female patients with IBS-D, improvement in stool consistency was used as co-primary endpoints with global assessments and the ramonsetron 2.5 μg group showed superior response to the placebo group in both primary endpoints [25]. As a results, ramosetron 2.5 μg was approved for use by women in May 2015.

Thus, I found “improvement in stool consistency” is the best endpoint for clinical studies of ramosetron in patients with IBS-D to clearly show how ramosetron is effective for individual IBS symptoms, along with the pharmacologic profile of the drug.

Although it was unclear that an improvement of one chief complaint influenced the other IBS symptoms of patients, improvement in the chief complaint the patient had before administration was more frequent in the responder group in global assessment of relief of overall IBS symptoms compared to the non-responder group. These relationships were obtained not only for stool form, but also for abdominal pain/discomfort and stool frequency. In studies with larger patient numbers, ramosetron showed a statistically significant improvement in the severity of abdominal pain/discomfort and stool frequency compared to placebo at some evaluation points [25, 37]. Ramosetron was suggested to improve overall IBS symptoms throughout the improvement of individual IBS symptoms like abdominal pain/discomfort, stool form and stool frequency, which were assessed as secondary endpoints.

A greater change in the IBSSI-J overall score and percent change from baseline were also observed in the monthly responder group with respect to

global assessment of relief of overall IBS symptoms than in the non-responder group. This result suggests that global assessment also reflects improvement of the symptom severity of patients with IBS-D.

In the phase II study to find the optimal dose of ramosetron (1.25 μg, 2.5 μg and 5 μg) for female patients with IBS-D [24], the ramosetron 2.5 μg group showed a clear improvement in global assessment of relief of overall IBS symptoms compared to placebo group. On the other hand, weekly BSFS scores were lowest in the ramosetron 5 μg group and the incidence of constipation and hard stool increased in a dose-dependent manner. These results suggest that patients assessed global assessment of relief of overall IBS symptoms negatively, if they felt the effect of ramosetron is excessive. Ramosetron 2.5 μg was chosen as the optimal dose of ramosetron for female patients to show the most effective and least harmful option. These results are consistent with the results of the PK study for ramosetron [45]. Patients can assess global assessment of relief of overall IBS symptoms not only in a positive direction, but also a negative direction.

Thus, it is considered that global assessment of relief of overall IBS symptoms is the best endpoint to show clinically meaningful improvement by patients, which includes the assessments of improvement of chief complaint and severity of major IBS symptoms.

Future Prospects

In recent years, the concept of patient-centricity is increasingly emphasized in drug development in Europe and the United States. Patient reported outcome (PRO) was developed as a variable to capture evaluation of patients.

The United States Food and Drug Administration (FDA) proposed a study design for clinical trials focused on IBS that would assist the pharmaceutical industry and investigators who are developing drugs [46]. Although they recommend the use of abdominal pain and stool consistency as co-primary endpoints for IBS-D, these are provisional endpoints. They require the development of multi-item PRO instruments that can capture clinically important signs and symptoms of the IBS target population (e.g. IBS-C or IBS-D). Some PRO measurements are under development in the study of IBS [41, 47] in accordance with the FDA guidance for PRO [48]. In its PRO guidance, the FDA recommends that acceptable PRO must be couched in an explicit and evidence based conceptual framework. In the future, PRO measurements that include validated assessment of multiple chief complaints might be available in clinical trials related to IBS.

The Japanese Society of Gastroenterology developed evidence-based clinical practice guidelines for IBS [49]. They recommend treating IBS patients, as they can feel improvement in IBS symptoms, based on the assessment of patient-reported outcomes. Global assessment of relief of overall IBS symptoms in this study can be a very useful efficacy variable in IBS-D to meet with their recommendation. “Improvement in stool consistency” is calculated by

the stool form, which is also evaluated by patients using the objective standard BSFS. It showed the normalization of stool form and how ramoserton was effective for individual IBS symptoms. Figure 25 summarizes the efficacy variables in a clinical study of ramosetron for IBS-D. Using “improvement in stool consistency” in addition to global assessment is important to add scientific value to subjective evaluation by patients.

IBS is not a life-threatening disease, but has been shown to limit the activity of patients and to negatively impact social functioning, with substantial economic loss. QOL is impaired. Ramosetron (5 μg for male and 2.5 μg for female) significantly improved overall scores, dysphoria, interference with activity, and food avoidance included in IBS-QOL, disease specific health-related QOL compared to placebo [25, 37].

Development of new medicines using the evidence of PRO can increase treatment options for doctors and patients with IBS-D. As a result, it might improve medical economics. PRO is not yet very popular in Japan. This research is expected to contribute to the development of variables in clinical studies for other diseases, as patient-centricity becomes increasingly important.

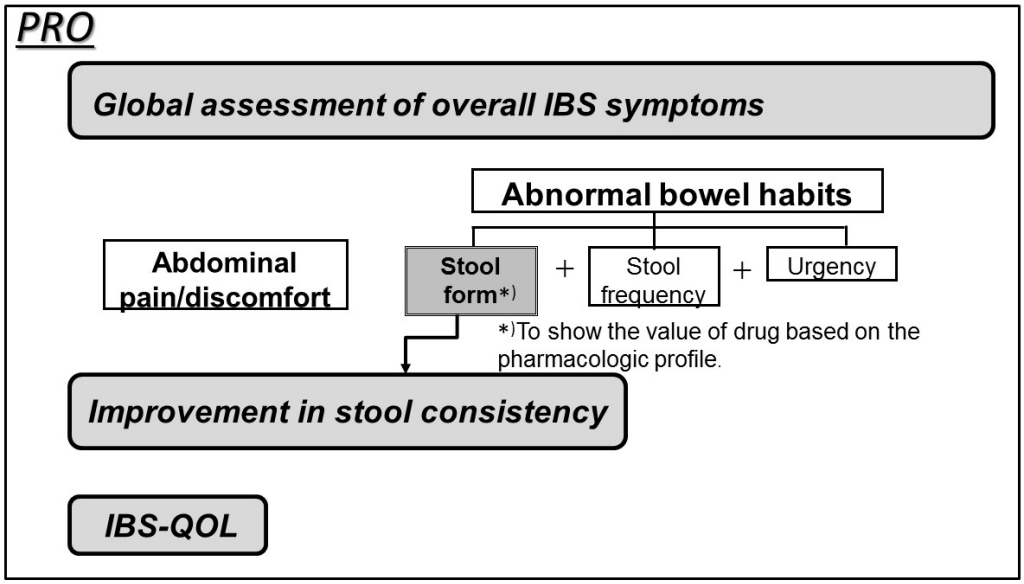

Figure 25. Summary of efficacy variables in clinical study of IBS-D.

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Acknowledgements

I would like to thank Prof. Hideyuki Shigemori, Associate Prof. Shigeki Yoshida, Associate Prof. Takeo Usui, and Associate Prof. Kosumi Yamada at the Faculty of Life and Environmental Sciences, the University of Tsukuba, for their discussion, advices and guidance on my doctoral dissertation.

I would like to thank Dr. Shin Fukudo, Department of Behavioral Medicine, Tohoku University, Graduate School of Medicine and Dr. Kei Matsueda, Sakura Life Clinic for their discussion, advices, guidance on conducting studies and preparing for this doctoral dissertation.

I would like to thank Mr. Yuta Watanabe, Vice president at Japan-Asia Planning & Administration and Dr. Taiji Sawamoto, Vice president at Research Program Management, at Astellas Pharma Inc. for giving me the opportunity for this doctoral dissertation and accommodation.

I would like to thank Dr. Akito Nishida, Development Project Management, Dr. Hiraku Akiho, Japan-Asia Clinical Development 2, Development and Mr. Yoshihiro Nakashima, Japan-Asia Data Science, Development at Astellas Pharma Inc. for their discussion, advices, guidance on this doctoral dissertation.

I would like to thank many colleagues involved in ramosetron projects at Astellas Pharma Inc. for giving me the opportunity for this doctoral dissertation. This study was based on their efforts to develop ramosetron.

At the end, I would like to thank my family and friends for always supporting me.

List of Published Articles

1. Motoko Ida, Akito Nishida, Hiraku Akiho, Yoshihiro Nakashima, Kei Matsueda, Shin Fukudo. Evaluation of the irritable bowel syndrome severity index in Japanese male patients with irritable bowel syndrome with diarrhea. BioPsychoSocial Medicine, 2017;11:7 DOI 10.1186/s13030-017-0092-x.
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