Report on the Deliberation Results

May 14, 2015

Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau,
Ministry of Health, Labour and Welfare

[Brand name]	Irribow Tablets 2.5 μg, Irribow Tablets 5 μg, Irribow OD Tablets 2.5 μg, Irribow OD Tablets 5 μg
[Non-proprietary name]	Ramosetron Hydrochloride (JAN*)
[Applicant]	Astellas Pharma Inc.
[Date of application]	July 14, 2014

[Result of deliberation]

In the meeting held on April 28, 2015, the First Committee on New Drugs concluded that the partial change application for the above products may be approved and that the review results should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The re-examination period for the products is 4 years.

[Conditions for approval]

The applicant is required to develop and appropriately implement a risk management plan.

**Japanese Accepted Name (modified INN)*

Review Report

April 7, 2015
The Pharmaceuticals and Medical Devices Agency

The results of a regulatory review conducted by the Pharmaceuticals and Medical Devices Agency on the following pharmaceutical products submitted for registration are as follows.

[Brand name]	(1) Irribow Tablets 2.5 μg, Irribow Tablets 5 μg (2) Irribow OD Tablets 2.5 μg, Irribow OD Tablets 5 μg
[Non-proprietary name]	Ramosetron Hydrochloride
[Applicant]	Astellas Pharma Inc.
[Date of application]	July 14, 2014
[Dosage form/Strength]	(1) Each film-coated tablet contains 2.5 μg or 5 μg of ramosetron hydrochloride. (2) Each orally disintegrating tablet contains 2.5 μg or 5 μg of ramosetron hydrochloride.
[Application classification]	Prescription drugs; (4) Drugs with a new indication; (6) Drugs with a new dosage
[Items warranting special mention]	None
[Reviewing office]	Office of New Drug I

Review Results

April 7, 2015

[Brand name] (1) Irribow Tablets 2.5 μg,
Irribow Tablets 5 μg
(2) Irribow OD Tablets 2.5 μg,
Irribow OD Tablets 5 μg

[Non-proprietary name] Ramosetron Hydrochloride

[Applicant] Astellas Pharma Inc.

[Date of application] July 14, 2014

[Results of review]

Based on the submitted data, the Pharmaceuticals and Medical Devices Agency (PMDA) concluded that the efficacy of the products in female patients with diarrhea-predominant irritable bowel syndrome has been demonstrated and their safety is acceptable in view of its observed benefits.

As a result of its regulatory review, PMDA concluded that the products may be approved for the following indication and dosage and administration with the following conditions for approval.

[Indication]

Diarrhea-predominant irritable bowel syndrome

[Dosage and administration]

Male patients with diarrhea-predominant irritable bowel syndrome

The usual dose for male adults is 5 μg of ramosetron hydrochloride, administered once daily orally. The dose may be adjusted according to the patients' clinical condition. The daily dose should not exceed 10 μg.

Female patients with diarrhea-predominant irritable bowel syndrome

The usual dose for female adults is 2.5 μg of ramosetron hydrochloride, administered once daily orally.

The dose may be increased for patients who do not adequately respond to the initial dose. The daily dose should not exceed 5 μg.

(Underline denotes added text.)

[Conditions for approval]

The applicant is required to develop and appropriately implement a risk management plan.

Review Report (1)

March 6, 2015

I. Products submitted for registration

[Brand name]	(1) Irribow Tablets 2.5 μg, Irribow Tablets 5 μg (2) Irribow OD Tablets 2.5 μg, Irribow OD Tablets 5 μg
[Non-proprietary name]	Ramosetron Hydrochloride
[Applicant]	Astellas Pharma Inc.
[Date of application]	July 14, 2014
[Dosage form/Strength]	(1) Each film-coated tablet contains 2.5 μg or 5 μg of ramosetron hydrochloride. (2) Each orally disintegrating tablet contains 2.5 μg or 5 μg of ramosetron hydrochloride.
[Proposed indication]	~~Male patients with~~ Diarrhea-predominant irritable bowel syndrome

(Double strikethrough denotes deleted text.)

[Proposed dosage and administration]

Male patients with diarrhea-predominant irritable bowel syndrome

The usual dose for male adults is 5 μg of ramosetron hydrochloride, administered once daily orally.

The dose may be adjusted according to the patients' clinical condition. The daily dose should not exceed 10 μg.

Female patients with diarrhea-predominant irritable bowel syndrome

The usual dose for female adults is 2.5 μg of ramosetron hydrochloride, administered once daily orally.

The dose may be increased to 5 μg once daily for patients who do not adequately respond to the initial dose.

(Underline denotes added text.)

II. Summary of the Submitted Data and Outline of the Review by the Pharmaceuticals and Medical Devices Agency

The submitted data and the review thereof by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below.

As the present application is for a new indication, no new data on the quality or non-clinical findings of the products have been submitted.

1. Origin or history of discovery, use in foreign countries, and other information.

Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder that is characterized by chronic

persistent or recurring abnormal bowel habits accompanied by abdominal pain or discomfort in the absence of organic disease that may explain the symptoms. IBS is considered attributable to several factors such as abnormal gastrointestinal motility, increased visceral perception, and psychosocial factors.[1] The Rome III criteria developed by international working groups on functional gastrointestinal disorders of the Rome Foundation classify IBS by predominant stool pattern into 4 subtypes: diarrhea-predominant IBS (IBS-D), constipation-predominant IBS (IBS-C), mixed IBS (IBS-M), and unsubtyped IBS.[2]

In Japan, the Evidence-based Clinical Practice Guidelines for Irritable Bowel Syndrome published by the Japanese Society of Gastroenterology (Nankodo, 2014) recommend that IBS-D should be initially treated with dietary therapy and behavioral modification, and drug therapy should then be given to patients who do not respond to those measures. Drug therapies listed in the Guidelines include probiotics, high molecular-weight polymers, and prokinetic drugs, as well as serotonin-3 (5-HT_3)[3] receptor antagonists[4] for male patients.

Ramosetron Hydrochloride is a selective serotonin 5-HT_3 receptor antagonist synthesized by the applicant, and controls excessive bowel movement and diarrhea by inhibiting 5-HT_3 receptors[5] in the intestinal tract. Ramosetron Hydrochloride was approved as film-coated tablets in July 2008 and as orally disintegrating tablets in August 2013 for the indication of treatment of male patients with diarrhea-predominant irritable bowel syndrome.[6] The indications and dosage and administration proposed in the initial application for Ramosetron Hydrochloride for the treatment of IBS-D, covered both male and female patients with IBS-D. However, the pharmacokinetics, efficacy profile, and incidence of adverse events tended to differ between male and female patients. PMDA thus concluded that the submitted clinical study data did not clearly define the optimal dose for female patients with IBS-D, and requested the applicant to further assess the optimal dose, efficacy, and safety of Ramosetron Hydrochloride in female patients with IBS-D (see the Review Report for Irribow Tablets 2.5 μg and Irribow Tablets 5 μg, dated April 10, 2008 [in Japanese only]).

In response to the above advice, the applicant conducted a phase II study, phase III study, and long-term treatment study in female patients with IBS-D in Japan. The applicant has claimed that the efficacy and safety of Ramosetron Hydrochloride has been demonstrated in this patient population and accordingly has submitted a partial change application for the product.

As of February 2015, Ramosetron Hydrochloride is approved for the treatment of male patients with

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[1] Rome III: The Functional Gastrointestinal Disorders 3rd ed. McLean. Degnon Associates, Inc; 2006: 490-509

[2] *Gastroenterology,* 2006;130:1480-1491,

[3] 5-HT represents 5-hydroxytryptamine, which is serotonin.

[4] Ramosetron Hydrochloride is the only currently available drug indicated for the treatment of male patients with IBS-D in Japan.

[5] 5-HT_3 receptors in ganglion neurons in the intestine, and thereby promote intestinal transit and motility and water secretion (Pharmacol Toxicol, 2003;93:1-13; J Surg Res, 1993;55:55-59). The secretion of 5-HT in the fed state has been reported to be higher in some patients with IBC-D than in healthy adults (Gut, 1998;42:42-46).

[6] Ramosetron Hydrochloride was approved in July 1996 under a brand name of Nasea Injection 0.3 mg and in June 1998 under a brand name of Nasea OD tablets 0.1 mg for the treatment of gastrointestinal symptoms (nausea and vomiting) associated with therapy with antineoplastic drugs (e.g., cisplatin).

IBS-D in Korea and Thailand as well, but not for the treatment of female patients with IBS-D in any countries or regions.

2. Clinical data

2.(i) Summary of biopharmaceutical studies and associated analytical methods, and summary of clinical pharmacology studies

No new data were submitted on biopharmaceutical studies or associated analytical methods, or the results of clinical pharmacology studies.

2.(ii) Summary of clinical efficacy and safety

2.(ii).A. Summary of the submitted data

The efficacy and safety evaluation data consisted of the results of 3 clinical studies in Japan, i.e., a phase II study, phase III study, and long-term treatment study. These 3 studies enrolled female patients with diarrhea-predominant irritable bowel syndrome (IBS-D) who met the inclusion criteria listed in Table 1.

Table 1. Key inclusion criteria for the clinical studies

1. Patients with recurrent abdominal pain or discomfort at least 3 days per month in the last 3 months, associated with two or more of the following (those who satisfy the Rome III Criteria). The onset of abdominal pain or discomfort should be at least 6 months before the preliminary enrollment. 1) Improvement with defecation 2) Onset associated with a change in frequency of stool 3) Onset associated with a change in form (appearance) of stool
2. Patients who had soft stool (caddy stool) or watery stool (Type 6 or 7 of the Bristol Stool Form Scale [BSFS])[7] in at least 25% of defecations and hard or lumpy stool (BSFS Type 1 or 2) in less than 25% of defecations for the last 3 months.
3. Patients who had the symptoms of IBS and in whom no organic changes were observed by total colonoscopy or barium enema examination (or sigmoidoscopy for patients <50 years of age at the time of preliminary enrollment) within 5 years prior to the preliminary enrollment.
4. Patients ≥20 years of age at the time of informed consent and ≤64 years of age at the time of preliminary enrollment.
5. Patients who met the following 5 conditions during the run-in period: 1) Patients who did not receive any drugs or undergone bowel examinations that might affect efficacy evaluation of the drug, starting 3 days before the first day of the run-in period. 2) Patients who recorded all items of the patient diary for at least 5 days during the run-in period. 3) Patients who had an average score of abdominal pain or discomfort[8] of 0.7 or higher during the run-in period. 4) Patients who had no stool of BSFS Type 1 or 2 during the run-in period. 5) Patients who had at least 3 defecations per week during the run-in period.

2.(ii).A.(1) Phase II dose-finding study (5.3.5.1-1: Study YM060/CL-701; November 2010 to November 2011)

A multi-center, randomized, double-blind, parallel-comparison study was conducted in female patients ≥20 years of age with IBS-D (target sample size: ≥360 patients) (Table 1) at 61 study sites in Japan to determine the recommended dose and safety of Ramosetron Hydrochloride (hereinafter referred also to as "ramosetron").

Participants received ramosetron at doses of 1.25, 2.5, or 5 μg or placebo orally once daily before breakfast for 12 weeks.

[7] 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, smooth and soft; Type 5, Soft blobs with clear-cut edges (passing easily); Type 6, Fluffy pieces with ragged edges, a mushy stool; and Type 7, Watery, no solid pieces.

[8] The severity of abdominal pain or discomfort was rated using a 5-rank scale (0, none; 1, mild; 2, moderate; 3, severe; and 4, very severe).

All the 409 patients (102 patients in the placebo group; and 104 patients in the ramosetron 1.25 μg group, 104 patients in the ramosetron 2.5 μg group, and 99 patients in the ramosetron 5 μg group) who received the study drug were included in the full analysis set (FAS) and the safety analysis set. The FAS served as the primary efficacy analysis population. The study was discontinued in 42 patients (12 patents in the placebo group; and 7, 6, and 17 patients in the 1.25, 2.5, and 5 μg groups, respectively). The reasons of the discontinuation included adverse events in 14 patients (4 patients in the placebo group; and 2, 2, and 6 patients in the 1.25, 2.5, and 5 μg groups, respectively); withdrawal of informed consent in 9 patients (3 patients in the placebo group; and 3 and 3 patients in the 1.25 and 5 μg groups, respectively); lack of efficacy in 5 patients (1 patient in the placebo group; and 1, 1, and 2 patients in the 1.25, 2.5, and 5 μg groups, respectively); protocol deviation in 2 patients (1 patient in the placebo group; and 1 patient in the 5 μg group); violation of the inclusion or exclusion criteria in 1 patient in the 5 μg group; worsening of IBS-D in 1 patient in the placebo group; lost to follow-up in 1 patient in the 1.25 μg group; and other reasons in 9 patients (2 patients in the placebo group; and 3 and 4 patients in the 2.5 and 5 μg groups, respectively).

Table 2 shows the results of efficacy evaluation on the basis of the primary endpoint of the study, that is, the percentage (95% confidence interval [CI]) of monthly responders[9] in overall improvement rating in IBS symptoms[10] at Month 1. There were no significant differences between the ramosetron groups and the placebo group (P = 0.048 [one-sided] in the 5 μg group vs. the placebo group; Shirley-Williams test with a one-sided significance level of 2.5%).

Table 2. Percentage of monthly responders in overall improvement rating in IBS symptoms at Month 1 (FAS)

Treatment group	Number of responders (patients)	Percentage of responders (%) [95%CI]	Difference from the placebo group (%) [95% CI]	P value (one-sided)[a)]
Placebo (102 patients)	29	28.4 [19.9, 38.2]	–	–
Ramosetron 1.25 μg (104 patients)	41	39.4 [30.0, 49.5]	11.0 [-1.8, 23.8]	–
Ramosetron 2.5 μg (104 patients)	40	38.5 [29.1, 48.5]	10.0 [-2.8, 22.8]	–
Ramosetron 5 μg (99 patients)	40	40.4 [30.7, 50.7]	12.0 [-1.1, 25.0]	P = 0.048

a) Shirley-Williams test with a one-sided significance level of 2.5%

Adverse events developed in 43.1% (44 of 102 patients) in the placebo group, and 54.8% (57 of 104 patients) in the 1.25 μg group, 54.8% (57 of 104 patients) in the 2.5 μg group, and 70.7% (70 of 99 patients) in the 5 μg group. Adverse events for which a causal relationship to the study drug could not be ruled out (adverse drug reactions) developed in 20.6% (21 of 102 patients) in the placebo group, 32.7% (34 of 104 patients) in the 1.25 μg group, 35.6% (37 of 104 patients) in the 2.5 μg group, and 52.5% (52 of 99 patients) in the 5 μg group. Adverse events and adverse drug reactions observed in ≥2% of patients in any group are listed in Tables 3 and 4.

[9] A patient with a weekly IBS symptom score of 0 or 1 was defined as a weekly responder, and a patient who was a weekly responder in ≥2 weeks in a month (4 weeks) were defined as a monthly responder.

[10] Every week, patients assessed all their symptoms comprehensively and scored the severity as compared with those during the run-in period (0, symptoms disappeared; 1, symptoms improved markedly; 2, symptoms improved slightly; 3, no change; and 4, symptoms worsened).

Table 3. Adverse events observed in ≥2% of patients in any group

	Placebo (102 patients)		Ramosetron 1.25 μg (104 patients)		Ramosetron 2.5 μg (104 patients)		Ramosetron 5 μg (99 patients)	
	Incidence	n	Incidence	n	Incidence	n	Incidence	n
Overall	43.1%	44	54.8%	57	54.8%	57	70.7%	70
Faeces hard	6.9%	7	19.2%	20	23.1%	24	30.3%	30
Constipation	5.9%	6	12.5%	13	11.5%	12	25.3%	25
Nasopharyngitis	13.7%	14	7.7%	8	12.5%	13	16.2%	16
Abdominal distension	4.9%	5	2.9%	3	8.7%	9	5.1%	5
Hepatic function abnormal	0%	0	1.0%	1	1.0%	1	4.0%	4
Nausea	0%	0	1.0%	1	0%	0	3.0%	3
Upper respiratory tract inflammation	2.0%	2	0%	0	0%	0	3.0%	3
Pharyngitis	0%	0	1.0%	1	1.0%	1	2.0%	2
Blood urea increased	1.0%	1	1.0%	1	1.0%	1	2.0%	2
Gamma-glutamyltransferase increased	0%	0	0%	0	1.0%	1	2.0%	2
Headache	0%	0	4.8%	5	0%	0	2.0%	2
Back pain	1.0%	1	1.9%	2	0%	0	2.0%	2
Somnolence	0%	0	1.0%	1	0%	0	2.0%	2
Genital haemorrhage	0%	0	0%	0	0%	0	2.0%	2
Oropharyngeal pain	0%	0	0%	0	0%	0	2.0%	2
Enteritis infectious	0%	0	0%	0	2.9%	3	1.0%	1
Protein urine present	0%	0	3.8%	4	0%	0	1.0%	1
Cystitis	1.0%	1	2.9%	3	1.9%	2	0%	0
Gingivitis	2.0%	2	0%	0	1.0%	1	0%	0
Vomiting	2.0%	2	1.0%	1	0%	0	0%	0

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Table 4. Adverse drug reactions observed in ≥2% of patients in any group

	Placebo (102 patients)		Ramosetron 1.25 μg (104 patients)		Ramosetron 2.5 μg (104 patients)		Ramosetron 5 μg (99 patients)	
	Incidence	n	Incidence	n	Incidence	n	Incidence	n
Overall	20.6%	21	32.7%	34	35.6%	37	52.5%	52
Faeces hard	6.9%	7	19.2%	20	23.1%	24	30.3%	30
Constipation	5.9%	6	12.5%	13	10.6%	11	25.3%	25
Abdominal distension	4.9%	5	2.9%	3	7.7%	8	5.1%	5
Hepatic function abnormal	0%	0	1.0%	1	1.0%	1	3.0%	3
Blood urea increased	1.0%	1	0%	0	1.0%	1	2.0%	2
Gamma-glutamyltransferase increased	0%	0	0%	0	0%	0	2.0%	2

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No deaths occurred during the study. Serious adverse events developed in 1.0% (1 of 102 patients; gastroenteritis) in the placebo group; 1.0% (1 of 104 patients; granulocytopenia) in the 1.25 μg group; 1.0% (1 of 104 patients; blood potassium increased) in the 2.5 μg group. A causal relationship with the study drug was not ruled out for the case of blood potassium increased in 1 patient in the 2.5 μg group.[11] Adverse events leading to study discontinuation developed in 4.9% (5 of 102 patients) in the placebo group, 1.9% (2 of 104 patients) in the 1.25 μg group, 1.9% (2 of 104 patients) in the 2.5 μg group, and 6.1% (6 of 99 patients) in the 5 μg group.[12]

2.(ii).A.(2) Phase III study (5.3.5.1-2: Study YM060/CL-702; February 2013 to February 2014)

A multi-center, randomized, double-blind, parallel-comparison study conducted in female patients ≥20

[11] The outcome of blood potassium increased was "recovered/resolved". The event persisted for 36 days.

[12] The adverse events leading to study discontinuation included abdominal distension, constipation, irritable bowel syndrome, vomiting, and gastroenteritis in 1 patient each in the placebo group; granulocytopenia, and enterocolitis/pneumonia in 1 patient each in the 1.25 μg group; blood potassium increased and depressed level of consciousness/tremor in 1 patient each in the 2.5 μg group; and faeces hard in 3 patients, hepatic function abnormal in 2 patients, and constipation in 1 patient in the 5 μg group.

years of age with IBS-D (target sample size: 580 patients) (Table 1[13]) at 70 study sites in Japan to evaluate the efficacy and safety of ramosetron.

Participants received ramosetron 2.5 μg or placebo orally once daily before breakfast for 12 weeks.

All the 576 patients (284 patients in the placebo group, 292 patients in the 2.5 μg group) who received the study drug were included in the FAS and the safety analysis set. The FAS served as the primary efficacy analysis population. The study was discontinued in 47 patients (21 patients in the placebo group, 26 patients in the 2.5 μg group). The reasons of the discontinuation included adverse events in 13 patients (8 patients in the placebo group, 5 patients in the 2.5 μg group); withdrawal of informed consent in 13 patients (4 patients in the placebo group, 9 patients in the 2.5 μg group); lack of efficacy in 9 patients (6 patients in the placebo group, 3 patients in the 2.5 μg group); lost to follow-up in 3 patients in the 2.5 μg group; violation of the inclusion or exclusion criteria in 2 patients (1 patient each in both groups); worsening of IBS-D in 1 patient in the placebo group; protocol deviation in 1 patient in the 2.5 μg group; violation of the rescue treatment criteria in 1 patient in the 2.5 μg group; and other reasons in 4 patients (1 patient in the placebo group, 3 patients in the 2.5 μg group).

The primary efficacy endpoints were the percentage of monthly responders[9] in overall improvement rating in IBS symptoms at the final evaluation[14] and the percentage of monthly responders[15] in terms of normalization of stool form at the final evaluation.[14] It was defined that ramosetron 2.5 μg was to be determined to be superior to placebo if significant differences in these endpoints were observed between the 2.5 μg group and the placebo group. Tables 5 and 6 show the results of efficacy evaluation. The percentage of responders was significantly higher in the 2.5 μg group than in the placebo group in both endpoints ($P < 0.001$, chi-square test with a two-sided significance level of 5%).

Table 5. The percentage of monthly responders in overall improvement rating in IBS symptoms at the final evaluation (FAS)

Treatment group	Number of responders (patients)	Percentage of responders (%) [95% CI]	Difference from the placebo group (%) [95% CI]	*P* value[a)]
Placebo (284 patients)	91	32.0 [26.7, 37.8]	-	-
Ramosetron 2.5 μg (292 patients)	148	50.7 [44.8, 56.6]	18.6 [10.7, 26.5]	$P < 0.001$

a) Chi-square test with a two-sided significance level of 5%

[13] Item 5.5) of the selection criteria was changed to "patients who have had stool forms recorded at least 5 days per week during the run-in period".

[14] The final month was defined as from Week -4 to Week -1 (excluding the run-in period) when the week at which the final data for weekly responder analysis was adopted was defined as Week -1.

[15] A weekly responder was defined as a patient whose mean BSFS score for one week (7 days) during the treatment period was 3 to 5, which was lower than the mean BSFS score during the run-in period by ≥1 score. A monthly responder was defined as a patient who was a weekly responder for ≥2 weeks during a month (4 weeks).

Table 6. Percentage of responders in terms of normalization of stool form at the final evaluation

Treatment group	Number of responders (patients)	Percentage of responders (%) [95% CI]	Difference from the placebo group (%) [95% CI]	*P* value[a)]
Placebo (284 patients)	69	24.3 [19.4, 29.7]	-	-
Ramosetron 2.5 μg (292 patients)	119	40.8 [35.1, 46.6]	16.5 [8.9, 24.0]	$P < 0.001$

a) Chi-square test with a two-sided significance level of 5%

Adverse events developed in 41.5% (118 of 284 patients) in the placebo group, and 52.7% (154 of 292 patients) in the 2.5 μg group. Adverse drug reactions developed in 17.6% (50 of 284 patients) in the placebo group, and 32.5% (95 of 292 patients) in the 2.5 μg group. Adverse events and adverse drug reactions observed in ≥2% of patients in either group are listed in Tables 7 and 8.

Table 7. Adverse events observed in ≥2% of patients in either group

	Placebo (284 patients)		Ramosetron 2.5 μg (292 patients)	
	Incidence	n	Incidence	n
Overall	41.5%	118	52.7%	154
Faeces hard	5.6%	16	22.6%	66
Nasopharyngitis	12.0%	34	11.6%	34
Constipation	4.6%	13	11.0%	32
Pharyngitis	1.8%	5	2.1%	6
Hepatic function abnormal	2.1%	6	0%	0

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Table 8. Adverse drug reactions observed in ≥2% of patients in either group

	Placebo (284 patients)		Ramosetron 2.5 μg (292 patients)	
	Incidence	n	Incidence	n
Overall	17.6%	50	32.5%	95
Faeces hard	5.6%	16	22.6%	66
Constipation	4.6%	13	11.0%	32

MedDRA/J ver15.0

No deaths occurred during the study. Serious adverse events developed in 0.7% (2 of 284 patients) in the placebo group (anemia and enterocolitis infectious in 1 patient each). A causal relationship with the study drug was ruled out for both cases. Adverse events leading to study discontinuation developed in 3.2% (9 of 284 patients) in the placebo group, and 2.1% (6 of 292 patients) in the ramosetron 2.5 μg group.[16]

2.(ii).A.(3) Long-term treatment study (5.3.5.2-1: Study YM060/CL-703; September 2012 to May 2014)

A multi-center, open-label, uncontrolled study was conducted in female patients ≥20 years of age with IBS-D (target sample size: 120 patients) (Table 1[13]) at 47 study sites in Japan to evaluate the long-term efficacy and safety of ramosetron.

Patients received ramosetron 2.5 μg orally once daily before breakfast for 52 weeks. Patients who met

[16] Adverse events leading to study discontinuation included abdominal distension, abdominal discomfort, irritable bowel syndrome, nausea/abdominal pain upper, constipation, vertigo, enterocolitis infectious, faeces hard, and calculus ureteric in 1 patient each in the placebo group; and faeces hard, constipation, drug eruption, headache/abdominal pain upper/nausea, enteritis infectious, and functional uterine haemorrhage in 1 patient each in the 2.5 μg group.

the criteria for dose increase (Table 9) at Week 4 were allowed to receive an increased dose (5 μg) at Week 5, and after dose increase, patients who met the criteria for dose reduction (Table 9) were allowed to receive a decreased dose (2.5 μg).

Table 9. Criteria for dose increase and criteria for dose reduction after dose increase

(1) Criteria for dose increase to 5 μg: The patient should meet all the following conditions at Week 4. - Absence of overall improvement in IBS symptoms at Month 1 (from Week 1 to Week 4) - Absence of BSFS Type 1 το 4 stool at Week 4 (from Day 22 to Day 28) - At Week 4, the investigator (subinvestigator) determines that the patient needs dose increase - At Week 4, the investigator (subinvestigator) determines that the patient has no safety problems (according to the signs/symptoms from Week 1 to Week 4). - The patient wants to receive the drug at a higher dose.
(2) Criteria for dose reduction to 2.5 μg in patients after dose increase: The patient should meet all the following conditions at Week 12 in principle. - After dose increase, excessive effects of the treatment are observed in bowel movement, and adverse events that may reflect the pharmacological action of ramosetron (such as constipation, faeces hard, and abdominal distension) develop. - The investigator (subinvestigator) determines that dose reduction is required. - The patient wants to reduce the dose of the study drug.

All the 151 patients (132 patients in ramosetron 2.5 μg dose maintenance group, and 19 patients in 5 μg dose increase group[17]) who received the study drug were included in the safety analysis set, and 150 patients were included in the FAS. The remaining 1 patient (the 2.5 μg group) was excluded from the analysis because of no available efficacy data after the start of treatment. The FAS served as the efficacy analysis population. The study treatment was discontinued in 28 patients (26 patients in the 2.5 μg dose maintenance group, and 2 patients in the 5 μg dose increase group) due to withdrawal of informed consent in 8 patients in the 2.5 μg dose maintenance group; occurrence of adverse events in 7 patients (6 patients in the 2.5 μg dose maintenance group, and 1 patient in the 5 μg dose increase group); lack of efficacy in 3 patients in the 2.5 μg dose maintenance group; worsening of IBS-D in 1 patient in the 2.5 μg dose maintenance group; lost to follow-up in 1 patient in the 2.5 μg dose maintenance group; and other reasons in 8 patients (7 patients in the 2.5 μg dose maintenance group, and 1 patient in the 5 μg dose increase group).

As for efficacy, Table 10 and Figure 1 indicate changes over time in the percentage and 95% confidence interval of monthly responders in overall improvement rating in IBS symptoms, and Table 11 and Figure 2 indicate those in monthly responders in terms of normalization of stool form.

[17] Patients who met the criteria for dose increase at Week 4 of treatment
The data from 1 patient in whom the dose was decreased to 2.5 μg at Week 12 were included in the data of the 5 μg dose increase group.

Table 10. Percentage of monthly responders in overall improvement rating in IBS symptoms (FAS)

Timepoints	Ramosetron 2.5 μg dose maintenance group (131 patients)			Ramosetron 5 μg dose increase group (19 patients)			Overall (150 patients)		
	Number of responders	Discontinuations /drop-outs (accumulated number)	Percentage of responders (%) [95% CI]	Number of responders	Discontinuations /drop-outs (accumulated number)	Percentage of responders (%) [95% CI]	Number of responders	Discontinuations /drop-outs (accumulated number)	Percentage of responders (%) [95% CI]
Month 1	42	1	32.1 [24.2, 40.8]	0	0	0 [0.0, 17.6]	42	1	28.0 [21.0, 35.9]
Month 2 (1 month after dose increase)	56	4	42.7 [34.1, 51.7]	9	0	47.4 [24.4, 71.1]	65	4	43.3 [35.3, 51.7]
Month 7 (6 months after dose increase)	69	18	52.7 [43.8, 61.5]	12	0	63.2 [38.4, 83.7]	81	18	54.0 [45.7, 62.2]
Month 13 (12 months after dose increase)	81	25	61.8 [52.9, 70.2]	15	2	78.9 [54.4, 93.9]	96	27	64.0 [55.8, 71.7]
Final evaluation	90	25	68.7 [60.0, 76.5]	16	2	84.2 [60.4, 96.6]	106	28	70.7 [62.7, 77.8]

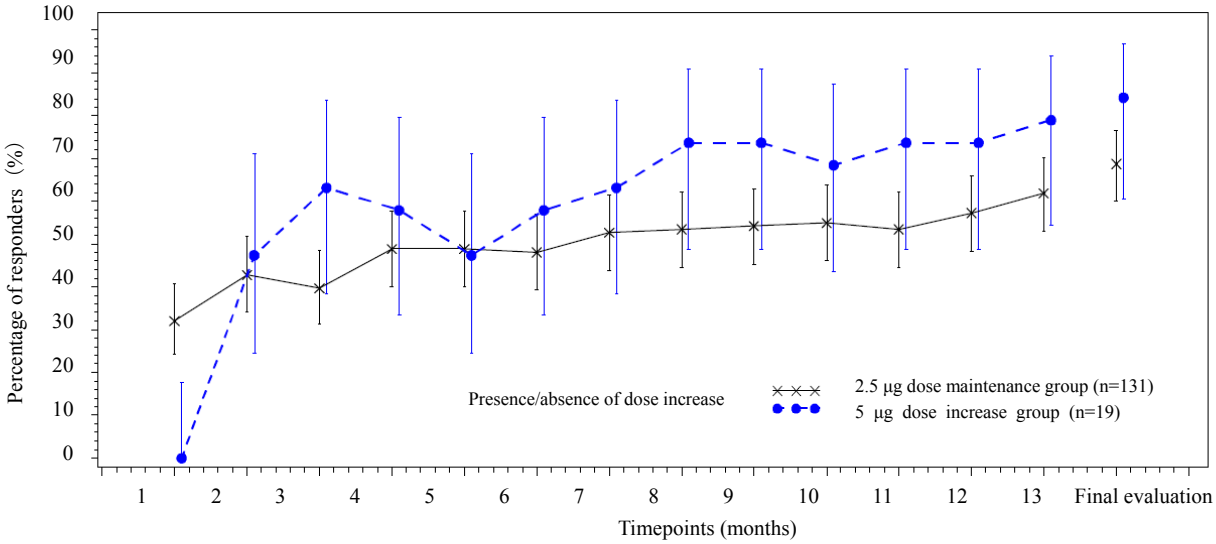

Figure 1. Change over time in the percentage (95% CI) of monthly responders in overall improvement rating

Table 11. Percentage of monthly responders in terms of normalization of stool form (FAS)

Timepoints	Ramosetron 2.5 μg dose maintenance group (131 patients)			Ramosetron 5 μg dose increase group (19 patients)			Overall (150 patients)		
	Number of responders	Discontinuations/ drop-outs (accumulated number)	Percentage of responders (%) [95% CI]	Number of responders	Discontinuations/ drop-outs (accumulated number)	Percentage of responders (%) [95% CI]	Number of responders	Discontinuations/ drop-outs (accumulated number)	Percentage of responders (%) [95% CI]
Month 1	56	1	42.7 [34.1, 51.7]	2	0	10.5 [1.3, 33.1]	58	1	38.7 [30.8, 47.0]
Month 2 (1 month after dose increase)	51	4	38.9 [30.5, 47.8]	6	0	31.6 [12.6, 56.6]	57	4	38.0 [30.2, 46.3]
Month 7 (6 months after dose increase)	61	18	46.6 [37.8, 55.5]	6	0	31.6 [12.6, 56.6]	67	18	44.7 [36.6, 53.0]
Month 13 (12 months after dose increase)	55	25	42.0 [33.4, 50.9]	10	2	52.6 [28.9, 75.6]	65	27	43.3 [35.3, 51.7]
Final evaluation	68	25	51.9 [43.0, 60.7]	10	2	52.6 [28.9, 75.6]	78	28	52.0 [43.7, 60.2]

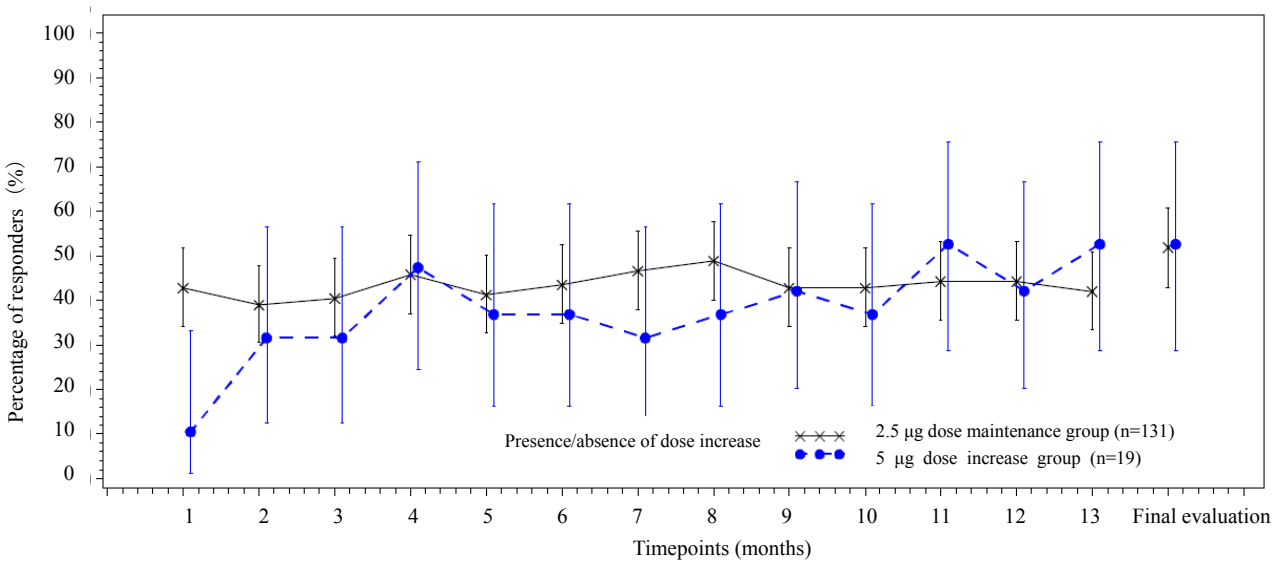

Figure 2. Change over time in the percentage (95% CI) of monthly responders in terms of normalization of stool form

As for safety, the overall incidence of adverse events was 82.1% (124 of 151 patients). The incidence in the 2.5 μg dose maintenance group was 83.3% (110 of 132 patients), and in the 5 μg dose increase group 73.7% (14 of 19 patients). The overall incidence of adverse drug reactions was 49.0% (74 of 151 patients), and the incidence in the 2.5 μg dose maintenance group was 52.3% (69 of 132 patients), and in the 5 μg dose increase group 26.3% (5 of 19 patients). Adverse events and adverse drug reactions observed in ≥2% of patients in either group are listed in Tables 12 and 13.

Table 12. Adverse events observed in ≥2% of patients in either group

	Ramosetron 2.5 μg dose maintenance group (132 patients)		Ramosetron 5 μg dose increase group (19 patients)		Overall (151 patients)	
	Incidence	n	Incidence	n	Incidence	n
Overall	83.3%	110	73.7%	14	82.1%	124
Nasopharyngitis	37.9%	50	26.3%	5	36.4%	55
Faeces hard	32.6%	43	0%	0	28.5%	43
Constipation	19.7%	26	10.5%	2	18.5%	28
Gastroenteritis	7.6%	10	10.5%	2	7.9%	12
pharyngitis	5.3%	7	5.3%	1	5.3%	8
Hepatic function abnormal	3.8%	5	5.3%	1	4.0%	6
Blood potassium increased	3.0%	4	10.5%	2	4.0%	6
Headache	3.8%	5	5.3%	1	4.0%	6
Abdominal pain upper	3.8%	5	0%	0	3.3%	5
Influenza	3.8%	5	0%	0	3.3%	5
Dental caries	3.0%	4	0%	0	2.6%	4
Gastritis	2.3%	3	5.3%	1	2.6%	4
Cystitis	3.0%	4	0%	0	2.6%	4
Iron deficiency anaemia	2.3%	3	0%	0	2.0%	3
Gastrooesophageal reflux disease	2.3%	3	0%	0	2.0%	3
Pyrexia	0.8%	1	10.5%	2	2.0%	3
Bronchitis	2.3%	3	0%	0	2.0%	3
Gastroenteritis viral	2.3%	3	0%	0	2.0%	3
White blood cell count increased	0.8%	1	10.5%	2	2.0%	3
Tenosynovitis	2.3%	3	0%	0	2.0%	3
Upper respiratory tract inflammation	1.5%	2	5.3%	1	2.0%	3
Anaemia	0.8%	1	5.3%	1	1.3%	2
Vertigo positional	0.8%	1	5.3%	1	1.3%	2
Dry eye	0.8%	1	5.3%	1	1.3%	2
Seasonal allergy	0.8%	1	5.3%	1	1.3%	2
Ligament sprain	0.8%	1	5.3%	1	1.3%	2
Thermal burn	0.8%	1	5.3%	1	1.3%	2
Back pain	0.8%	1	5.3%	1	1.3%	2
Metrorrhagia	0.8%	1	5.3%	1	1.3%	2
Hyperthyroidism	0%	0	5.3%	1	0.7%	1
Keratitis	0%	0	5.3%	1	0.7%	1
Gastritis erosive	0%	0	5.3%	1	0.7%	1
Laryngitis	0%	0	5.3%	1	0.7%	1
Skin infection	0%	0	5.3%	1	0.7%	1
Urinary tract infection	0%	0	5.3%	1	0.7%	1
Musculoskeletal stiffness	0%	0	5.3%	1	0.7%	1
Menopausal symptoms	0%	0	5.3%	1	0.7%	1

MedDRA/J ver15.0

Table 13. Adverse drug reactions observed in ≥2% of patients in either group

	Ramosetron 2.5 μg dose maintenance group (132 patients)		Ramosetron 5 μg dose increase group (19 patients)		Overall (151 patients)	
	Incidence	n	Incidence	n	Incidence	n
Overall	52.3%	69	26.3%	5	49.0%	74
Faeces hard	32.6%	43	0%	0	28.5%	43
Constipation	19.7%	26	10.5%	2	18.5%	28
Hepatic function abnormal	1.5%	2	5.3%	1	2.0%	3
Anaemia	0.8%	1	5.3%	1	1.3%	2
Vertigo positional	0.8%	1	0%	0	0.7%	1
Hyperthyroidism	0%	0	5.3%	1	0.7%	1
Gastritis	0%	0	5.3%	1	0.7%	1

MedDRA/J ver15.0

No deaths occurred during the study. Serious adverse events developed in 1.5% (2 of 132 patients; blood potassium increased and appendicitis/peritonitis in 1 patient each) in the 2.5 μg dose maintenance group, and a causal relationship with the treatment was ruled out for all the events. Adverse events which resulted in study discontinuation developed in 6.1% (8 of 132 patients) in the 2.5 μg dose maintenance group, and 5.3% (1 of 19 patients) in the 5 μg dose increase group.[18]

2.(ii).B Outline of the review by PMDA

2.(ii).B.(1) Efficacy

PMDA considers that the efficacy of ramosetron in the treatment of female patients with IBS-D has been demonstrated in the following discussions from 1) to 3). However, conclusion will be finalized, taking account of comments from the Expert Discussion.

2.(ii).B.(1).1) Primary endpoints

The applicant described the background for selecting the two primary efficacy endpoints, namely "the percentage of monthly responders in overall improvement rating in IBS symptoms at the time of final evaluation" and "the percentage of monthly responders in terms of normalization of stool form at the time of final evaluation" in the phase III study as follows.

In the data submitted at the application of the new drug for IBS-D (the initial application), the primary endpoint was only "the percentage of monthly responders in overall improvement rating in IBS symptoms at the time of final evaluation" in the phase III study (Study CL-202) in male and female patients with IBS-D. In Study CL-202, two of the secondary endpoints, "the improvement in bowel movement" and "the improvement in abdominal pain or discomfort" were found to be correlated with "the overall improvement in IBS symptoms". On the other hand, there were no apparent differences between the ramosetron groups and the placebo group in "abdominal pain or discomfort severity score," "presence or absence of defecation urgency," or "presence or absence of feeling of incomplete evacuation," among other measures. At the time of the new drug application for IBS-D, PMDA pointed out (i) it is understandable that "overall improvement in IBS symptoms" was set as the

[18] The adverse events leading to study discontinuation include blood potassium increased and faeces hard in 2 patients each, constipation, irritable bowel syndrome/proctalgia, appendicitis/peritonitis, and gastrointestinal motility disorder in 1 patient each in the 2.5 μg dose maintenance group; and hyperthyroidism in 1 patient in the 5 μg dose increase group.

primary endpoint, considering that IBS is diagnosed on the basis of symptoms and that no endpoints have been established to evaluate the severity of IBS, (ii) however, in addition to overall assessment, the applicant should assess for clinically significant improvement according to the severity of patient complaints and major symptoms of IBS to clarify effectiveness and characteristics of ramosetron on IBS symptoms. According to the above suggestion by PMDA, the applicant conducted a postmarketing clinical study (Study CL-500) in male patients with IBS-D to explore measures that can delineate the effects of the drug.[19] In Study CL-500, the treatment effect of ramosetron on symptoms of IBS-D was most clearly confirmed when stool form was compared between ramosetron and placebo groups. It is known that stool form is affected by intestinal transit time and fecal water content.[20] Ramosetron is believed to inhibit the intestinal transit and abnormal water transport induced by intrinsic 5-HT through inhibiting serotonin 3 (5-HT_3) receptors and thereby normalize stool form. The applicant considered that the "normalization of stool form" may be used as an endpoint that delineates the effect of the drug. As Bristol Stool Form Scores (BSFS) of 3 to 5 are considered normal in the Rome III Criteria, the applicant defined a weekly responder in terms of “normalization of stool form” as a patient with a weekly mean BSFS of 3 to 5 during the treatment period which were lower than the weekly BSFS during the run-in period by at least 1 score, and a monthly responder in terms of “normalization of stool form” as a weekly responder for ≥2 weeks in a month (4 weeks). When Study CL-501, a post-marketing clinical study of ramosetron in male IBS-D patients in whom symptoms in light of stool form were relatively severe (a mean weekly BSFS of >5 during the run-in period)[21] was conducted, “the percentage of monthly responders in terms of normalization of stool form” was set as the primary endpoint. As a result, the superiority of ramosetron 5 μg over placebo[22] in terms of normalization of stool form was verified, and the normalization of stool form was confirmed to be valid as an endpoint. In Study CL-701, the phase II study of ramosetron in female patients with IBS-D, the drug was suggested to be effective in terms of both overall improvement rating in IBS symptoms and normalization of stool form [see "2.(ii).B.(4).1) Usual dose"].

The applicant also explained the timing of efficacy evaluation as follows:

PMDA commented, "Since the data of clinical studies in female patients are limited, and it is unclear when the efficacy of ramosetron in female patients should be evaluated, the applicant should explore the optimal dose and timing of efficacy evaluation in female patients." Accordingly, the applicant investigated an optimal timing of efficacy evaluation in Study CL-701, the phase II study in female patients with IBS-D. In the clinical setting, the dose for male patients with IBS-D is allowed to be adjusted based on changes in symptoms for approximately 1 month during treatment, and the Rome III Criteria recommend physicians assess the efficacy of drugs for symptomatic treatment at weeks 2 to 6

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19 In order to explore and evaluate measures for clinically significant improvement in the severity of patients’ chief complaints and major symptoms of IBS, a multi-center, single-blind, placebo-controlled, parallel comparison study in male patients with IBS-D (target sample size: ≥60 patients) was conducted at 25 medical institutions in Japan. Participants received ramosetron 5 μg or placebo once daily before breakfast for 12 weeks.

20 *Scand J Gastroenterol*, 1997;32:920-924

21 In order to investigate the superiority of ramosetron over placebo, with the primary endpoint being the percentage of monthly responders in terms of normalization of stool form after 1-month treatment, a multi-center, double-blind, placebo-controlled, parallel group comparison study in male patients with IBS-D (target sample size: 260 patients) was conducted at 52 medical institutions in Japan. Participants received ramosetron 5 μg or placebo once daily before breakfast for 12 weeks.

22 *Clin Gastroenterol Hapatol*, 2014;12:953-959

of treatment. Women in the phase II study were, thus, to be assessed at Month 1 of treatment, the primary evaluation timepoint, as well as Months 2 and 3, and the final 4 weeks of treatment (the final evaluation, the common timepoint for the evaluation in previous studies). There was no clear dose-response relationship in the percentage of monthly responders in overall improvement rating in IBS symptoms at Month 1 (Table 2). The difference in this endpoint between patients receiving ramosetron at 2.5 μg, which was selected as the recommended dose, and those receiving placebo was smaller at Month 1 as compared with those at Month 2, Month 3, and the final evaluation. The percentage of monthly responders in overall improvement rating in IBS symptoms at Month 1 was 10% higher at least in the 1.25 μg group than in the placebo group, but the difference decreased over time and disappeared by the end of the study. These findings indicate that the results at Month 1 do not predict changes at later timepoints. The efficacy of treatment was suggested in the percentage of monthly responders in overall improvement rating in IBS symptoms at final evaluation (Table 14), and the percentage of monthly responders in terms of normalization of stool form at the final evaluation among FAS patients with a mean weekly BSFS score of >5 during the run-in period (Table 15). On the basis of these results, it was considered appropriate in the phase III study in women to assess the efficacy of treatment at the final evaluation of 3-month treatment, which was used as the common timepoint for the evaluation in previous studies.

Table 14. Percentage of monthly responders in overall improvement rating in IBS symptoms at the final evaluation in the Phase II study (FAS)

Treatment group	Number of responders (patients)	Percentage of responders (%) [95% CI]	Difference from the placebo group (%) [95% CI]
Placebo (102 patients)	39	38.2 [28.8, 48.4]	−
Ramosetron 1.25 μg (104 patients)	41	39.4 [30.0, 49.5]	1.2 [-12.1, 14.5]
Ramosetron 2.5 μg (104 patients)	55	52.9 [42.8, 62.8]	14.6 [1.2, 28.1]
Ramosetron 5 μg (99 patients)	49	49.5 [39.3, 59.7]	11.3 [-2.4, 24.9]

Table 15. Percentage of monthly responders in terms of normalization of stool form at the final evaluation in the phase II study (FAS [a)])

Treatment group	N umber of responders (patients)	Percentage of responders (%) [95% CI]	Difference from the placebo group (%) [95% CI]
Placebo (57 patients)	15	26.3 [15.5, 39.7]	−
Ramosetron 1.25 μg (70 patients)	32	45.7 [33.7, 58.1]	19.4 [3.1, 35.7]
Ramosetron 2.5 μg (67 patients)	33	49.3 [36.8, 61.8]	22.9 [6.4, 39.5]
Ramosetron 5 μg (67 patients)	34	50.7 [38.2, 63.2]	24.4 [7.9, 41.0]

a) Analysis was made for FAS patients with a mean weekly BSFS score of >5 during the run-in period.

According to the above findings, “the percentages of monthly responders in terms of overall improvement rating in IBS symptoms and normalization of stool form” were set as the primary endpoints for the phase III study in women (Study CL-702), and were to be evaluated at the final timepoint of the study.

PMDA’s view:

Considering that IBS is diagnosed on the basis of symptoms such as abdominal pain and abnormal bowel movement, and that different patients have different chief complaints, and improvement in a particular symptom may not always lead to satisfaction with treatment, there is no particular problem with using "overall improvement rating in IBS symptoms" evaluated by patients as a primary endpoint in the phase III study in women as done in the studies for the new drug application (the initial application).

Also, taking into account the pharmacological action of ramosetron and the results of clinical studies (Study CL-500 and Study CL-501) exploring measures for evaluation, as well as the clinical significance of improvement in diarrhea, which is a chief complaint in patients with IBS-D, it is understandable the applicant states that characterizing ramosetron is possible by setting "normalization of stool form" as an endpoint. PMDA considers that there is no particular problem in selecting the percentages of monthly responders in terms of overall improvement rating and normalization of stool form as the primary endpoints for the phase III study.

Considering the timepoint for primary efficacy evaluation in the previous studies, there is no particular problem with evaluating the efficacy of treatment at the final evaluation of the 3-month treatment in the phase III study.
Based on the above, the percentages of monthly responders in terms of overall improvement rating in IBS symptoms and normalization of stool form at the final evaluation were significantly greater in the ramosetron groups than in the placebo group in the phase III study in female patients (Tables 5 and 6), and the efficacy of the drug was considered to be demonstrated.

2.(ii).B.(1).2) Secondary endpoints

Patients with IBS-D are treated to alleviate their symptoms such as abdominal pain and abnormal bowel movement (and improve the quality of life [QOL] through symptomatic improvement). The secondary endpoints including the following 5 endpoints were set in the phase III study.

(a) Alleviation of abdominal pain or discomfort

In the phase III study, the percentage [95% CI] of monthly responders in improvement in abdominal pain or discomfort at the final evaluation[23] was 51.4% [45.5%, 57.2%] in the ramosetron groups, and 37.7% [32.0%, 43.6%] in the placebo group.

(b) Improvement in bowel movement

In the phase III study, the percentage [95% CI] of monthly responders in improvement in bowel movement at the final evaluation[24] was 50.3% [44.5%, 56.2%] in the ramosetron groups, and 31.0%

[23] A weekly responder was defined as a patient with an abdominal pain/discomfort symptom score of 0 or 1 at the weekly timepoints, and a monthly responder was defined as a patient who was a weekly responder in at least 2 weeks during a month. The abdominal pain/discomfort symptom was scored as follows: 0, symptoms disappeared; 1, markedly improved; 2, slightly improved; 3, no change; and 4, worsened.

[24] A weekly responder was defined as a patient with a bowel movement score of 0 or 1 at the weekly timepoints, and a monthly responder was defined as a patient who was a weekly responder in at least 2 weeks during a month. The bowel movement was scored as follows: 0, nearly normal; 1, markedly improved; 2, slightly improved; 3, no change; and 4, worsened.

[25.7%, 36.7%] in the placebo group.

(c) Change in mean defecation frequency per week

In the phase III study, change in mean defecation frequency per week from baseline at the final evaluation[25] (mean ± SD) was -0.56 ± 0.85 times per week in the ramosetron groups, and -0.32 ± 0.81 times per week in the placebo group.

(d) The percentages of days without defecation urgency and days without feeling of incomplete evacuation during the treatment period

In the phase III study, the percentage of days without defecation urgency at the final evaluation[26] (mean ± SD) was 75.0 ± 29.5% in the ramosetron groups and 67.3 ± 32.9% in the placebo group. The percentage of days without feeling of incomplete evacuation at the final evaluation[27] (mean ± SD) was 70.4 ± 35.1% in the ramosetron groups and 65.5 ± 37.6% in the placebo group.

(e) QOL

In the phase III study, change in IBS-QOL-Japanese version (IBS-QOL-J) total score at the final evaluation from baseline (baseline-adjusted) [95% CI] was 18.3 [16.7, 19.9] in the ramosetron groups and 14.6 [12.9, 16.2] in the placebo group.

The applicant's explanation on QOL, one of the secondary endpoints:

IBS is not a fatal disease, but its symptoms limit activities of daily living and deteriorate QOL significantly. QOL is thus a good measure to evaluate the beneficial effects of treatment in patients with IBS. At the time of the new drug application of IBS-D (the initial application), assessment of QOL in patients with IBS was still under exploration, and no disease-specific measures assessing QOL were available in Japan. As a result, the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36), a major QOL scale that has been widely used in various epidemiological studies, was used in the pre-approval clinical studies of ramosetron. However, the SF-36 total score may underestimate IBS-specific symptoms such as abnormal stool form and defecation frequency. This may explain the fact that the improvement in IBS symptoms was not reflected in the QOL score in male and female patients with IBS-D in the phase III study (Study CL-202). The applicant decided to explore IBS-specific measures assessing QOL after the market launch of the drug. In a post-marketing clinical study of ramosetron (Study CL-500), the validity of IBS-QOL,[28] an IBS-specific QOL measure of which a questionnaire is available in Japanese, was assessed in an exploratory manner. The IBS-QOL was used as a secondary endpoint in Study CL-501, a post-marketing clinical study conducted after Study CL-500. In that study, ramosetron 5 μg was demonstrated to improve QOL in male patients with

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[25] Patients were instructed to record the defecation frequency per day in their patient diary. The change in mean defecation frequency per week from that during the run-in period was calculated for each week of treatment.

[26] Patients were instructed to record the presence or absence of defecation urgency every day. The percentage of days without defecation urgency per week was calculated.

[27] Patients were instructed to record the presence or absence of feeling of incomplete evacuation every day. The percentage of days without feeling of incomplete evacuation per week was calculated.

[28] *Biopsychosoc Med,* 2007;1: 6 (doi: 10.1186/1751-0759-1-6)

IBS-D as compared with placebo. Accordingly, in the phase III study in female patients with IBS-D, patients were assessed for the IBS-QOL as a secondary endpoint to evaluate the effect of ramosetron on QOL.

PMDA's view:
The QOL in patients with IBS has been assessed not only with the IBS-QOL but also with the Izumo scale[29] and GSRS,[30] among other measures; however, none of them have been established as a commonly-used efficacy measure for IBS drugs. Nonetheless, there is no particular problem with using the IBS-QOL, which was assessed as a measure to identify features of ramosetron in post-marketing clinical studies of ramosetron in male patients, in the phase III study in female patients with IBS-D.

PMDA confirmed that the efficacy of ramosetron versus placebo has been generally suggested in all secondary endpoints used in the studies, and the results were consistent with the findings with the primary endpoints.

2.(ii).B.(1).3) Efficacy of long-term treatment

Table 10 and Figure 1 show change over time in the percentage of monthly responders in overall improvement rating in IBS symptoms by Month 13, and Table 11 and Figure 2 show change over time in the percentage of monthly responders in terms of normalization of stool form by Month 13. The efficacy of treatment did not tend to decrease over time.

2.(ii).B.(2) Safety

According to the consideration and confirmation described in the following sections 1) to 3), PMDA considers that the safety of ramosetron in female patients with IBS-D is acceptable when appropriate precautions are taken as in the case for male patients with IBS-D. However, data on the occurrence of faeces hard, constipation, colitis ischaemic, and cardiovascular disorders in female patients receiving ramosetron should be collected during post-marketing surveillance or from other appropriate studies.

The above conclusion on safety will be finalized, taking account of comments from the Expert Discussion.

[29] *Nihon Shokakibyo Gakkai Zasshi,* 2009;106:1478-1487
[30] *Dig Dis Sci* 33: 129-134, 1988; *Scand J Gastroenterol,* 1995;30:1046-1052

2.(ii).B.(2).1) Comparison with the placebo group

Table 16 summarizes the occurrence of adverse events in a pooled female patient population from 2 pre-approval clinical studies, Studies CL-201[31] and CL-202,[32] in male and female patients with IBS-D as well as 2 clinical studies, Studies CL-701 and CL-702 in female patients with IBS-D. Adverse events that developed in the ramosetron groups at an incidence ≥2% higher than that in the placebo group were faeces hard, constipation, and abdominal distension.

Table 16. Adverse events observed in ≥2% of female patients with IBS-D in any group (pooled analysis of comparative studies)

	Placebo group (451 patients)		Ramosetron 1.25 μg group[33] (125 patients)		Ramosetron 2.5 μg group (396 patients)		Ramosetron 5 μg group (185 patients)		Ramosetron 10 μg group (22 patients)		All ramosetron groups (728 patients)	
	Incidence	n	Incidence	n	Incidence	n	Incidence	n	Incidence	n	Incidence	n
Overall	45.9%	207	54.4%	68	53.3%	211	73.0%	135	86.4%	19	59.5%	433
Faeces hard	5.3%	24	16.0%	20	22.7%	90	21.1%	39	22.7%	5	21.2%	154
Constipation	4.9%	22	11.2%	14	11.1%	44	17.8%	33	40.9%	9	13.7%	100
Nasopharyngitis	13.3%	60	8.8%	11	11.9%	47	16.8%	31	18.2%	4	12.8%	93
Abdominal distension	1.6%	7	2.4%	3	3.0%	12	8.1%	15	0%	0	4.1%	30
Pharyngitis	1.6%	7	0.8%	1	1.8%	7	3.2%	6	9.1%	2	2.2%	16
Upper respiratory tract inflammation	1.8%	8	0.8%	1	0%	0	5.9%	11	4.5%	1	1.8%	13
Abdominal pain upper	1.8%	8	1.6%	2	1.8%	7	2.2%	4	0%	0	1.8%	13
Headache	1.8%	8	4.8%	6	1.0%	4	1.6%	3	0%	0	1.8%	13
Cystitis	1.3%	6	3.2%	4	1.8%	7	0%	0	0%	0	1.5%	11
Gastroenteritis	0.7%	3	0.8%	1	1.5%	6	1.1%	2	4.5%	1	1.4%	10
White blood cell count increased	1.3%	6	0.8%	1	1.0%	4	2.7%	5	0%	0	1.4%	10
Protein urine present	0.7%	3	4.0%	5	0.3%	1	1.6%	3	0%	0	1.2%	9
Hepatic function abnormal	1.6%	7	0.8%	1	0.3%	1	2.7%	5	4.5%	1	1.1%	8
Nausea	1.1%	5	0.8%	1	0.5%	2	2.2%	4	4.5%	1	1.1%	8
Alanine aminotransferase increased	0.2%	1	2.4%	3	0.5%	2	0.5%	1	0%	0	0.8%	6
Eczema	0%	0	0%	0	0.3%	1	1.6%	3	4.5%	1	0.7%	5
Bronchitis	1.1%	5	0.8%	1	0.3%	1	1.1%	2	4.5%	1	0.7%	5
Dysmenorrhoea	0%	0	0.8%	1	0.5%	2	0.5%	1	4.5%	1	0.7%	5
Oropharyngeal pain	0.2%	1	0%	0	0.3%	1	2.2%	4	0%	0	0.7%	5
Contusion	0.4%	2	0%	0	0.3%	1	0.5%	1	9.1%	2	0.5%	4
Blood potassium decreased	0%	0	0.8%	1	0%	0	1.1%	2	4.5%	1	0.5%	4
Anal fissure	0%	0	0%	0	0.3%	1	0.5%	1	4.5%	1	0.4%	3
Diarrhoea	0.7%	3	0%	0	0%	0	0.5%	1	4.5%	1	0.3%	2
Arthralgia	0.2%	1	0.8%	1	0%	0	0%	0	4.5%	1	0.3%	2
Gastritis	0.7%	3	0.8%	1	0%	0	0%	0	4.5%	1	0.3%	2
Malaise	0%	0	0%	0	0%	0	0%	0	4.5%	1	0.1%	1
Clavicle fracture	0%	0	0%	0	0%	0	0%	0	4.5%	1	0.1%	1
Muscle strain	0%	0	0%	0	0%	0	0%	0	4.5%	1	0.1%	1
Blood lactate dehydrogenase decreased	0%	0	0%	0	0%	0	0%	0	4.5%	1	0.1%	1
Hyperlipidemia	0%	0	0%	0	0%	0	0%	0	4.5%	1	0.1%	1
Migraine	0%	0	0%	0	0%	0	0%	0	4.5%	1	0.1%	1

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[31] A multi-center, double-blind, placebo-controlled, parallel-group comparison study was conducted at 49 medical institutions in Japan in order to determine the recommended doses and safety of ramosetron for male and female patients with IBS-D (target sample size: ≥400 patients) with the primary endpoint being the percentage of monthly responders in overall improvement rating in IBS symptoms at the final evaluation. Participants received ramosetron at doses of 1, 5, or 10 μg or placebo once daily orally before breakfast for 12 weeks.

[32] A multi-center, double-blind, placebo-controlled, parallel-group comparison study was conducted at 51 medical institutions in Japan in order to determine the superiority of ramosetron over placebo in male and female patients with IBS-D (target sample size: ≥460 patients) with the primary endpoint being the percentage of monthly responders in overall improvement rating in IBS symptoms at the final evaluation. Participants received ramosetron 5 μg or placebo once daily orally before breakfast for 12 weeks.

[33] In the pooled analysis of comparative studies, data from patients in the 1 μg group in Study CL-201 were included in the subgroup of patients in the 1.25 μg group.

The incidence of serious adverse events was 1.1% (5 of 451 patients) in the placebo group, and 0.5% (4 of 728 patients) in the ramosetron groups.[34] The incidence of adverse events resulting in study discontinuation was 3.3% (15 of 451 patients) in the placebo group, and 3.8% (28 of 728 patients) in the ramosetron groups. As a result, the incidences were not higher in the ramosetron groups than in the placebo group. Findings on faeces hard, constipation, and abdominal distention, which tended to develop more often in the ramosetron groups than in the placebo group are separately described in "2.(ii).B.(2).3) (a) Faeces hard, constipation, and abdominal distension."

2.(ii).B.(2).2) Adverse events associated with long-term treatment

Table 12 summarizes adverse events that occurred in 2% or more of patients either in the 2.5 μg dose maintenance group or the 5 μg dose increase group in the long-term treatment study. The profile of adverse events in the long-term study did not differ substantially from those in the phase II and phase III studies. Table 17 summarizes the occurrence of adverse events in each 4-week period during the treatment. The incidence of adverse events did not increase over time during the treatment period.

Table 17. Incidence of adverse events in each 4-week period during the long-term treatment study (Study CL-703)

Weeks of treatment	Ramosetron 2.5 μg dose maintenance group		Ramosetron 5 μg dose increase group		Overall	
	Incidence	n/N	Incidence	n/N	Incidence	n/N
Weeks 1 to 4	40.9%	54/132 patients	15.8%	3/19 patients	37.7%	57/151 patients
Weeks 5 to 8	38.2%	50/131 patients	10.5%	2/19 patients	34.7%	52/150 patients
Weeks 9 to 12	25.2%	32/127 patients	5.3%	1/19 patients	22.6%	33/146 patients
Weeks 13 to 16	19.7%	24/122 patients	0%	0/19 patients	17.0%	24/141 patients
Weeks 17 to 20	17.6%	21/119 patients	15.8%	3/19 patients	17.4%	24/138 patients
Weeks 21 to 24	18.3%	21/115 patients	15.8%	3/19 patients	17.9%	24/134 patients
Weeks 25 to 28	15.8%	18/114 patients	26.3%	5/19 patients	17.3%	23/133 patients
Weeks 29 to 32	19.5%	22/113 patients	0%	0/19 patients	16.7%	22/132 patients
Weeks 33 to 36	13.4%	15/112 patients	31.6%	6/19 patients	16.0%	21/131 patients
Weeks 37 to 40	20.0%	22/110 patients	26.3%	5/19 patients	20.9%	27/129 patients
Weeks 41 to 44	20.9%	23/110 patients	22.2%	4/18 patients	21.1%	27/128 patients
Weeks 45 to 48	20.0%	22/110 patients	0%	0/17 patients	17.3%	22/127 patients
Weeks 49 to 52	11.0%	12/109 patients	0%	0/17 patients	9.5%	12/126 patients
Week 53 and thereafter	8.6%	6/70 patients	23.1%	3/13 patients	10.8%	9/83 patients
Entire treatment period	83.3%	110/132 patients	73.7%	14/19 patients	82.1%	124/151 patients

2.(ii).B.(2).3) Adverse events of special interest in patients receiving ramosetron

(a) Faeces hard, constipation, and abdominal distension

Data of the new drug application indicated that adverse events such as constipation, solid stool, and abdominal distension tended to occur more frequently in female patients than in male patients (see the review report of Irribow Tablets 2.5 μg and 5 μg, dated April 10, 2008).

[34] The serious adverse events included gastroenteritis, anaemia, enterocolitis infectious, hepatic function abnormal, and pyrexia/nausea/eosinophil count increased/C-reactive protein increased/abdominal pain/upper gastrointestinal haemorrhage/vomiting/ gastroesophageal reflux disease/constipation in 1 patient each in the placebo group; granulocytopenia and anxiety disorder in 1 patient each in the 1.25 μg group; blood potassium increased in 1 patient in the 2.5 μg group; and enterocolitis in 1 patient in the 10 μg group. A causal relationship with the treatment was ruled out in the events other than hepatic function abnormal, pyrexia/nausea/eosinophil count increased/C-reactive protein increased/abdominal pain/upper gastrointestinal haemorrhage/vomiting/constipation in the placebo group, and blood potassium increased in the 2.5 μg group. The outcome was “recovering/resolving” or “recovered/resolved” in all events other than pyrexia/nausea/eosinophil count increased/C-reactive protein increased/abdominal pain/upper gastrointestinal haemorrhage/vomiting/ gastroesophageal reflux disease/constipation.

Tables 18, 19, and 20 summarize the occurrence of faeces hard, constipation, and abdominal distension obtained from a pooled analysis of female patient populations from 2 pre-approval clinical studies in male and female patients with IBS-D (Studies CL-201 and CL-202) and 2 clinical studies in female patients with IBS (Studies CL-701 and CL-702). The adverse events tended to occur more frequently in the ramosetron groups than in the placebo group, but were mild or moderate in severity.

Table 18. Occurrence of faeces hard in female patients with IBS-D (pooled data analysis of comparative studies)

	Placebo group (451 patients)		Ramosetron 1.25 μg group[33] (125 patients)		Ramosetron 2.5 μg group (396 patients)		Ramosetron 5 μg group (185 patients)		Ramosetron 10 μg group (22 patients)		All ramosetron groups (728 patients)	
	Incidence	n	Incidence	n	Incidence	n	Incidence	n	Incidence	n	Incidence	n
Adverse events	5.3%	24	16.0%	20	22.7%	90	21.1%	39	22.7%	5	21.2%	154
Mild	5.3%	24	16.0%	20	22.5%	89	19.5%	36	9.1%	2	20.2%	147
Moderate	0%	0	0%	0	0.3%	1	1.6%	3	13.6%	3	1.0%	7
Severe	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0
Adverse drug reactions	5.3%	24	16.0%	20	22.7%	90	21.1%	39	22.7%	5	21.2%	154
Serious Adverse events	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0
Adverse events leading to study discontinuation	0.2%	1	0%	0	0.3%	1	2.2%	4	4.5%	1	0.8%	6
Adverse events leading to study interruption	4.4%	20	12.0%	15	20.2%	80	18.4%	34	22.7%	5	18.4%	134

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Table 19. Occurrence of constipation in female patients with IBS-D (pooled data analysis of comparative studies)

	Placebo group (451 patients)		Ramosetron 1.25 μg group[33] (125 patients)		Ramosetron 2.5 μg group (396 patients)		Ramosetron 5 μg group (185 patients)		Ramosetron 10 μg group (22 patients)		All ramosetron groups (728 patients)	
	Incidence	n	Incidence	n	Incidence	n	Incidence	n	Incidence	n	Incidence	n
Adverse events	4.9%	22	11.2%	14	11.1%	44	17.8%	33	40.9%	9	13.7%	100
Mild	4.4%	20	11.2%	14	11.1%	44	16.2%	30	27.3%	6	12.9%	94
Moderate	0.4%	2	0%	0	0%	0	1.6%	3	13.6%	3	0.8%	6
Severe	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0
Adverse drug reactions	4.9%	22	11.2%	14	10.9%	43	17.8%	33	40.9%	9	13.6%	99
Serious adverse events	0.2%	1	0%	0	0%	0	0%	0	0%	0	0%	0
Adverse events leading to study discontinuation	0.4%	2	0%	0	0.3%	1	2.7%	5	4.5%	1	1.0%	7
Adverse events leading to study interruption	4.0%	18	10.4%	13	10.4%	41	15.1%	28	36.4%	8	12.4%	90

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Table 20. Occurrence of abdominal distension in female patients with IBS-D (pooled data analysis of comparative studies)

	Placebo group (451 patients)		Ramosetron 1.25 μg group[33] (125 patients)		Ramosetron 2.5 μg group (396 patients)		Ramosetron 5 μg group (185 patients)		Ramosetron 10 μg group (22 patients)		All ramosetron groups (728 patients)	
	Incidence	n	Incidence	n	Incidence	n	Incidence	n	Incidence	n	Incidence	n
Adverse events	1.6%	7	2.4%	3	3.0%	12	8.1%	15	0%	0	4.1%	30
Mild	1.1%	5	2.4%	3	3.0%	12	7.6%	14	0%	0	4.0%	29
Moderate	0.4%	2	0%	0	0%	0	0.5%	1	0%	0	0.1%	1
Severe	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0
Adverse drug reactions	1.6%	7	2.4%	3	2.8%	11	8.1%	15	0%	0	4.0%	29
Serious Adverse events	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0
Adverse events leading to study discontinuation	0.4%	2	0%	0	0%	0	1.1%	2	0%	0	0.3%	2
Adverse events leading to study interruption	0.7%	3	0.8%	1	1.3%	5	0.5%	1	0%	0	1.0%	7

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PMDA's view:

Faeces hard, constipation, and abdominal distension tended to occur more commonly in female patients with IBS-D than in male patients, but were mild or moderate in severity. These events disappeared after appropriate measures such as discontinuing treatment. Faeces hard and constipation are known adverse drug reactions to ramosetron in male patients with IBS-D. Physicians are instructed to confirm the absence of constipation before prescribing ramosetron to patients with IBS, and take appropriate measures such as interrupting/discontinuing treatment if faeces hard or constipation occurs during treatment. With these precautions, no specific problems in terms of safety have occurred in the clinical setting after market launch. Accordingly, the safety of ramosetron treatment in female patients with IBS-D may be ensured with similar measures. However, in female patients with IBS-D, faeces hard and constipation occurred more often [see 2.(ii).B.(5) Clinical positioning of ramosetron in the treatment of female patients with IBS-D] and resulted in treatment interruption more frequently than in male patients. These facts should be described in the package insert and materials for ramosetron to alert healthcare professionals, and data on these events should be collected during post-marketing surveillance and from other studies continuously.

(b) Colitis ischaemic

In the United States, patients died of colitis ischaemic during treatment with alosetron hydrochloride, a 5-HT_3 receptor antagonist indicated for the treatment of female patients with IBS-D, which is not approved in Japan. Since then, the occurrence of colitis ischaemic has been described in the warning section in the prescribing information of the drug in the US, and the use of the drug has been limited to patients with severe IBS-D from June 2002 onward.[35] In approximately 1,300 patients who received ramosetron and were analyzed for safety, no cases of colitis ischaemic occurred during pre-approval clinical studies for the initial application. However, considering the experience with alosetron hydrochloride, colitis ischaemic was listed as a priority survey item for the specified drug-use survey

[35] *Am J Gastroenterol*, 2010;105:866-875

of ramosetron to collect data on this event (see the review report of Irribow Tablets 2.5 μg and 5 μg, dated April 10, 2008). In the specified use-results survey, melena and colitis ischaemic developed in 0.03% (1 of 2862 patients) each. No cases of colitis ischaemic were reported in 2 post-marketing clinical studies of ramosetron in male patients with IBS-D (98 patients in Study CL-500, and 296 patients in Study CL-501). During the period from market launch to July 2014, 3 spontaneous adverse drug reactions of colitis ischaemic were reported. The current package insert for ramosetron describes that "as colitis ischaemic or serious constipation may develop, patients should be instructed to contact their physicians or other healthcare professionals when abdominal pain, bloody stool, constipation, or faeces hard develop during treatment." No new measures were considered necessary (see the re-examination report of Irribow Tablets 2.5 μg and 5 μg, dated February 5, 2014).

In the clinical studies of ramosetron in female patients with IBS-D, no cases of colitis ischaemic were observed.

PMDA's view:
It is also essential to encourage physicians (i) to monitor closely the onset of colitis ischaemic in female patients with IBS-D as in male patients, and (ii) to instruct patients through appropriate materials to contact the physicians when the patients experience, during treatment with ramosetron, symptoms suggestive of colitis ischaemic such as abdominal pain and bloody stool. At the same time, appropriate measures such as discontinuing treatment are considered important as already described in the package insert for ramosetron. Since alosetron hydrochloride was used for female patients with IBS-D, colitis ischaemic developed mainly in female patients, and pathology may differ between men and women [see "2.(ii).B.(5) Clinical positioning of ramosetron in the treatment of female patients with IBS-D"], the safety profile of ramosetron may differ between men and women. Data on the occurrence of colitis ischaemic in female patients with IBS-D should be collected during post-marketing surveillance or from other studies of ramosetron.

(c) Cardiovascular disorders
In the US, increased risk of cardiovascular adverse events such as heart attack, stroke, and serious cardiac chest pain has been suggested in a pooled analysis of clinical studies of tegaserod maleate, a 5-HT_4 receptor partial agonist indicated for the treatment of female patients with IBS-D and patients <65 years of age with chronic constipation, which is not approved in Japan.[36] PMDA asked the applicant whether the cardiovascular risk as observed with tegaserod maleate may also be observed in female patients with IBS-D receiving ramosetron.

The applicant's explanation:
In a pooled analysis of data from clinical studies in patients with IBS-D (i.e., Studies CL-201, CL-202,

[36] In a pooled analysis of 29 studies in which 11,614 patients received tegaserod maleate and 7,031 patients received placebo, 13 patients receiving tegaserod maleate (0.1%) experienced serious and life-threatening cardiovascular adverse events, specifically heart attack in 4 patients (1 patient died), cardiac chest pain that may rapidly lead to heart attack in 6 patients, and stroke in 3 patients, while 1 patient receiving placebo (0.01%) experienced symptoms suggestive of the onset of stroke.

CL-500, CL-501, CL-701, and CL-702), the incidence of cardiovascular adverse events was 1.1% (15 of 1372 patients) in patients receiving ramosetron, and 0.7% (7 of 963 patients) in those receiving placebo. The incidence did not differ markedly between the two populations, and all cardiovascular adverse events observed in patients receiving ramosetron were mild or moderate in severity. Incidences of cardiovascular adverse reactions in the specified use-results survey of ramosetron in male patients with IBS-D were 0.03% (1 of 2862 patients) each for hypertension, chest discomfort, and chest pain observed. All of these reactions were non-serious. During the period from market launch to January 2015, the following cardiovascular adverse drug reactions were reported: blood creatine phosphokinase increased (4 patients); blood pressure increased (3 patients); palpitations and oedema peripheral (2 patients each); and arrhythmia, extrasystoles, palpitations/blood pressure increased, ventricular extrasystoles, ventricular fibrillation, angiosclerosis, hot flashes, chest discomfort, and heart rate decreased (1 patient each). All events were non-serious except for blood creatine phosphokinase (2 patients), chest discomfort (1 patient), and ventricular fibrillation (1 patient). No increase in cardiovascular risk was observed in the pooled analysis.

In a pooled analysis of data from the phase II study (Study CL-701) and phase III study (Study CL-702) in female patients with IBS-D, incidence of cardiovascular adverse events were 1.2% (7 of 599 patients) in the ramosetron groups and 0.5% (2 of 386 patients) in the placebo groups, while in the long-term treatment study, 0.7% (1 of 151 patients) in the ramosetron groups. All of these adverse events were mild in severity. No serious adverse events were observed.

Based on the above findings, there is no particular concern for cardiovascular disorders associated with ramosetron treatment in patients with IBS-D. There is no difference between male and female patients with IBS-D in the risk of cardiovascular disorders associated with ramosetron.

PMDA considers that there is no problem in terms of the risk of cardiovascular disorders associated with ramosetron in female patients with IBS-D because no cardiovascular events that needed additional measures were observed in post-marketing surveillance or other studies in male patients with IBS-D, and the results of clinical studies do not indicate any marked difference in occurrence of cardiovascular adverse events between male and female patients receiving ramosetron. However, as the number of female patients evaluated in clinical studies of ramosetron is limited, female patients should be assessed for the occurrence of cardiovascular adverse events in the postmarketing period as in the case of male patients.

2.(ii).B.(3) Indication

As the phase III study and the long-term treatment study in female patients with IBS-D demonstrated that ramosetron is effective and does not raise any significant safety concerns [see "2.(ii).B.(1) Efficacy" and "2.(ii).B.(2) Safety"], PMDA concluded that an indication of the treatment of female patients with diarrhea-predominant irritable bowel syndrome may be added to the current indication so that ramosetron is indicated for the treatment of diarrhea-predominant irritable bowel syndrome.

2.(ii).B.(4) Dosage and administration

Based on the following considerations in 1) and 2), PMDA considers that there is no particular problem in setting the dose for female patients with IBS-D according to the results of the phase III study and the long-term treatment study in the relevant patient population. This conclusion will be finalized, taking account of comments from the Expert Discussion.

2.(ii).B.(4).1) Usual dose

The applicant explained the rationale for selecting 2.5 μg as the dose of ramosetron in the phase III study in female patients with IBS-D as follows.

In the clinical studies of ramosteron conducted for the new drug application for the treatment of IBS-D (the initial application), the exposure to the drug was higher in women than in men, and the incidences of adverse events considered related to the pharmacological effect of the drug such as constipation, faeces hard, and abdominal distention were higher in women than in men. The optimal dose for female patients is likely to be lower than that for male patients. Additionally, the dose-response relationship in female patients has not been investigated adequately due to the limited study data obtained through the previous studies. As a result, participants in the phase II study were to receive placebo or ramosetron at doses of 1.25, 2.5, or 5 μg.

In the phase II study, no significant difference between the ramosetron groups and the placebo group was observed in the primary endpoint, the percentage of monthly responders in overall improvement rating in IBS symptoms at Month 1 of treatment (Table 2). However, at the final evaluation of the 3-month treatment, the percentage of monthly responders in overall improvement rating in IBS symptoms tended to be higher in the ramosetron 2.5 group and 5 μg group than in the placebo group, while it did not differ between the 1.25 μg group and the placebo group throughout the treatment period (Table 14). The percentage of monthly responders in terms of normalization of stool form among FAS patients with a mean BSFS score of >5 during the run-in period was higher in all the ramosetron groups than in the placebo group (Table 15).

Safety analysis revealed no concerns regarding tolerability in any ramosetron groups, but the incidence of faeces hard and constipation, which are considered related to the pharmacological action of the drug, increased dose-dependently (Table 3).

The applicant determined that ramosetron 2.5 μg may be administered in the phase III study because its efficacy had been suggested, and at the same time it was the dose enabling the lowest possible incidence of constipation and faeces hard, which are adverse events of special interest in ensuring the safety of treatment.

PMDA's view:

There are no particular problems in selecting 2.5 μg as the dose for the Phase III study of ramosetron since (i) the percentages of monthly responders in terms of overall improvement rating in IBS symptoms and normalization of stool form at the final evaluation were higher in the ramosetron 2.5 μg

group than in the placebo group and (ii) no tolerability concerns were noted at this dose.

In the phase III study in female patients with IBS-D, the superiority of ramosetron 2.5 μg over placebo was investigated in terms of the percentages of monthly responders in terms of overall improvement rating in IBS symptoms and normalization of stool form at the final evaluation, and the results demonstrated the efficacy of the drug. Safety analysis revealed that the incidences of constipation and faeces hard were higher in the ramosetron 2.5 μg group than in the placebo group (Table 4), but all events were mild or moderate in severity and resolved after taking appropriate measures, including study discontinuation. Additionally, there were no particular safety concerns in the long-term treatment study [see "2.(ii).B.(2).2) Adverse events associated with long-term treatment"].

Based on the above findings, it is concluded that the usual dose of ramosetron for the treatment of female patients with IBS-D may be set at 2.5 μg.

2.(ii).B.(4).2) Dose increase

In the long-term treatment study, the dose of ramosetron was allowed to be increased at Week 4, and the increased dose was allowed be decreased to 2.5 μg when appropriate at Week 12 (Table 9). The dose of ramosetron was increased to 5 μg in 19 patients at Week 4, and the dose was decreased to 2.5 μg in only 1 of the 19 patients at Week 12. In the remaining 18 patients, the dose was not decreased to 2.5 μg throughout the study period.

PMDA considers that there is no particular problem in allowing dose increase to 5 μg according to the severity of IBS symptoms, considering (i) that in the long-term treatment study the percentages of monthly responders in terms of overall improvement rating in IBS symptoms and normalization of stool form were generally maintained at Month 2 and thereafter although the number of patients with dose increase to 5 μg was only 19; (ii) that at Week 52, the percentage of patients who completed the scheduled treatment was similar between the 5 μg dose increase group and the 2.5 μg dose maintenance group (81.5% in overall patients; 80.3% [106 of 132 patients] in the 2.5 μg dose maintenance group; and 89.5% [17 of 19 patients] in the 5 μg dose increase group); and (iii) that the incidences of adverse events did not increase over time during long-term treatment. Since the incidences of constipation and faeces hard in the clinical studies of ramosetron were higher in female patients than in male patients, appropriate precautions on dose adjustment should be made for female patients as in the case for male patients to avoid unnecessary dose increase based on short-term symptoms, and treatment should be interrupted or discontinued when constipation and/or abdominal pain develop in order to ensure the safety of treatment.

2.(ii).B.(5) Clinical positioning of ramosetron in the treatment of female patients with IBS-D

The applicant explained the difference in the etiology and pathophysiology of IBS between male and female patients as follows:

As described at the time of the new drug application for the treatment of IBS-D(the initial application), men and women differ in many clinical and physiological responses due to their differences in reactive

responses to stress, the type and level of sex hormones, and central nervous system activation in response to visceral sensation, which lead to the difference in the etiology and pathophysiology of IBS-D between male and female patients (see the review report of Irribow Tablets 2.5 μg and 5 μg, dated April 10, 2008).

Since the submission of the new drug application, new findings below have indicated the relationship of sex hormones with visceral hyperesthesia and gastrointestinal motility disorders.[37]
It is known that 5-HT plays an important role in inducing gastrointestinal motility disorders associated with IBS, and it has been reported that an increase in 5-HT concentration in blood after meals may induce the disorders in patients with IBS-D. In female patients with IBS, 5-HT concentration in blood increases during the menstrual period when blood levels of estrogen and progesterone are low. It has thus been suggested that ovarian hormones cause change in gastrointestinal motility through affecting 5-HT concentration in patients with IBS-D. Female patients with IBS feel abdominal pain more intensely during the menstrual period when ovarian hormone levels are low, which suggest that estrogen decrease the perception of abdominal pain. Moreover, it has been suggested that the 5-HT system is involved in the difference between male and female patients in the severity of painful IBS symptoms through affecting the control of sensitivity of digestive tract in the peripheral and emotion circuits in the brain where central pain signals are processed.

The applicant explained the difference between male and female patients in optimal dose, efficacy and safety of ramosetron for the treatment of IBS-D as follows:
In the clinical pharmacology study conducted for the new drug application (the initial application),[38] the exposure to the drug was higher in females than in males with a female to male ratio of geometric mean of C_{max} and AUC_{inf} being1.511 and 1.745, respectively. The findings in clinical studies for the new drug application also suggested a difference in efficacy between male and female patients and for the safety, the incidences of adverse events such as constipation, faeces hard, and abdominal distension tended to be higher in female patients than in male patients, which indicated that further studies should be conducted to determine optimal dose of ramosetron for female patients (see the review report of Irribow Tablets 2.5 μg and 5 μg, dated April 10, 2008).
In the efficacy evaluation in the phase III study in female patients with IBS-D (Study CL-702), the superiority of ramosetron 2.5 μg over placebo was verified [see "2.(ii).B.(1) Efficacy"]. The difference in the overall improvement rating in IBS symptoms between the ramosetron and placebo groups in the phase III study in female patients (Study CL-702) was not markedly different from that between the male patient population and the placebo group in the phase III study where both male and female patients with IBS-D participated (Study CL-202) (Table 21).

[37] *World J Gastroenterol*, 2014;20: 6725-6743
[38] An open-label study was conducted at 1 medical institution in Japan in healthy male and female adult volunteers (target sample size: 20 adults for each sex) to investigate sex difference in the pharmacokinetic profile and safety after a single administration of ramosetron 5 μg.

Table 21. Percentage of monthly responders in overall improvement rating in IBS symptoms at the final evaluation in the Phase III studies (Studies CL-202 and CL-702) (FAS)

Treatment group		Study CL-202 (Ramosetron 5 μg)		Study CL-702 (Ramosetron 2.5 μg)
		Men	Women	Women
Placebo	N	226	42	284
	Percentage of monthly responders [95% CI] (No. of patients)	23.9% [18.5%, 30.0%] (54)	40.5% [25.6%, 56.7%] (17)	32.0% [26.7%, 37.8%] (91)
Ramosetron	N	215	54	292
	Percentage of monthly responders [95% CI] (No. of patients)	46.0% [39.3%, 53.0%] (99)	44.4% [30.9%, 58.6%] (24)	50.7% [44.8%, 56.6%] (148)
Between-group difference [95% CI]		22.2% [13.5%, 30.8%]	4.0% [-15.9%, 23.9%]	18.6% [10.7%, 26.5%]

Safety analysis revealed that faeces hard and constipation tended to develop more frequently among female patients in the phase III CL-702 study than in male patients in the phase III CL-202 study (Table 22), but all events were mild or moderate in severity and resolved after taking appropriate measures such as interrupting treatment [see "2.(ii).B.(2).3) (a) Faeces hard, constipation, and abdominal distension"]. In the long-term treatment study CL-703, no adverse events associated with the long-term use of the drug were observed, or the incidences of adverse events observed in the study did not increase over time.

Table 22. Incidence of faeces hard, constipation, and abdominal distension in the phase III studies (Studies CL-202 and CL-702)

	Placebo group						Ramosetron group					
	Study CL-202				Study CL-702		Study CL-202 (ramosetron 5 μg)				Study CL-702 (ramosetron 2.5 μg)	
	Men (227 patients)		Women (42 patients)		Women (284 patients)		Men (215 patients)		Women (55 patients)		Women (292 patients)	
Adverse events	Incidence	n	Incidence	n	Incidence	n	Incidence	n	Incidence	n	Incidence	n
Overall	49.3%	112	69.0%	29	41.5%	118	56.3%	121	76.4%	42	52.7%	154
Faeces hard	0.4%	1	2.4%	1	5.6%	16	6.0%	13	12.7%	7	22.6%	66
Constipation	1.3%	3	4.8%	2	4.6%	13	4.2%	9	9.1%	5	11.0%	32
Abdominal distension	1.3%	3	2.4%	1	0.4%	1	2.3%	5	12.7%	7	1.0%	3

The applicant also explained the difference between male and female patients in the safety of ramosetron at the recommended human dose.

Faeces hard and constipation, which are considered to be related to the pharmacological action of ramosetron, tended to develop more frequently in female patients than in male patients, but no adverse events specific to female patients were observed. When the drug was approved for the treatment of IBS-D in male patients (the initial approval), detailed precautions were included in the package insert to ensure safety, and since then physicians were encouraged to properly use the drug accordingly; thus, and furthermore through the specified use-results survey and other studies, the safety of the drug has been established. Since the incidences of faeces hard and constipation were higher in female patients than in male patients in the clinical studies of ramosetron for this application, it is necessary that the following additional precaution be included in the package insert to raise the awareness on these events occurring in female patients: "Additional attention should be given to female patients as constipation and faeces hard develop more frequently in female patients than in male patients." Also,

the precautions in the package insert should be thoroughly informed of as in the case of male patients.

PMDA's view:

Although the sex differences in the etiology and pathophysiology are recognized, ramosetron may be provided as an option of pharmacological treatment of female patients with IBS-D due to the following reasons: (i) The efficacy and safety of ramosetron 2.5 μg have been confirmed in female patients with IBS-D; (ii) no substantial differences were detected in efficacy and safety of the drug between male and female patients; and (iii) ramosetron has been established as a first-line therapy for male patients with IBS-D through accumulated clinical experience (the Evidence-based Clinical Practice Guidelines for Irritable Bowel Syndrome published by the Japanese Society of Gastroenterology; Nankodo, 2014). However, it is necessary to inform healthcare professionals and patients that faeces hard and constipation develop more frequently in female patients than in male patients through the package insert and other materials, and to continue to collect information on these events during post-marketing surveillance and from other studies in order to evaluate the safety of the drug in female patients with IBS-D in detail.

2.(ii).B.(6) Post-marketing investigations

The applicant explained that the specified use-results survey will be conducted as shown in Table 23.

Table 23. Outline of the specified use-results survey (draft)

Purpose	Obtain post-marketing data on the safety, efficacy, and other information on the proper use of the drug in the clinical setting
Survey method	Central registration system
Participants	Female patients with diarrhea-predominant irritable bowel syndrome
Target sample size	600 patients
Expected participating institutions	Approximately 120 medical institutions
Survey period	2 years (Registration period: 1 year and 6 months)
Observation period	24 weeks
Major survey items	- Patient characteristics (e.g., gender [female], age, weight, duration of illness, medical history, and complications) - Details on administration of ramosetron (daily dose, number of doses per day and timing, duration of treatment, and adherence to treatment) - Previous and concomitant drug treatment [names of drugs, daily dose (only for patients with adverse events), duration of treatment, and reasons for concomitant use] - Efficacy (clinical course, and overall improvement rating) - Laboratory examinations (barium enema examination, colonoscopy) - Adverse events (date of onset, seriousness, treatment, outcome, causal relationship with the drug) - Priority survey items: Occurrence of constipation/faeces hard and colitis ischaemic.

PMDA considers that there is no major problem with the outline of the specified drug use-results survey protocol (draft), but data on the safety and efficacy of the drug during long-term treatment should be collected as ramosetron is expected to be administered to patients for a long period of time. The detailed survey plans will be finalized, taking account of comments from the Expert Discussion.

III. Results of compliance assessment concerning the data submitted in the regulatory application and conclusion by PMDA

1. PMDA's conclusion on the results of document-based GLP/GCP inspections and data

integrity assessment

A document-based compliance inspection and data integrity assessment were conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the regulatory application. PMDA concluded that there should be no problems with conducting a regulatory review based on the submitted application documents.

2. PMDA's conclusion on the results of GCP on-site inspection

A GCP on-site inspection was conducted in accordance with the provisions of the pharmaceutical affairs act for the data submitted in the regulatory application (5.3.5.1-1, 5.3.5.1-2, 5.3.5.2-1, and 5.3.5.2-1.1). PMDA concluded that there should be no problems with conducting a regulatory review based on the submitted application documents.

IV. Overall evaluation

Based on the submitted data, PMDA concluded that the efficacy of Ramosetron Hydrochloride in women with diarrhea-predominant irritable bowel syndrome has been demonstrated and its safety is acceptable in view of its observed benefits. PMDA also considers that further consideration should be made for efficacy, safety, dosage/administration, and survey items of post-marketing surveillance.

PMDA has concluded that this application may be approved if Ramosetron Hydrochloride is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

April 3, 2015

I. Products submitted for registration

[Brand name]	(1) Irribow Tablets 2.5 μg, Irribow Tablets 5 μg (2) Irribow OD Tablets 2.5 μg, Irribow OD Tablets 5 μg
[Non-proprietary name]	Ramosetron Hydrochloride
[Applicant]	Astellas Pharma Inc.
[Date of application]	July 14, 2014

II. Content of the review

The comments from the Expert Discussion and the subsequent review by the Pharmaceuticals and Medical Devices Agency (PMDA) are outlined in the following sections. The expert advisors for the Expert Discussion were nominated based on their declarations or other relevant information concerning the products submitted for registration, in accordance with the provisions of the “Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency” (PMDA administrative Rule No. 27/1 dated February 26, 2015).

(1) Efficacy

Irritable bowel syndrome (IBS) is diagnosed on the basis of symptoms such as abdominal pain and abnormal bowel movement. Different patients have different chief complaints. Improvement in a particular symptom may not always lead to satisfaction with treatment. Considering the above, it is not problematic that the overall improvement rating in IBS symptoms evaluated by patients themselves was used as a primary endpoint in the Phase III study in women. Also, considering the pharmacological action of Ramosetron Hydrochloride (hereinafter referred also to as "ramosetron"), the clinical significance of improvement in diarrhea, a chief complaint in patients with IBS-D, and the results obtained from post-marketing clinical trials (Studies CL-500 and CL-501) that were conducted to determine the endpoints after the approval of the drug for the indication of treatment of male patients with IBS-D, the drug may be characterized by "normalization of stool form." Accordingly, there was no particular problem in using the percentages of monthly responders in terms of overall improvement rating and normalization of stool form as primary endpoints in the phase III study in female patients with IBS-D.

In the phase III study in female patients, statistically significant differences between the ramosetron and placebo groups were observed in the primary endpoints of percentages of monthly responders in terms of overall improvement rating in IBS symptoms and normalization of stool form at the final evaluation.

Efficacy of ramosetron over placebo was also suggested in improvement rating in abdominal pain or

discomfort, improvement rating in bowel movement, mean defecation frequency per week, number of days without defecation urgency, number of days without feeling of incomplete evacuation, and IBS-QOL-J total score, showing a tendency similar to those noted in the primary endpoints.

In the long-term treatment study, efficacy did not tend to decrease over time.

PMDA has concluded that these findings demonstrate the efficacy of ramosetron in the treatment of female patients with IBS-D.

The above conclusion of PMDA was supported by the expert advisors.

(2) Safety

In a pooled analysis of the female patient populations from 2 clinical studies (Studies CL-201 and CL-202 in male and female patients with IBS-D) submitted in the initial application and 2 clinical studies (Studies CL-701 and CL-702 in female patients with IBS-D), the incidences of adverse events, faeces hard, constipation, and abdominal distension were higher in females receiving ramosetron than in those receiving placebo. However, all these events were mild or moderate in severity, and resolved after taking appropriate measures such as discontinuing treatment. Also, these are known adverse reactions to ramosetron in male patients with IBS-D. Physicians have been instructed in the precaution section of the package insert to take appropriate measures according to patients' condition such as interrupting/discontinuing treatment if faeces hard or constipation develops during treatment. With measures including the precaution above, no specific problems in terms of safety have occurred in the clinical setting after market launch. PMDA thus considered that these events may be dealt with through appropriate safety measures similar to those taken for male patients with IBS-D.

In the long-term treatment study, the incidences of adverse events did not tend to increase over time.

PMDA has concluded that the safety of ramosetron in the treatment of female patients with IBS-D is acceptable when appropriate measures similar to those for male patients with IBS-D are taken.

However, it is necessary to appropriately inform healthcare professionals and patients that the incidences of faeces hard and constipation are higher in female patients than in male patients by including it in the package insert and other materials. Data on these events should be collected continuously during post-marketing surveillance or from other studies. Data on the occurrence of colitis ischaemic and cardiovascular disorders and those on the safety of long-term treatment with the drug should also be collected during post-marketing surveillance or from other studies.

The above conclusion of PMDA was supported by the expert advisors.

(3) Indication

On the basis of the review of efficacy and safety data, PMDA has concluded that ramosetron may be indicated additionally for female patients with IBS-D, and it is appropriate to indicate the drug for the treatment of diarrhea-predominant irritable bowel syndrome.

The above conclusion of PMDA was supported by the expert advisors, and PMDA has concluded that the indication for ramosetron may be set as follows:

[Indication]
Diarrhea-predominant irritable bowel syndrome

(4) Dosage and administration

On the basis of the review of efficacy and safety data, PMDA has concluded that the recommended dose regimen in the clinical setting may be set according to that used in the phase III study in female patients with IBS-D.

PMDA also considers that there is no particular problem in allowing dose increase to 5 μg according to the severity of IBS symptoms, considering (i) that in the long-term treatment study the percentages of monthly responders in terms of overall improvement rating in IBS symptoms and normalization of stool form were generally maintained at Month 2 and thereafter although the number of patients with dose increase to 5 μg was only 19; (ii) that the percentage of patients who completed the scheduled treatment to Week 52 was 81.5% in overall patients, 80.3% (106 of 132 patients) in the 2.5 μg dose maintenance group, and 89.5% (17 of 19 patients) in the 5 μg dose increase group; and (iii) that the incidences of adverse events did not increase over time during long-term treatment. Regarding dose increase, since faeces hard and constipation developed more frequently in female patients than in male patients, appropriate precautions on dose adjustment should be made for female patients as in the case for male patients to avoid unnecessary dose increase based on short-term symptoms, and treatment should be interrupted or discontinued when constipation and/or abdominal pain develop in order to ensure the safety of treatment.

As the above conclusion of PMDA was supported by the expert advisors, PMDA accepted the descriptions in the "Precautions for Dosage and Administration" section as proposed by the applicant. PMDA requested the applicant to modify the "Dosage and Administration" section as described below. The applicant responded appropriately, and PMDA accepted the revised version.

[Dosage and Administration]
The usual dose for female adults is 2.5 μg of ramosetron hydrochloride, administered once daily orally.
The dose may be increased for patients who do not adequately respond to treatment, but the daily dose should not exceed 5 μg.

Precautions for Dosage and Administration

The dose adjustment should be performed only after examining changes in symptoms for approximately 1 month during treatment. Frequent dose adjustment according to short-term symptomatic change should be avoided.

(5) Draft risk management plan

PMDA considers that there is no major problem with the outline of the specified drug use-results survey protocol (draft) while data on the safety and efficacy of the product during long-term treatment as well as occurrence of cardiovascular disorder should be collected.

The above conclusion by PMDA was supported by the expert advisors. The following comments were raised from the expert advisors:

Cardiovascular adverse events related to treatment with tegaserod maleate (not approved in Japan) were reported in female patients. It is thus appropriate to collect data on the occurrence of cardiovascular adverse events as a priority survey item during post-marketing surveillance of ramosetron.

On the basis of the above discussions, PMDA asked the applicant to review the risk management plan (draft). The applicant submitted the safety and efficacy specifications (Table 24), additional pharmacovigilance activities and risk minimization actions (Table 25), and the outline of the specified drug-use survey protocol (draft) (Table 26), and PMDA accepted them.

Table 24. Safety and efficacy specifications in the draft risk management plan (draft)

Safety Specification		
Important identified risks	Important potential risks	Important missing information
・Constipation/faeces hard	・Colitis ischaemic	Not applicable
Efficacy Specification		
・Effectiveness in female patients in routine clinical use		

Table 25. Outline of additional pharmacovigilance activities, and additional risk minimization actions in the draft risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization actions
・Early post-marketing phase vigilance ・Specified drug use-results survey in women	・Providing information through early post-marketing phase vigilance ・Preparing and providing materials for patients ・Preparing and providing materials for healthcare professionals

Table 26. Outline of the specified drug use-results survey protocol (draft)

Purpose	Obtain post-marketing data on the safety, efficacy, and other information on the appropriate use of the drug in routine clinical use
Survey method	Central registration system
Eligible patients	Female patients with diarrhea-predominant irritable bowel syndrome
Target sample size	600 patients
Expected participating institutions	Approximately 120 medical institutions
Survey period	2 years and 6 months (Registration period: 1 year and 6 months)
Observation period	52 weeks
Major survey items	- Patient characteristics (e.g., gender [female], age, weight, duration of illness, medical history, and complications) - Details on administration of ramosetron (daily dose, number of doses per day and timing, duration of treatment, and adherence to treatment) - Previous and concomitant drug treatment [names of drugs, daily dose (only for patients with adverse events), duration of treatment, and reasons for concomitant use] - Efficacy (clinical course, and overall improvement rating) - Laboratory examinations (barium enema examination, colonoscopy) - Adverse events (date of onset, seriousness, treatment, outcome, causal relationship with the drug) - Priority survey items: Occurrence of constipation/faeces hard, colitis ischaemic, and cardiovascular disorder.

III. Overall evaluation

As a result of the above review, PMDA has concluded that the product may be approved with the following conditions for approval after modifying the indication and the dosage and administration as shown below. As this application is submitted for the approval of a new indication and dosage, the re-examination period should be 4 years for the indication and dosage and administration to be added this time.

[Indication]

~~Male patients with~~ Diarrhea-predominant irritable bowel syndrome

(Double strikethrough denotes deleted text.)

[Dosage and administration]

Male patients with diarrhea-predominant irritable bowel syndrome

The usual dose for male adults is 5 μg of ramosetron hydrochloride, administered once daily orally. The dose may be adjusted according to the patients' clinical condition. The daily dose should not exceed 10 μg.

Female patients with diarrhea-predominant irritable bowel syndrome

The usual dose for female adults is 2.5 μg of ramosetron hydrochloride, administered once daily orally.

The dose may be increased for patients who do not adequately respond to the initial dose. The daily dose should not exceed 5 μg.

(Underline denotes added text.)

[Conditions for approval]

The applicant is required to develop and appropriately implement a risk management plan.