Gastroenterology 2016;150:358–366

# CLINICAL—ALIMENTARY TRACT

## Ramosetron Reduces Symptoms of Irritable Bowel Syndrome With Diarrhea and Improves Quality of Life in Women

Shin Fukudo,[1] Yoshikazu Kinoshita,[2] Toshikatsu Okumura,[3] Motoko Ida,[4] Hiraku Akiho,[5] Yoshihiro Nakashima,[6] Akito Nishida,[7] and Ken Haruma[8]

[1]Department of Behavioral Medicine, Tohoku University Graduate School of Medicine, Sendai, Japan; [2]Department of Gastroenterology, Faculty of Medicine, Shimane University, Izumo, Japan; [3]Department of General Medicine, Asahikawa Medical University, Asahikawa, Japan; [4]Japan-Asia Planning and Administration, Medical and Development, [5]Japan-Asia Clinical Development 2, [6]Japan-Asia Data Science, [7]Development Project Management, Astellas Pharma, Inc, Tokyo, Japan; [8]Department of Gastroenterology, Kawasaki Medical School, Kurashiki, Japan

**BACKGROUND & AIMS:** Previous studies have indicated that serotonin-3–receptor antagonists might have a sex-specific effect in patients with irritable bowel syndrome with diarrhea (IBS-D). Alosetron has been approved for the treatment of only women, and ramosetron has been approved for the treatment for only men. We performed a randomized, placebo-controlled, phase 3 study to determine whether ramosetron reduces symptoms of IBS-D in women. **METHODS:** We performed a prospective study of 576 female outpatients with IBS-D (according to the Rome III criteria), from February 2013 through February 2014, at 70 academic Gastroenterology Departments in Japan. After a 1-week baseline period, subjects received either 2.5 $\mu$g ramosetron (n = 292) or placebo (n = 284) once daily for 12 weeks. Primary end points were the monthly rates of response for relief from overall IBS symptoms and increased stool consistency at the last evaluation point. Quality of life (QOL) also was quantified. **RESULTS:** A significantly higher proportion of patients given ramosetron reported global improvement (50.7%; 95% confidence interval [CI], 44.8–56.6) than patients given placebo (32.0%; 95% CI, 26.7–37.8)—a difference of 18.6% (95% CI, 10.7–26.5; $P <$ .001). The relative risk was 1.58 (95% CI, 1.29–1.94) and the number needed to treat was 6 (95% CI, 4–10). A significantly higher proportion of patients in the ramosetron group reported increased stool consistency (40.8%; 95% CI, 35.1%–46.6%) than in the placebo group (24.3%; 95% CI, 19.4%–29.7%)—a difference of 16.5% (95% CI, 8.9%–24.0%; $P <$ .001). Patients receiving ramosetron had significant reductions in abdominal pain and discomfort ($P =$ .001) and greater improvement in QOL ($P =$ .002) compared with placebo. Ramosetron induced constipation in 11.0% of patients. **CONCLUSIONS:** In a randomized, placebo-controlled study of 576 women with IBS-D, 2.5 $\mu$g ramosetron per day reduced symptoms and increased stool consistency and QOL. Clinicaltrials.gov no: NCT01870895.

*Keywords:* 5-Hydroxytryptamine-3–Receptor Antagonist; Abdominal Pain; Discomfort; 5-HT.

Irritable bowel syndrome (IBS) is a common disorder of the gastrointestinal system.[1] The effect of IBS on society is now well recognized because IBS causes a profound disturbance in the quality of life (QOL) of individuals, causes economic loss to individuals and society,[2] and increases the risk of developing depressive and anxiety disorders, similar to other functional gastrointestinal disorders.[3] IBS, as defined by the Rome III criteria,[4] is classified into 4 subtypes: IBS with diarrhea (IBS-D), IBS with constipation, mixed-type IBS, and unsubtyped IBS. Among these subtypes, patients with IBS-D, together with IBS with constipation, have more well-defined phenotypes to use as a basis for the development of pharmacotherapy.[5]

Many agents have been developed for IBS-D, and evidence for the 5-hydroxytryptamine receptor 3 (5-$HT_3$) antagonist, alosetron, has shown that it suppresses the cardinal symptoms of IBS-D.[6,7] However, serious adverse drug reactions including ischemic colitis mandate that the use of alosetron be limited to a specialist prescription.[7,8] Moreover, alosetron has been approved in the United States only for female patients.[6] Another 5-$HT_3$ antagonist, ramosetron,[9–11] was developed in Japan, initially for nausea in cancer patients receiving chemotherapy, and later for IBS-D.[12–14] No ischemic colitis was reported in 901 IBS-D patients who received ramosetron in a previous study.[12–15] In contrast to alosetron, the clinical efficacy of ramosetron for IBS-D has been shown only in men.[12–15] These data resulted in the use of ramosetron being limited to male patients with IBS-D in Japan,[12–14] Korea,[15] and Thailand. There is, however, no logical explanation why 5-$HT_3$ antagonists would be effective solely in women with IBS-D in Western countries and only in men with IBS-D in Asian countries. Values for relative risk (RR) with alosetron and cilansetron have been reported to be lower in studies that included only women (1.23; 95% confidence interval [CI], 1.14–1.32) compared with studies including both sexes or men alone (1.39; 95% CI, 1.28–1.51; RR ratio, 0.88; 95% CI, 0.76–0.98).[7]

Given the preceding context, it is natural to test the hypothesis that ramosetron also could be effective in female

***Abbreviations used in this paper:*** **BSFS, Bristol Stool Form Scale; CI, confidence interval; FDA, Food and Drug Administration; 5-HT, 5-hydroxytryptamine; 5-$HT_3$, 5-hydroxytryptamine receptor 3; IBS, irritable bowel syndrome; IBS-D, irritable bowel syndrome with diarrhea; MCID, minimal clinically important difference; NNH, number needed to harm; NNT, number needed to treat; QOL, quality of life; RR, relative risk.**

**Most current article**


0016-5085
http://dx.doi.org/10.1053/j.gastro.2015.10.047

patients with IBS-D in a study with a sufficient sample size. This study aimed to verify this hypothesis, and provide compelling evidence and a rationale for the use of 5-$HT_3$ antagonists in patients with IBS-D, regardless of sex.

## Patients and Methods

### Patient Population

This study was conducted from February 2013 to February 2014 at 70 Japanese centers that have Gastroenterology Departments. Female outpatients aged 20–64 years were diagnosed as having IBS-D according to the Rome III criteria.[4] The study protocol was designed in accordance with the Declaration of Helsinki and was approved by the institutional review boards at all sites. All patients provided written informed consent before participating in study-related procedures. Patients satisfying the inclusion and exclusion criteria were monitored during a 1-week baseline period during which data on the severity of abdominal pain/discomfort and stool consistency[16] were collected to ensure that patients met the criteria. See the Patient Population section in the Supplementary materials for more detail.

### Study Design

Based on previous studies,[12–14] this randomized, double-blind, placebo-controlled clinical study comprised a provisional registration period, a 1-week baseline period, and a 12-week treatment period. After the baseline period, eligible patients were assigned randomly to 12 weeks of oral treatment with placebo or ramosetron hydrochloride (2.5 $\mu$g once daily) before breakfast. Visits were scheduled at weeks 2, 4, 8, and 12 (or at the time of discontinuation) to assess treatment efficacy, drug compliance, and occurrence of adverse events. Randomization was performed in a 1:1 ratio using a block size of 4 with a web-based randomization system. The randomization schedule was developed by a third-party contract research organization (EPS Corporation, Tokyo, Japan). All patients, investigators, and sponsors were blinded until all observations and evaluations were completed, statistical analysis plans were finalized, and all data had been locked. All authors had access to the study data and reviewed and approved the final manuscript.

### Data Collection

During the baseline and treatment periods, patients recorded their IBS symptoms each day on paper diary cards at bedtime, and electronically entered data into a database daily using an interactive voice response system to support the completion of data entry in the paper diary cards. This system of evaluating IBS symptoms has been reported previously as reliable and valid.[12–14] Patients were assessed for disease-specific health-related QOL[17] every 4 weeks using the Japanese version of the IBS-QOL measurement instrument.[18] See the Supplementary Data Collection section for more detail.

### Efficacy and Safety End Points

One of the co-primary end points was monthly responder rates for global assessment of relief from overall IBS symptoms at the last evaluation point. The Pharmaceuticals and Medical Devices Agency of Japan approved use of this measure as a primary end point for IBS studies in 2002.[12,13] Patients with scores of 0 or 1 at each weekly evaluation point were regarded as weekly responders, and patients who were weekly responders for at least 2 of the 4 weeks were regarded as monthly responders.

Another co-primary end point was the monthly responder rate for improvement in stool consistency at the last evaluation point. The US Food and Drug Administration (FDA) proposed a study design for clinical trials focused on IBS,[5] suggesting use of abdominal pain and stool consistency as co-primary end points for IBS-D. Importantly, the FDA guidance permits trials of drugs that target only one of these end points if the mechanism of action of the drug applies to only one of these symptoms.[5]

Secondary end points included relief of abdominal pain/discomfort and improvement in abnormal bowel habits. Scales measuring IBS symptoms, including severity of abdominal pain/discomfort, the Bristol Stool Form Scale (BSFS), stool frequency, urgency and feeling of incomplete evacuation, and IBS-QOL also were established for the secondary end points. All adverse events were recorded during the intervention period. See the Supplementary Efficacy and Safety End Points section for more detail.

### Statistical Analysis

Sample sizes of 580 patients (290 patients/group) were calculated to provide 90% power to detect both a difference in monthly responder rates for global assessment of relief from overall IBS symptoms at the last evaluation point between the placebo group (38%) and the 2.5-$\mu$g ramosetron group (53%), and monthly responder rates for improvement in stool consistency at the last evaluation point between the placebo group (21%) and the 2.5-$\mu$g ramosetron group (40%) based on the subpopulation of the phase II clinical study (Clinicaltrials.gov ID: NCT01274000),[19] using a $\chi^2$ test with a 2-sided significance level of 0.05. Efficacy analyses included the full analysis set, which was as complete as possible and as close as possible to the intention-to-treat ideal of including all randomized subjects.[20] This analysis was in keeping with the International Conference on Harmonisation E9, generated by the regulatory authorities and pharmaceutical industries of the European Union, United States, and Japan, based on each party's agreement.[20] The full analysis set included all patients who received at least one dose of the study drug during the treatment period and for whom more than one end point could be evaluated. Safety analyses were performed for all patients who received at least one dose of the study drug during the treatment period.

Monthly responder rates for global assessment of relief from overall IBS symptoms at the last evaluation point are expressed as a percentage of responders, and 95% CIs are provided. The treatment groups were compared using a $\chi^2$ test with a 2-sided significance level of 0.05. Other monthly responder rate parameters were analyzed similarly. Missing values were treated as nonresponders. The superiority of 2.5 $\mu$g ramosetron over placebo was established by showing a statistically significant difference compared with placebo for both co-primary end points. BSFS and changes in stool frequency were evaluated using the $t$ test. To compare the ramosetron group with the placebo group, analysis of covariance was performed with the treatment groups as a factor and