

University of Texas Rio Grande Valley

ScholarWorks @ UTRGV

School of Medicine Publications and Presentations

School of Medicine

4-2020

Efficacy of the Combination of Pinaverium Bromide 100mg Plus Simethicone 300mg in Abdominal Pain and Bloating in Irritable Bowel Syndrome: A Randomized, Placebo-controlled Trial

Max J. Schmulson

Jazmin Chiu-Ugalde

Adolfo Saez-Rios

Aurelio Lopez-Colombo

Gualberto J. Mateos-Perez

See next page for additional authors

Follow this and additional works at: https://scholarworks.utrgv.edu/som_pub



Part of the [Chemicals and Drugs Commons](#)

Recommended Citation

Schmulson, Max J.; Chiu-Ugalde, Jazmin; Saez-Rios, Adolfo; Lopez-Colombo, Aurelio; Mateos-Perez, Gualberto J.; Remes-Troche, Jose Mario; Sobrino-Cossio, Sergio; Soto-Perez, Julio C.; Tamayo de la Cuesta, Jose L.; Teramoto-Matsubara, Oscar T.; and Lopez-Alvarenga, Juan C., "Efficacy of the Combination of Pinaverium Bromide 100mg Plus Simethicone 300mg in Abdominal Pain and Bloating in Irritable Bowel Syndrome: A Randomized, Placebo-controlled Trial" (2020). *School of Medicine Publications and Presentations*. 67.

https://scholarworks.utrgv.edu/som_pub/67

This Article is brought to you for free and open access by the School of Medicine at ScholarWorks @ UTRGV. It has been accepted for inclusion in School of Medicine Publications and Presentations by an authorized administrator of ScholarWorks @ UTRGV. For more information, please contact justin.white@utrgv.edu, william.flores01@utrgv.edu.

Authors

Max J. Schmulson, Jazmin Chiu-Ugalde, Adolfo Saez-Rios, Aurelio Lopez-Colombo, Gualberto J. Mateos-Perez, Jose Mario Remes-Troche, Sergio Sobrino-Cossio, Julio C. Soto-Perez, Jose L. Tamayo de la Cuesta, Oscar T. Teramoto-Matsubara, and Juan C. Lopez-Alvarenga

Efficacy of the Combination of Pinaverium Bromide 100 mg Plus Simethicone 300 mg in Abdominal Pain and Bloating in Irritable Bowel Syndrome: A Randomized, Placebo-controlled Trial

Max J. Schmulson, MD,*†‡ Jazmin Chiu-Ugalde, MSc,§
 Adolfo Sáez-Ríos, MD,||¶# Aurelio López-Colombo, MD, MSc,**
 Gualberto J. Mateos-Pérez, MD,†† José María Remes-Troche, MD, MSc,‡‡
 Sergio Sobrino-Cossio, MD,§§||| Julio C. Soto-Pérez, MD,¶¶###
 José L. Tamayo de la Cuesta, MD,### Oscar T. Teramoto-Matsubara, MD,†
 and Juan C. López-Alvarenga, MD, PhD***†††

Goals: We aimed to evaluate the efficacy and safety of PB+S (pinaverium bromide 100 mg plus simethicone 300 mg) in patients with irritable bowel syndrome (IBS).

Background: IBS is a multifactorial disorder; thus, combination therapy with different mechanisms of action is expected to be useful. PB+S has shown effectiveness in an open-label clinical study in IBS. However, there are no placebo-controlled trials.

Materials and Methods: IBS-Rome III patients with abdominal pain/discomfort for at least 2 days within the week prior to baseline assessment were included in this 12-week, randomized, double-blind, placebo-controlled study of PB+S versus placebo, bid. The primary endpoint was overall symptom improvement, evaluated

weekly by the patient (Likert Scale). Secondary endpoints included the weekly improvement in the severity of abdominal pain and bloating assessed both by patients (10-cm Visual Analogue Scale) and investigators (Likert Scale); frequency of Bristol Scale stool types (consistency) evaluated by patients and the IBS Quality of Life scores.

Results: A total of 285 patients (female: 83%; 36.5 ± 8.9 y old) received at least 1 dose of PB+S (n = 140) or placebo (n = 145). No difference was observed in overall symptom improvement between the groups (P = 0.13). However, PB+S was superior in abdominal pain (effect size: 31%, P = 0.038) and bloating (33%, P = 0.019). Patients with IBS-C and IBS-M showed the best improvement in the frequency of stool types with PB+S. No differences were observed in IBS Quality of Life scores and adverse events.

Received for publication March 13, 2019; accepted June 6, 2019.

From the *Laboratory of Liver, Pancreas and Motility (HIPAM)-Unit of Research in Experimental Medicine, Faculty of Medicine, National Autonomous University of Mexico (UNAM), General Hospital of Mexico "Dr. Eduardo Liceada"; †Gastroenterology and Endoscopy in MGP, ABC Medical Center; ‡Lomas Altas SC Clinic, Mexico City; §Medical Information, Takeda Mexico; ||Central Military Hospital; ¶Faculty of Medicine, and Mano Amiga Foundation-Anahuac University, Mexico City; #Medical Department Takeda Ecuador and Peru; **Department of Health Education and Research, Specialty Hospital-Manuel Avila Camacho National Medical Center, National Institute of Social Security (IMSS), Puebla; ††Department of Gastroenterology, Endoscopy and Surgery, Angeles del Pedregal Hospital, Mexico City; †††Laboratory of Digestive Physiology and Gastrointestinal Motility, Institute of Medical-Biologic Research, University of Veracruz, Veracruz, Ver.-México; §§Pedregal Angeles Hospital; ||||Service of Gastroenterology and Digestive Endoscopy, High Specialty South Central Hospital of Petroleos Mexicanos (PEMEX), Mexico City; ¶¶Digestive Physiology Clinic, Metropolitan Angeles Hospital; ###Center for Research and Education in Health Sciences, Autonomous University of Sinaloa, Civil Hospital of Culiacan; ***Department of Human Genetics, School of Medicine, University of Texas Rio Grande Valley, TX; and †††Research Division Mexican-American University of the North (UMAN), Reynosa, Tamaulipas, Mexico.

Supported by Takeda Mexico SA de CV (formerly Nycomed).

M.J.S.: planning and study conceptualization, recruiting patients, processing, analyzing, and interpreting the data and drafting the manuscript and has approved the final draft. J.C.-U.: processing, analyzing, and interpreting the data and drafting the manuscript and has approved the final draft. A.S.-R.: drafting the manuscript and has approved the final draft. A.L.-C.: study planning and recruiting patients and has approved the final draft. G. J.M.-P.: study planning and recruiting patients and has approved the final draft. J.M.R.-T.: study planning and recruiting patients and has approved the final draft. S.S.-C.: recruiting patients, processing, analyzing, and interpreting the data and has approved the final draft. J.C.S.-P.: study planning and recruiting patients and has approved the final draft. J.L.T.d.I.C.: study planning and recruiting patients and has approved the final draft. O.T.T.-M.: study planning and recruiting patients and has approved the final draft. J.C.L.-A.: planning and study conceptualization, recruiting patients, processing, analyzing, and interpreting the data and drafting the manuscript and has approved the final draft.

M.J.S. has received grant supports from Alfa Wasserman. During the last year, he served as a consultant for Commonwealth Diagnostics International Inc. and has been a speaker for Takeda Mexico. J.C.L.-A. was a Takeda Mexico employee at the time of the trial and J.C.-U. and A.S.-R. are current employees of Takeda Mexico. A.L.-C. has been a speaker for Takeda Mexico and Alfa Wasserman. G.J.M.-P. has been a speaker for Takeda Mexico and Cook Medical. J.M.R.-T. has served on the Advisory Board of Allergan, Carnot, and Sanfer. He has been a consultant for Alfa Wasserman, Almirall, Commonwealth Laboratories Inc., Takeda Mexico, Asofarma Mexico, and Sanfer. He has also been a speaker for Alfa Wasserman, Takeda Mexico, Carnot, Sanfer, and Almirall. He has received grant supports from Alfa Wasserman and Sanfer. S.S.-C. has been a speaker for Takeda Mexico and Cook Medical and has served as a Consultant for Cook Medical. J.C.S.-P. has been a speaker for Takeda Mexico. J.L.T.d.I.C. has been a speaker for Takeda Mexico. O.T.T.-M. has been a speaker for Takeda, Asofarma, and Sanfer and has served as a consultant for Takeda and Menarini.

Address correspondence to: Max J. Schmulson, MD, Laboratorio de Higado, Páncreas y Motilidad (HIPAM)-Unidad de Investigación en Medicina Experimental, Facultad de Medicina-Universidad Nacional Autónoma de México (UNAM), Hospital General de México, Dr. Balmis #148, Col. Doctores C.P.06726, México D.F., México (e-mail: maxjulio@prodigy.net.mx).

Copyright © 2019 The Author(s). Published by Wolters Kluwer Health, Inc. This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

DOI: 10.1097/MCG.0000000000001242

Conclusions: PB+S was superior to placebo in improving abdominal pain and bloating in patients with active IBS. The effect on the frequency of stool consistency was particularly significant in IBS-C and IBS-M.

Key Words: irritable bowel syndrome, pinaverium bromide-simethicone, combined therapy, bloating, abdominal pain

(*J Clin Gastroenterol* 2020;54:e30–e39)

Irritable bowel syndrome (IBS) is a functional bowel disorder, characterized by abdominal pain and/or discomfort, associated with changes in bowel habits.¹ Diagnosis is currently performed using Rome IV criteria^{2,3}; however, IBS prevalence can vary from 1.1% to 45% according to the used criteria.^{4,5} In Mexico, 2 different population-based studies using Rome II criteria have estimated a prevalence of 16%,^{6,7} whereas a study using Rome III criteria has reported a much lower prevalence of 4.4%.⁸ In several studies, IBS has shown a negative impact on patients' quality of life (QoL) and is associated with a significant burden in terms of health-related direct and indirect costs.^{9,10}

Several plausible pathophysiological mechanisms have been linked to IBS, including digestive motor disturbances, visceral hypersensitivity, brain-gut axis dysfunction, low-grade inflammation in the gut mucosa, immune activation, and dysbiosis; notwithstanding, most probably IBS is a multifactorial disorder.^{11–14} Nevertheless, most available drug treatments are directed toward a single mechanism, a single IBS subtype (eg, IBS-D or IBS-C) and to alleviate isolated symptoms.^{15,16} However, as a multifactorial disease, IBS is likely to require a combination of therapies targeted at different mechanisms. In fact, the combination of mosapride with probiotics showed to be effective in relieving symptoms of nondiarrheal IBS patients.¹⁷ Moreover, the combination of alverine citrate with simethicone, an antispasmodic with an antiflatulent agent, has been reported to be effective on abdominal pain/discomfort and on the global symptom improvement, compared with placebo in patients with IBS.¹⁸ More recently, in an on-demand trial, it was shown to significantly improve QoL, global symptom severity, and abdominal pain and bloating, compared with usual treatments.¹⁹

Pinaverium bromide (PB) [*N*-(bromo-2-dimethoxy-4,5-benzyl)-*N*[(dimethyl-6,6 norpinanyl-2)-2 ethoxy]-2 ethyl morpholinium bromide] is a quaternary ammonium derivative that acts as an antispasmodic agent by blocking both muscarinic receptors²⁰ and calcium channels in the gut smooth muscle cells. In vitro assays have demonstrated that PB binds the α -1 subunit²¹ of L-type (long-lasting)²² voltage-operated channels, on the external surface of intestinal smooth muscle cells,²³ exerting a calcium-channel inhibition. Calcium entry into these channels is the main pathway to trigger contractile activity; thus, by blocking them, an antispasmodic effect is produced. One of the main features of PB is its poor systemic absorption and selective pharmacological effects on the gastrointestinal tract, rather than the cardiovascular system, thus providing a high safety profile.²⁴

In contrast, simethicone (S), also known as activated dimethicone (dimethylpolysiloxane [(CH₃)₂[Si(CH₃)₂O]_n]), is a chemically inert compound of silica gel not absorbed in the gastrointestinal tract. It is physiologically inactive and nontoxic when used orally. Its antifoaming action has been studied in vitro, showing that it has the property of

decreasing the surface tension of liquid;²⁵ therefore, it has been used in vivo to help as a visualization agent during endoscopy and colonoscopy by preventing bubble formation and gas retention.^{26,27} S has been available since the 1960s as a well-tolerated medication.^{28–30} However, S alone is not effective to reduce the median time to complete relieving of gas-related abdominal discomfort or the median time to last unformed stool, unless combined with loperamide,^{31,32} in patients with acute diarrhea with gas-related abdominal discomfort.

The effectiveness of 100 mg pinaverium bromide and 300 mg of simethicone (PB+S) as a combination therapy for IBS has previously been shown in a nationwide open-label 4-week clinical trial in Mexico.³³ In that study, PB+S improved abdominal pain and bloating in all IBS subtypes after 4 weeks of treatment. In addition, PB+S improved stool frequency and consistency in patients with all IBS subtypes. Therefore, in the current study, we aimed to assess the efficacy, QoL, and safety profile of PB+S PO, bid, for 12 weeks compared with placebo in patients with active Rome III-IBS.

MATERIALS AND METHODS

Study Design

This was a randomized, double-blind, placebo-controlled, parallel group, multicenter study conducted from November 2008 to December 2009. Patients were recruited among those consulting 19 physicians in Mexico (gastroenterologists 55.4%, general surgeons 26.6%, and endoscopists 18%). Those who met eligibility criteria and volunteered for the study were randomized to either PB+S or matching placebo for 12 weeks.

Patient Eligibility

Patients were eligible for inclusion if they were aged 18 years or above and 50 years or below, had a body mass index (BMI) <35 kg/m², and fulfilled Rome III criteria for IBS. In addition, patients needed to have active IBS at enrollment. Active IBS was considered in the presence of abdominal pain and/or discomfort in at least 2 days during the week before baseline assessment. Although patients were recruited independently of the bowel habit subtype, these were classified according to Rome III as IBS with constipation (IBS-C), diarrhea (IBS-D), mixed (IBS-M), or untyped (IBS-U). Endoscopic examination (either upper endoscopy and/or colonoscopy) was optional at the investigators' discretion.

Patients were excluded if they had received any treatment for IBS (eg, pure PB, trimebutine, tegaserod, etc.) within the last 30 days before the start of the study protocol; if they presented any alarm symptoms such as anemia, rectal bleeding, unexplained weight loss, general health status impairment; and if they presented any abnormal laboratory parameters and/or vital signs considered as clinically relevant by the investigators. Other exclusion criteria included confirmed or suspected malignancy in any system or organ; women who were pregnant or suspected to be pregnant or breastfeeding; confirmed or suspected rectal or anal stenosis and/or esophageal varices; history of unspecified ulcerative colitis or Crohn's disease, rectal or anal ulcers, or any related complications and/or celiac disease; history of major upper or lower abdominal surgery (except for appendectomy), gastrointestinal tract malformations, or intestinal obstruction; any severe or unstable organ or systemic condition (eg, diabetes, thyroid

disease, cardiovascular disorders), history of alcohol or drug abuse or known allergies to any of the components of the study combination.

Study Medication

Study medication included 100 mg of pinaverium bromide and 300 mg of simethicone (PB+S) packed in gelatine capsules. PB+S and placebo were provided by Takeda Mexico SA de CV (formerly Nycomed) and were identical in shape and color. The assigned treatment was taken twice a day, 10 to 15 minutes before breakfast and dinner.

Randomization and Blinding

Patients were randomized to either PB+S or placebo in a 1:1 ratio. Allocation of patients to treatment groups was carried out using block randomization (blocks of 4). The randomization scheme (stratified by site) was generated using the SAS program (SAS Institute Inc., Cary, NC). This was a triple-blind study, in which all study personnel and participants and the Statistician (J.C.L.-A.) were blinded to the true identity of the treatment assigned until statistical analysis was finalized.

Prohibited Concomitant Medications

Any treatment likely to interfere with the study drug evaluation was prohibited during the study (eg laxatives, antiarrhythmic medications, and antispasmodics). If absolutely necessary, patients were allowed to use concomitant treatments for other chronic diseases (eg, controlled diabetes mellitus, systemic arterial hypertension). In addition, patients were advised not to change their regular diet throughout the study period.

Data Collection and Efficacy Endpoints

Study visits were scheduled at randomization (V0, basal assessment) and then at weeks 4 (V1), 8 (V2), and 12 (V3). Throughout the duration of the study, patients had to report in a paper diary their evolution in all efficacy endpoints relating to the previous week. In addition, assessments by investigators were performed at each study visit, as described below.

Primary Efficacy Endpoint

The primary efficacy endpoint was the overall symptom improvement score reported by the patient at the end of the treatment period (week 12: V3) according to the following statement: 'The treatment helped to improve my bowel problems', using a 5-point Likert Scale (0: strongly disagree, 1: disagree, 2: neither agree nor disagree, 3: agree, and 4: strongly agree). Efficacy was considered to be achieved if the difference between the treatment groups in the effect size was at least 30%, favoring the PB+S group at V3.

Secondary Efficacy Endpoints

Secondary endpoints included the severity of individual symptoms (abdominal pain and bloating), frequency of Bristol stool types (stool consistency), and QoL. The severity of abdominal pain and bloating was evaluated by the patients using 10-cm Visual Analogue Scale ("nothing" to "extremely intense"), and by the physicians using 5-point Likert Scales (0: nothing, 1: mild, 2: moderate, 4: severe, and 5: very severe). Efficacy was considered to be achieved if the difference (effect size) between treatment groups in terms of severity of abdominal pain and/or bloating, assessed by the patients (Visual Analogue Scale score), was at least 30% (lower severity in the PB+S vs. placebo group) at V3. The

same criterion applied to physician's assessment (Likert Scales).

Stool consistency was assessed by both, the patients (daily) and the physicians (at each visit, evaluating the last 7 d) using the Bristol Scale, which is an appropriate instrument for capturing the stool consistency in IBS trials.³⁴ Stool frequency was recorded in a diary that included the stool-type pictograms of the Bristol Scale, thus patients recorded each bowel movement according to the corresponding stool type, as previously reported.³³

To assess QoL, patients answered the Irritable Bowel Syndrome Quality of Life (IBS-QOL) questionnaire at randomization and at the end of treatment (V0 and V3, respectively). The IBS-QOL is a self-administered questionnaire³⁵ that has been previously validated in Spanish-Mexico.³⁶ It includes 34 items summarized in 8 subscales: Dysphoria (DY), Interference with Activity (IN), Body Image (BI), Health Worry (HW), Food Avoidance (FA), Social Reaction (SR), Sexual (SX), and Relationships (RL) and are combined for an Overall score (OV).

Safety

Standard laboratory tests for blood chemistry and hematology were performed at inclusion (V0) and at the end of treatment (V3). Blood chemistry included serum creatinine, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, and total bilirubin. Hematology workup included hemoglobin and blood cell count. All adverse events (AEs) and serious adverse events (SAEs) were actively searched and recorded during each study visit.

Statistical Analysis

For statistical analysis, 2 data sets were considered: a) The intention to treat (ITT) data set, including all randomized subjects who participated in at least 1 post-baseline assessment, corresponding to V1 (n=275); and the per protocol (PP) data set, including all patients who did not deviate from the planned protocol and were compliant with at least 80% of the study medication (n=216). Efficacy analyses for the primary and secondary variables were conducted with both ITT and PP data sets. For the ITT set, missing values were imputed by maximum likelihood estimation with regression of available repeated measurements (for intermediate, not at random missing values) or by last-observation-carried-forward method (if dropout). The effect size for each data set is reported; however, no differences in effect sizes were observed between the ITT and PP data sets (differences ranging from 0% to 2%) in all efficacy variables.

Sample Size and Statistical Power

The standardized measure of effect size used in the analysis of variance (ANOVA) was obtained by a root mean square standardized effect.³⁷ Parameters to calculate the statistical power were obtained from a previous open-label clinical trial with PB+S;³³ the pooled mean change and SD of abdominal pain severity score measured by the patients (basal vs. final) was 1.5 (\pm 1.7), with a 0.5-point difference in the mean. The α error was set at 0.05, and the estimated effect size was 30%.

Descriptive demographics were expressed as mean \pm SD. A factor analysis linked to a general linear model was used to correct for confounding variables such as age, sex, and BMI. Comparisons between fixed factors (treatment

and IBS subtypes) were analyzed by multivariate ANOVA for repeated measurements, incorporating the main outcomes of all visits, using the Fisher post hoc test.

The effect size for overall symptom assessment, abdominal pain, and bloating measured by the patient and physicians, were calculated with partial η^2 as follows ($SS =$ squared sums): $\eta_p^2 = SS_{\text{Effect}} / (SS_{\text{Effect}} + SS_{\text{Error}})$. The partial η^2 is used for ANOVA designs that have nonindependent measurements. For easier interpretation, they were transformed to Cohen d .³⁸

The data from the Bristol Scale that were collected by the physicians at each study visit were analyzed as relative frequency distributions (density probability functions), and weekly changes in consistency and frequency were further analyzed according to the IBS subtype over the 12 weeks of treatment. Only the IBS-C, IBS-D and IBS-M subtypes were analyzed due to the high variability that was present in the IBS-U group. Unweighted means of the weekly stool consistency type [$x = \sum (\text{Type})$] and frequency [$x = \sum (\text{Frequency})$] were estimated. Each curve was smoothed for interpolation of the Bristol levels and then was normalized to obtain a unity for the complete area under the curve (AUC). Three segments were calculated (Bristol 1 to 3, 3 to 5, and 5 to 7). Treatment contrasts were based on the ratio of AUC of the drug/placebo, and extraction of the null value (= 1) was conducted to draw the comparisons.

Finally, the score of each subscale of the IBS-QOL Scale was calculated using an SPSS program syntax based on the IBS-QOL scoring system. The raw score values were transformed into percentages, which allowed calculating a comparison dimension between subscales in spite of having a different number of questions.

Ethics

The protocol was approved by an independent ethics committee (Teaching, Research and Ethics Committee, General Hospital, Naucalpan-State of Mexico, Mexico), and the study was conducted in accordance with the International Conference on Harmonization, Guidelines for Good Clinical Practices, Declaration of Helsinki, and applicable local regulations. Before entry, all patients received detailed information with regard to the study and signed informed consent.

RESULTS

Patients' Baseline Characteristics

Between November 2008 and December 2009, 300 patients were screened. Sample attrition is depicted in Figure 1. Fifteen patients were screen failure (10 because of abdominal hysterectomy, 4 because of BMI > 35 kg/m², and 1 because of age older than 50 y) and were excluded from the analyses. Therefore, 285 were randomized and entered the 12-week treatment period (women: 83%; age: 36.5 ± 8.9 y old; BMI: 26.7 ± 5 kg/m²) (Table 1). IBS-C was the most frequent subtype (43.5%) followed by IBS-M (31.2%), IBS-D (23.2%) and IBS-U (2.1%). The majority of patients were from central Mexico and were similarly distributed into the treatment groups.

Among the 285 patients who entered the study, 30 withdrew prematurely (13 in the PB+S and 17 in the placebo group) because of AEs (n = 1), SAEs (n = 2), lack of efficacy (n = 4), consent is withdrawn (n = 4), lost to follow-up (n = 10), or noncompliance with the study treatment (n = 9) (Fig. 1, Table 2).

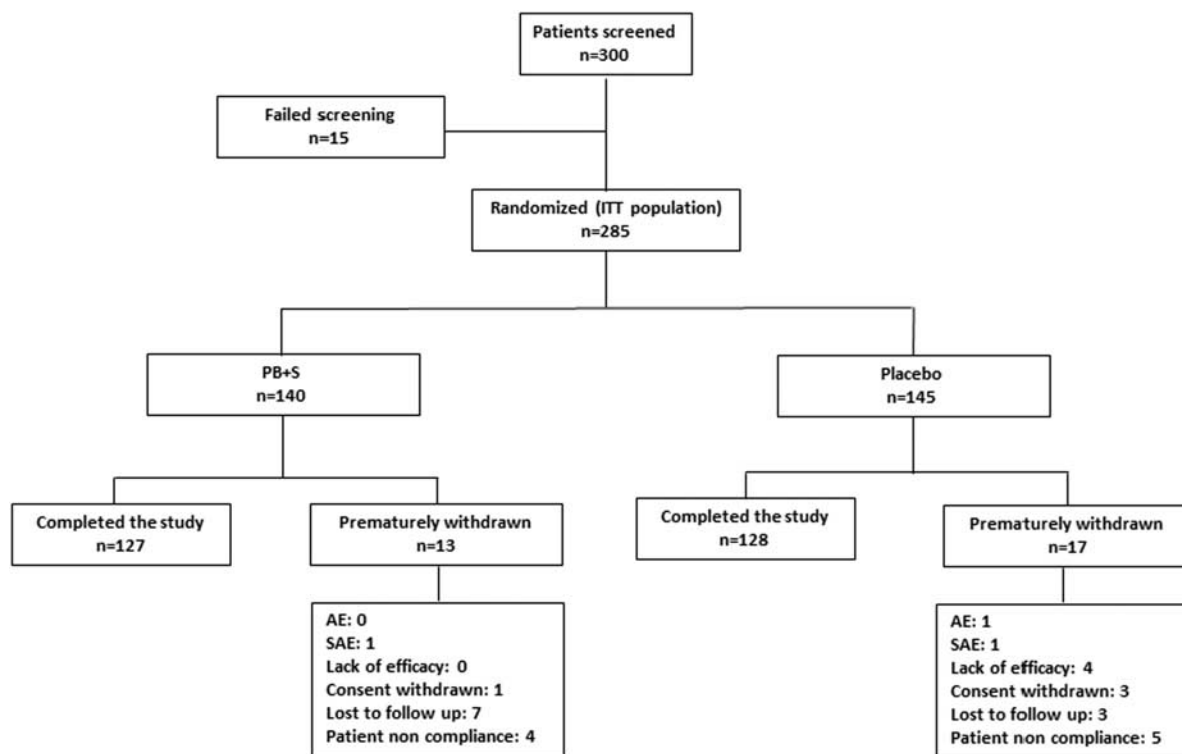


FIGURE 1. Flowchart of patients through the study. AE indicates adverse event; ITT, intention to treat; PB+S, pinaverium bromide 100 mg plus simethicone 300 mg; SAE, serious adverse event.

TABLE 1. Baseline Characteristics of the Intention to Treat Population

	PB+S (N = 140)	Placebo (N = 145)	P
Female/male ratio (n)*	118/22	119/26	0.99
First-time consulting*	65 (46.4)	54 (37.2)	0.12
Age (y)†	35.3 (8.8)	36.5 (9.0)	0.24
Waist circumference (cm)†	90.3 (11.9)	90.1 (10.9)	0.91
Body mass index (kg/m ²)†	26.3 (4.5)	26.7 (5.9)	0.54
Heart rate (beats/min)†	73.6 (6.7)	74.4 (7.8)	0.37
Respiratory rate (breaths/min)†	17.6 (1.8)	17.6 (1.8)	0.84
Temperature (°C)†	36.3 (0.4)	36.4 (0.5)	0.08
Systolic BP (mm Hg)†	112 (12.3)	114.2 (12.6)	0.13
Diastolic BP (mm Hg)†	70.7 (9.0)	72.9 (9.4)	0.04
IBS subtypes*			
IBS-C	62 (44.3)	62 (42.8)	0.99
IBS-D	32 (22.9)	34 (23.4)	
IBS-M	43 (30.7)	46 (31.7)	
IBS-U	3 (2.1)	3 (2.1)	
Geographic area*			
Northern Mexico	28 (20.9)	33 (23.7)	0.39
Central Mexico	59 (44.0)	68 (48.9)	
Southern Mexico	47 (35.1)	38 (27.3)	
Physician specialties*			
Gastroenterologists	71 (52.2)	82 (57.3)	0.57
Endoscopic surgeons	28 (20.6)	23 (16.1)	
General surgeons	37 (27.2)	38 (26.6)	

Basal characteristics of randomized patients according to the treatment groups.

*Categorical variables are expressed as n (%) and contrast with the χ^2 test.

†Data are expressed as mean (SD), and were contrasted with the Student *t* test adjusted for homoscedasticity.

BP indicates blood pressure; IBS, irritable bowel syndrome; IBS-C, irritable bowel syndrome with constipation; IBS-D, irritable bowel syndrome with diarrhea; IBS-M, mixed-type irritable bowel syndrome; IBS-U, unsubtyped irritable bowel syndrome; PB+S, pinaverium bromide 100 mg plus simethicone 300 mg.

Efficacy Results

Overall Symptom Improvement

There was a significant improvement over time in the overall symptom assessment in both treatment groups. However, the difference in effect size (Cohen *d*) between the groups was a marginal 20% in favor of PB+S over placebo both in the PP and ITT data sets (both, $P=0.13$) and corresponding to a post hoc power of 20% for this endpoint (Fig. 2).

Individual Symptoms

Patient assessment. PB+S was significantly superior to placebo ($P=0.04$) in improving the severity of abdominal pain, with a total effect size of 30% (ITT: 29%, PP: 31%)

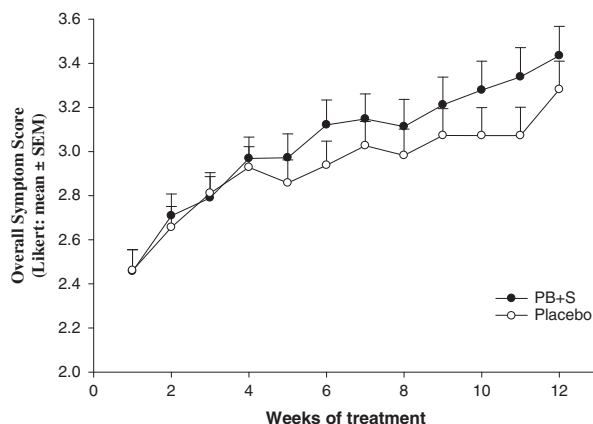


FIGURE 2. Overall irritable bowel syndrome symptom assessment by the patients. Values represent the mean overall improvement scores graded weekly by the patients using a Likert Scale. The total effect size reported as Cohen *d* was 20% between the treatment groups ($P=0.13$). Data are expressed as mean \pm SEM. V0=baseline visit, V1=4 weeks of treatment, V2=8 weeks of treatment, and V3=12 weeks. PB+S indicates pinaverium bromide 100 mg plus simethicone 300 mg.

(Fig. 3A), and with regard to the severity of bloating ($P=0.02$), with an effect size of 33% (ITT: 32%, PP: 33%) (Fig. 3B).

Physician assessment. Abdominal pain showed the highest difference between PB+S and placebo ($P=0.009$), with an effect size of 36% favoring PB+S (ITT: 36%, PP: 36%) (Fig. 4A). As for bloating severity, the results were not significant ($P=0.09$), with a marginal total effect size of 26% (PP: 26%, ITT: 26%) (Fig. 4B).

Stool Consistency

Frequency distribution. Patients with IBS-C presented a clear predominance of Bristol types 1 and 2 at baseline (Figs. 5A, B). During the first 4 weeks of treatment, a shift to the right, toward type 4 was observed, and the peak progressively sharpened in the PB+S group (Fig. 5A). The placebo group showed a less sharpened peak curve, and differences between visits were less noticeable (Fig. 5B). Thus, patients with IBS-C receiving PB+S showed a clear improvement.

In IBS-D, the frequency distribution of the Bristol stool types at baseline was skewed to the right toward types 5 to 7 (Figs. 5D, E). Once the treatment started, the curves were displaced toward the left, showing a Bristol stool type centered over type 4 from week 8 onwards (Fig. 5E). It is worth mentioning that, despite the shift to the left, some subjects with Bristol types 6 and 7 remained as such, but with a lower frequency than at baseline. Both treatment groups showed a similar behavior; notwithstanding, the decrease in the

TABLE 2. Reasons For Patients' Premature Withdrawal From the Study

Causes	PB+S (n, Event)	Placebo (n, Event)	Total (n)
AEs	None	1, lower limb paresthesia	1
SAEs	1, acute pancreatitis plus hypertriglyceridemia	1, brain aneurism	2
Lack of efficacy	None	3, nonperceived efficacy	4
		1, increased abdominal bloating	

AE indicates adverse event; PB+S, pinaverium bromide 100 mg plus simethicone 300 mg; SAE, serious adverse event.

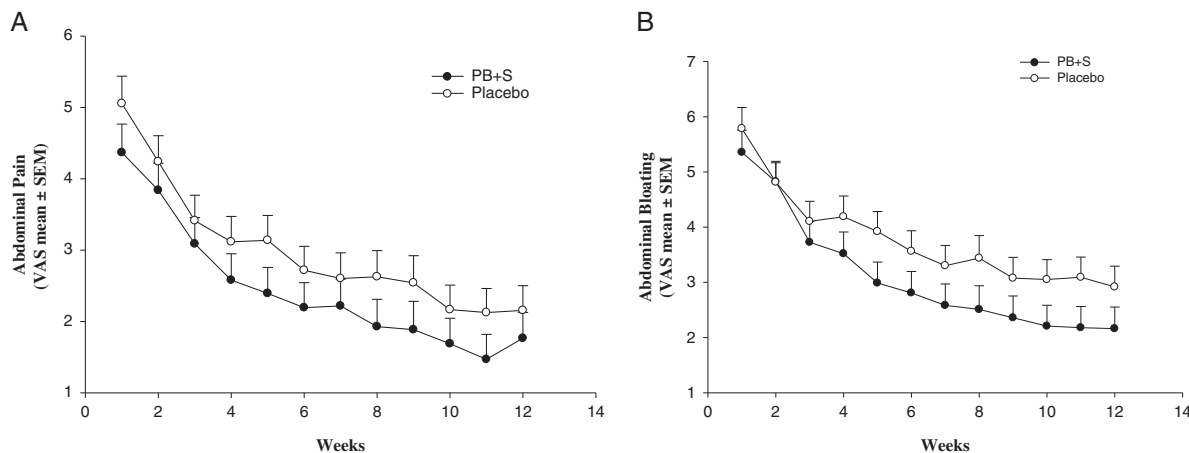


FIGURE 3. Severity of abdominal pain and bloating assessed by the patients. Numbers represent the mean values of abdominal pain (A) and bloating (B) severity graded weekly by the patients with a 10-cm VAS. The total effect size reported as Cohen *d* was 31% for pain ($P=0.038$) and 33% for bloating ($P=0.019$), both favoring PB+S over placebo. Data are expressed as mean ± SEM. V0 = baseline visit, V1 = 4 weeks of treatment, V2 = 8 weeks of treatment, and V3 = 12 weeks. PB+S indicates pinaverium bromide 100 mg plus simethicone 300 mg; VAS, Visual Analogue Scale.

frequency for the remnant Bristol types 6 and 7 was slightly larger with PB+S (Fig. 5D).

Patients with IBS-M showed a trimodal baseline curve, with 1 peak on types 1 and 2, the second peak on types 3 to 5, and a third one (the most frequent) on types 6 and 7 (Fig. 5G). The frequency curves shifted rapidly toward the center for both treatment groups (Figs. 5G, H); however, the PB+S group remained with significantly greater dispersion than the placebo group at the end of the treatment period.

Relative changes. In the IBS-C group, there was a decrease of at least 20% in Bristol 1 to 3 segments of the AUC and a significant increase of Bristol 5 to 7 segments in favor of PB+S (Fig. 5C). In the IBS-D, there was a decrease in the Bristol 1 to 3 segments in favor of placebo (Fig. 5F), whereas in IBS-M, there was a slight increase in Bristol 5 to 7 segments of the AUC, favoring PB+S (Fig. 5I).

IBS-QOL

All subscales and the OV score of the IBS-QOL improved significantly in both treatment groups without any significant difference between them (Table 3).

Safety Evaluation

Only 3.6% of the total sample (11/300) reported ≥ 1 AEs, 3.3% (5/150) in the PB+S group and 4% (6/150) in the placebo group. At least 1 non-SAE was reported by 5 patients in the PB+S group and by 6 patients in the placebo group. Only 2 patients experienced SAEs, corresponding to 1 patient in each treatment group (a case of acute pancreatitis in the active group and a brain aneurism in the placebo group); both withdrew from the study prematurely for these reasons (Table 2). They represented 0.6% (1/150) of each group. The case of acute pancreatitis was not considered to be related to the study medication.

DISCUSSION

This study demonstrates for the first time in a controlled trial in IBS-Rome III, the efficacy of the combination of PB+S over placebo in the treatment of abdominal pain and bloating assessed by the patients. Although there were no differences between PB+S and placebo on the overall symptom improvement of IBS, the primary outcome

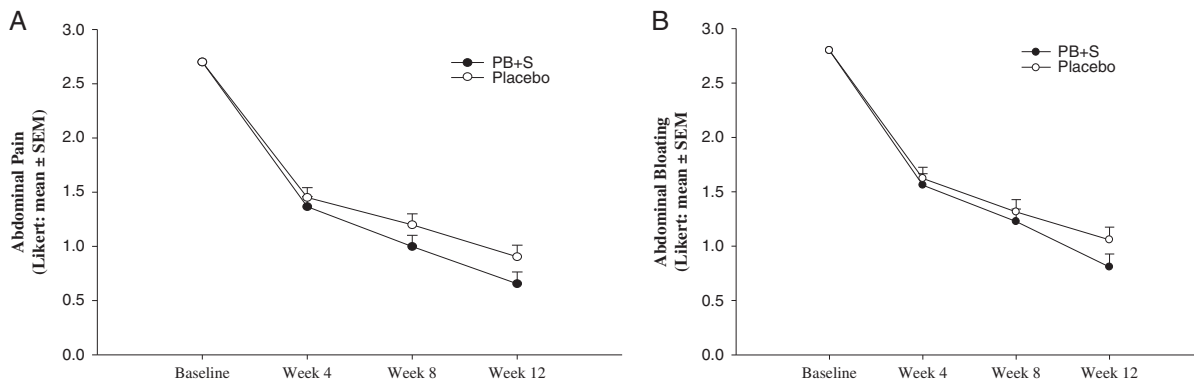


FIGURE 4. Severity of abdominal pain and bloating assessed by the physicians. Numbers represent the mean values of abdominal pain (A) and bloating (B) severity assessed by the physicians using 5-point Likert Scales. The baseline adjusted score (analysis of covariance) was 2.8. The total effect size was 36% for pain ($P < 0.009$) and 26% for bloating ($P < 0.09$), both favoring PB+S over placebo. Data are expressed as mean ± SEM. V0 = baseline visit, V1 = 4 weeks of treatment, V2 = 8 weeks of treatment, and V3 = 12 weeks. PB+S indicates pinaverium bromide 100 mg plus simethicone 300 mg.

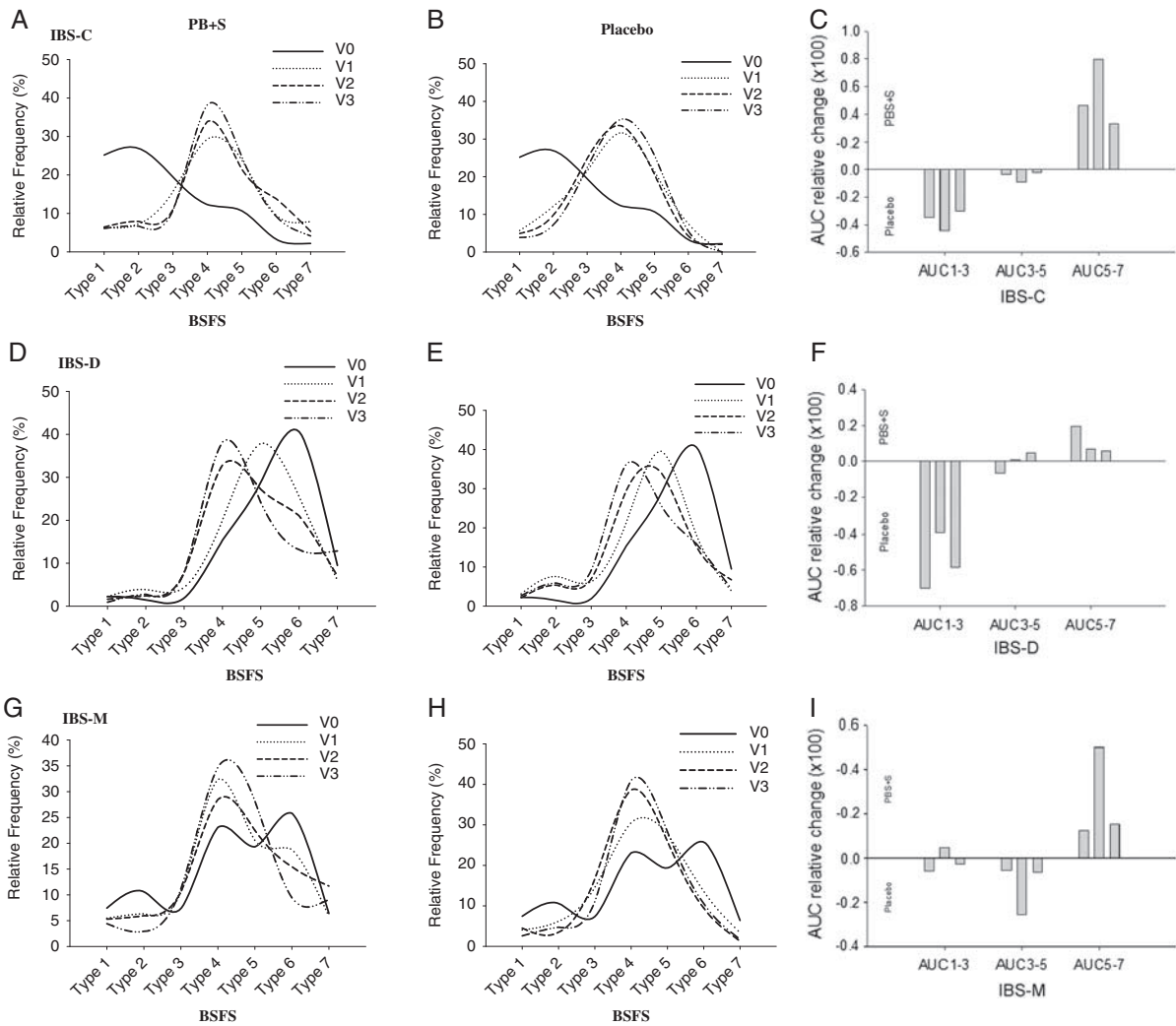


FIGURE 5. Frequency distribution of the BSFS stool types according to IBS subtypes and treatment groups. The density function of probability for each IBS subtype and changes by visits (from A, B, D, E, G, and H) are shown with solid black lines (baseline). Relative differences between placebo and PB+S can be seen on the right side bar figures [IBS-C (C); IBS-D (F); IBS-M (I)]. The clusters of 3 bars represent V1 to V3 for each segment of the AUC. A change of 0.2 at the “y” axis represents at least 20% change. The positive values (upper directions of the bars) are in favor of PB+S treatment, and the negative values (lower directions of the bars) represent an incremental AUC in favor of placebo. These changes must be compared with the left figures (A, B, D, E, G, and H) to understand the dynamics of the AUC functions. AUC indicates area under the curve; BSFS, Bristol Stool Form Scale; IBS, irritable bowel syndrome; IBS-C, irritable bowel syndrome with constipation; IBS-D, irritable bowel syndrome with diarrhea; IBS-M, mixed-type irritable bowel syndrome; PB+S, pinaverium bromide 100 mg plus simethicone 300 mg.

measure of this trial, using the frequency distribution of Bristol stool types (consistency), PB+S produced a shift toward Bristol stool types 3 to 5, mainly in the IBS-C and IBS-M patients. Finally, there were no differences in the IBS-QOL scores between the groups, and PB+S was safe and well-tolerated.

Because of the high response to placebo in previous IBS clinical trials, which has been reported in 37.5% (95% CI: 34.4, 40.6),³⁹ we carried out the present study analyzing several clinical outcomes addressed to evaluate the response to a combined treatment, PB+S. Among the different outcomes that we analyzed, there were scales that were assessed by the patients using diaries to evaluate any changes in the day before and scales that were assessed by the physician-investigators while interviewing the patients. Although there was no difference in the overall symptom improvement, the main outcome

measure, it is interesting that PB+S was effective on the severity of individual symptoms such as abdominal pain and bloating. The effect size for the severity of abdominal pain reached 31% when evaluated by the patients, which is slightly higher than that reported in other clinical trials in IBS,⁴⁰ and 36% when assessed by physician-investigators with similar figures for bloating, independently of the IBS subtype. These results support the current trend in clinical trials on IBS, for using more objective scales to assess specific symptoms such as abdominal pain, bloating, and stool consistency, as overall outcome measures may be too subjective.^{41–43}

The effect size of different monotherapies compared with placebo in different diseases has been previously analyzed in several meta-analyses. Achievement of effect sizes > 30% are of relevance particularly for treatments addressing functional gastrointestinal disorders, wherein a significant improvement

TABLE 3. IBS-QOL Subscale Score Values at Basal and Final Visits Using a Multivariate Approach

IBS-QOL Domains	Basal Evaluation [Mean (SE)]			Final Evaluation [Mean (SE)]		
	PB+S	Placebo	P*	PB+S	Placebo	P*
DY	62.94 (2.09)	62.81 (2.11)	0.966	85.3 (2.1)	83.2 (2.1)	0.179
IN	62.71 (1.97)	62.36 (2.00)	0.901	82.4 (2.2)	79.8 (2.1)	0.214
BI	52.01 (1.93)	54.73 (1.98)	0.327	80.0 (2.6)	76.8 (2.6)	0.179
HW	44.68 (2.14)	47.72 (2.15)	0.319	75.9 (2.9)	74.1 (2.8)	0.500
FA	42.12 (2.43)	42.38 (2.24)	0.938	63.1 (2.9)	62.5 (2.9)	0.848
SR	69.19 (2.26)	68.84 (2.08)	0.910	85.6 (2.3)	83.9 (2.2)	0.391
SX	76.67 (2.44)	76.66 (2.14)	0.996	90.6 (2.0)	88.7 (1.9)	0.279
RL	71.52 (2.32)	71.35 (2.02)	0.956	86.9 (2.1)	85.5 (2.0)	0.413
OV	60.56 (1.82)	61.01 (1.79)	0.859	81.7 (2.0)	79.7 (1.9)	0.270

All patients in the study improved remarkably in their quality of life scores in all domains of the IBS-QOL questionnaire; no significant differences were observed between treatments.

*Between treatment groups.

BI indicates body image; DY, dysphoria; FA, food avoidance; HW, health worry; IBS-QOL, Irritable Bowel Syndrome Quality of Life; IN, interference with activity; OV, overall; PB+S, pinaverium bromide 100 mg plus simethicone 300 mg; RL, relationships; SR, social reaction; SX, sexual.

attributable to placebo can be expected.^{44,45} Some meta-analyses on IBS have included a wide variety of antispasmodics using ORs as a measurement of differences. However, the effect index of such data can be transformed into Cohen *d* for comparison with our current data.^{38,46,47} Accordingly, fiber and tegaserod have previously shown effect sizes of around 19%. Other commonly used treatments, such as antispasmodics, have shown effect sizes ranging between 28 and 35%, whereas antidepressants reach effect sizes of around 35%.^{48,49}

The significant effect on bloating with PB+S independently of the bowel habit subtype shown in the present study, is an important one, as few treatments have proven to be effective on this common symptom,⁵⁰ and all of them including newer treatments are effective on specific IBS subtypes such as linaclotide in IBS-C.^{51,52} The improvement of bloating may have been exerted by the additional effect of the antifoaming S with the smooth muscle relaxant properties of PB. In fact, a systematic review and meta-analysis of antispasmodics available in Mexico reported that only the PB+S combination was effective on bloating.⁵³ Further, PB+S also improved abdominal pain in the current study. In earlier preclinical studies, intragastric administration of PB in rats decreased the abdominal cramps in response to distensions of the proximal colon, supporting its effect on visceral pain. Thus, it is plausible to believe that the combination of PB with S helps in relieving both symptoms. This is not the first trial using combination therapy for IBS, and our results are in agreement with those of an on-demand trial using alverine citrate also combined with simethicone, showing similar effects on bloating and abdominal pain.⁵⁴

The effect of PB+S in the higher frequency of Bristol stool types 3 to 5, mainly in the IBS-C and IBS-M patients, which was observed in the present study, is another important finding. One may speculate that the high dose (300 mg) of S used in the current trial helps patients to increase the frequency of bowel movements by dissolving the gas bubbles, thus facilitating bowel movements. The density function of stool types, which are shown for weekly probabilities used in the current trial (Fig. 5), may be useful for simulation analysis, as each IBS subtype shows a different pattern of response to active treatment and placebo when Bristol stool types are used. This density function allows dynamic changes expressed as an increase in relative

frequency toward the center of the curve to be observed while treatment time is passing. It is clear that important changes occur in short periods of time, even days, for all IBS subtypes, and then they stabilize around Bristol types 3 to 5.

The fact that we included patients within the age range of 18 years or above and 50 years or below is a limitation, as the efficacy of the PB+S cannot be extrapolated to IBS patients older than 50 years of age. However, in a previous multicenter epidemiological study conducted in Mexico in the same clinics from which the patients for the current study were enrolled, we found a mean age of the IBS-Rome III patients to be at 36.9 ± 8.8 years old.⁵⁵ Moreover, the proportion of men with colorectal cancer increases dramatically from the age of 50 years old and on, and roughly, 90% of colon cancer occurs in people older than this age despite their ethnic origin.^{56–58} Furthermore, although patients with alarm symptoms, known organic diagnoses, or malignancy were excluded from the current trial, endoscopic examination (either upper endoscopy and/or colonoscopy) was optional at the investigator’s discretion. Therefore, using the inclusion criteria of individuals below the cutoff age of 50 years, reasonably avoided any risk of confounders associated with age in the studied sample.

In conclusion, the combined therapy that includes PB +S has proven to be effective for the treatment of IBS. This study supports the concept that a treatment combination is a convenient approach for the treatment of IBS. Future analyses in clinical trials should include these kinds of methodologies for efficacy toward understanding the mechanism of improvement according to the IBS subtypes.

REFERENCES

1. Longstreth GF, Thompson WG, Chey WD, et al. Functional bowel disorders. *Gastroenterology*. 2006;130:1480–1491.
2. Drossman DA. Functional Gastrointestinal Disorders: History, Pathophysiology, Clinical Features and Rome IV. *Gastroenterology*. 2016;150:1262–1279.
3. Moayyedi P, Mearin F, Azpiroz F, et al. Irritable bowel syndrome diagnosis and management: A simplified algorithm for clinical practice. *United European Gastroenterol J*. 2017;5: 773–788.
4. Lovell RM, Ford AC. Global prevalence of and risk factors for irritable bowel syndrome: a meta-analysis. *Clin Gastroenterol Hepatol*. 2012;10:712.e4–721.e4.

5. Sperber AD, Dumitrascu D, Fukudo S, et al. The global prevalence of IBS in adults remains elusive due to the heterogeneity of studies: a Rome Foundation working team literature review. *Gut*. 2017;66:1075–1082.
6. López-Colombo A, Bravo-González D, Corona-López A, et al. First community-based study of functional gastrointestinal disorders (FGID) in Mexico using the Modular Rome II Questionnaire. *Gastroenterology*. 2006;130 (suppl 2):A508.
7. Valerio-Ureña J, Vásquez-Fernández F, Jiménez-Pineda A, et al. Prevalence of irritable bowel syndrome in Veracruz City, Mexico: a community-based survey. *Rev Gastroenterol Mex*. 2010;75:36–41.
8. Schmulson M, Lopez-Colombo A, Mendoza-Gomez A, et al. The Rome III Adult Questionnaire in Spanish-Mexico has a low sensitivity for identifying IBS and higher sensitivity for uninvestigated dyspepsia. *Gastroenterology*. 2012;142 (suppl 1):S829.
9. Agarwal N, Spiegel BM. The effect of irritable bowel syndrome on health-related quality of life and healthcare expenditures. *Gastroenterol Clin North Am*. 2011;40:11–19.
10. Spiegel B, Harris L, Lucak S, et al. Developing valid and reliable health utilities in irritable bowel syndrome: results from the IBS PROOF Cohort. *Am J Gastroenterol*. 2009;104:1984–1991.
11. Chang FY. Irritable bowel syndrome: the evolution of multidimensional looking and multidisciplinary treatments. *World J Gastroenterol*. 2014;20:2499–2514.
12. Mulak A, Bonaz B. Irritable bowel syndrome: a model of the brain-gut interactions. *Med Sci Monit*. 2004;10:RA55–RA62.
13. Camilleri M, Talley NJ. Pathophysiology as a basis for understanding symptom complexes and therapeutic targets. *Neurogastroenterol Motil*. 2004;16:135–142.
14. Rodríguez-Fandiño O, Hernández-Ruiz J, Schmulson M. From cytokines to toll-like receptors and beyond—current knowledge and future research needs in irritable bowel syndrome. *J Neurogastroenterol Motil*. 2010;16:363–373.
15. Nicandro JP, Shin P, Chuang E. Evaluation of treatment continuation with alosetron by IBS-D severity criteria. *Curr Med Res Opin*. 2012;28:449–456.
16. Wood P. Tegaserod in the treatment of constipation-predominant irritable bowel syndrome. Do the risks outweigh the benefits? *Naunyn Schmiedebergs Arch Pharmacol*. 2012;385:1–3.
17. Choi CH, Kwon JG, Kim SK, et al. Efficacy of combination therapy with probiotics and mosapride in patients with IBS without diarrhea: a randomized, double-blind, placebo-controlled, multicenter, phase II trial. *Neurogastroenterol Motil*. 2015;27:705–716.
18. Wittmann T, Paradowsk L, Ducrotté P, et al. Clinical trial: the efficacy of alverine citrate/simethicone combination on abdominal pain/discomfort in irritable bowel syndrome—a randomized, double-blind, placebo-controlled study. *Aliment Pharmacol Ther*. 2010;31:615–624.
19. Ducrotté P, Grumaud JC, Dapoigny M, et al. On-demand treatment with alverine citrate/simethicone compared with standard treatments for irritable bowel syndrome: results of a randomized pragmatic study. *Int J Clin Pract*. 2012;68:245–254.
20. Boyer JC, Magous R, Christen MO, et al. Contraction of human circular smooth muscle cells is inhibited by the calcium channel blocker pinaverium bromide. *Cell Calcium*. 2001;29:429–438.
21. Morel N, Buryi V, Feron O, et al. The action of calcium channel blockers on recombinant L-type calcium channel α 1-subunits. *Br J Pharmacol*. 1998;125:1005–1012.
22. Malysz J, Faraway LA, Christen MO, et al. Pinaverium acts as L-type calcium channel blocker on smooth muscle of colon. *Can J Physiol Pharmacol*. 1997;75:969–975.
23. Feron O, Wibo M, Christen MO, et al. Interaction of pinaverium (a quaternary ammonium compound) with 1, 4-dihydropyridine binding sites in rat ileum smooth muscle. *Br J Pharmacol*. 1992;105:480–484.
24. Christen MO, Tassignon JP. Pinaverium bromide: a calcium channel blocker acting selectively on the gastrointestinal tract. *Drug Dev Res*. 1989;18:101–112.
25. Brecevic L, Bosnan-Kilibarda I, Strajnar F. Mechanism of antifoaming action of simethicone. *J Appl Toxicol*. 1994;14:207–211.
26. Park JJ, Lee SK, Jang JY, et al. The effectiveness of simethicone in improving visibility during colonoscopy. *Hepato-gastroenterology*. 2009;56:1321–1325.
27. Wu L, Cao Y, Liao C, et al. Systematic review and meta-analysis of randomized controlled trials of simethicone for gastrointestinal endoscopic visibility. *Scand J Gastroenterol*. 2011;46:227–235.
28. Darlington HF. Treatment of the constipation-gas syndrome in geriatric patients: use of a magnesium hydroxide-simethicone emulsion. *J Am Geriatr Soc*. 1964;12:503–507.
29. Carless JE, Stenlake JB, Williams WD. The effect of particulate dispersing agents on the antifoaming properties of dimethicone 1000 in antiflatulent products. *J Pharm Pharmacol*. 1973;25:849–853.
30. Bernstein JE, Kasich AM. A double-blind trial of simethicone in functional disease of the upper gastrointestinal tract. *J Clin Pharmacol*. 1974;14:617–623.
31. Hanahuer SB, DuPont HL, Cooper KM, et al. Randomized, double-blind, placebo-controlled clinical trial of loperamide plus simethicone vs loperamide alone and simethicone alone in the treatment of acute diarrhea with gas-related abdominal discomfort. *Curr Med Res Opin*. 2007;23:1033–1043.
32. Kaplan MA, Prior MJ, Ash RR, et al. Loperamide-simethicone vs loperamide alone, simethicone alone, and placebo in the treatment of acute diarrhea with gas-related abdominal discomfort. A randomized controlled trial. *Arch Fam Med*. 1999;8:243–248.
33. López-Alvarenga JC, Sobrino-Cossío S, Remes-Troche JM, et al. Polar vectors as a method for evaluating the effectiveness of irritable bowel syndrome treatments: an analysis with pinaverium bromide 100 mg plus simethicone 300 mg po bid. *Rev Gastroenterol Mex*. 2013;78:21–27.
34. Camilleri M, Chang L. Challenges to the therapeutic pipeline for irritable bowel syndrome: end points and regulatory hurdles. *Gastroenterology*. 2008;135:1877–1891.
35. Patrick DL, Drossman DA, Frederick IO, et al. Quality of life in persons with irritable bowel syndrome: development and validation of a new measure. *Dig Dis Sci*. 1998;43:400–411.
36. Schmulson M, Ortiz O, Mejia-Arangure JM, et al. Further validation of the IBS-QOL: female Mexican IBS patients have poorer quality of life than females from North Carolina. *Dig Dis Sci*. 2007;52:2950–2955.
37. Degroot M. *Probability and Statistics*, 4th ed. Reading, MA: Addison-Wesley; 2012:225–234.
38. Cohen J. *Statistical Power Analysis for Behavioural Sciences*, 2nd edition. Hillsdale, NJ: Lawrence Erlbaum Associates Publishers; 1988:273–406.
39. Ford AC, Moayyedi P. Meta-analysis: factors affecting placebo response rate in the irritable bowel syndrome. *Aliment Pharmacol Ther*. 2010;32:144–158.
40. Evans BW, Clark WK, Moore DJ, et al. Tegaserod for the treatment of irritable bowel syndrome. *Cochrane Database Syst Rev*. 2004;1:CD003960.
41. Spiegel B, Bolus R, Harris LA, et al. Measuring irritable bowel syndrome patient-reported outcomes with an abdominal pain numeric rating scale. *Aliment Pharmacol Ther*. 2009;30:1159–1170.
42. Corsetti M, Tack J. FDA and EMA end points: which outcome end points should we use in clinical trials in patients with irritable bowel syndrome? *Neurogastroenterol Motil*. 2013;25:453–457.
43. Miller LE. Study design considerations for irritable bowel syndrome clinical trials. *Ann Gastroenterol*. 2014;27:338–345.
44. Kaptchuck TJ, Kelley JM, Conboy LA, et al. Components of placebo effect: randomized controlled trial in patients with irritable bowel syndrome. *Br Med J*. 2008;336:999–1003.

45. Duracinsky M, Chassagny O. How can an effective drug to treat irritable bowel syndrome be successfully developed? *Gastroenterol Clin Biol*. 2009;33 (suppl 1):S26–S34.
46. Borenstein M, Hedges LV, Higgins JPT, et al. Part two: 7 converting among effect sizes. In: Borenstein M, ed. *Introduction to Meta-Analysis*. Chichester: John Wiley & Sons, Ltd; 2009:45–49.
47. DeCoster J. Excel spread sheet for conversion from OR to Cohen's d. Available at: www.stat-help.com. Accessed May 2016.
48. Lesbros-Pantoflickova D, Michetti P, Fried M, et al. Meta-analysis: the treatment of irritable bowel syndrome. *Aliment Pharmacol Ther*. 2004;20:1253–1269.
49. Poynard T, Regimbeau C, Benhamou Y. Meta-analysis of smooth muscle relaxants in the treatment of irritable bowel syndrome. *Aliment Pharmacol Ther*. 2001;15:355–361.
50. Schmulson M, Chang L. Review article: the treatment of functional abdominal bloating and distension. *Aliment Pharmacol Ther*. 2011;33:1071–1086.
51. Chey WD, Lembo AJ, Lavins BJ, et al. Linaclotide for irritable bowel syndrome with constipation: a 26-week, randomized, double-blind, placebo-controlled trial to evaluate efficacy and safety. *Am J Gastroenterol*. 2012;107:1702–1712.
52. Quigley EM, Tack J, Chey WD, et al. Randomized clinical trials: linaclotide phase 3 studies in IBS-C—a prespecified further analysis based on European Medicines Agency-specified endpoints. *Aliment Pharmacol Ther*. 2013;37:49–61.
53. Martínez-Vázquez MA, Vázquez-Elizondo G, González-González JA, et al. Effect of antispasmodic agents, alone or in combination, in the treatment of Irritable Bowel Syndrome: systematic review and meta-analysis. *Rev Gastroenterol Mex*. 2012;77:82–90.
54. Ducrotte P, Grimaud JC, Dapoigny M, et al. On-demand treatment with alverine citrate/simethicone compared with standard treatments for irritable bowel syndrome: results of a randomised pragmatic study. *Int J Clin Pract*. 2014;68:245–254.
55. Schmulson M, Vargas JA, López-Colombo A, et al. Prevalence and clinical characteristics of the IBS subtypes according to the Rome III criteria in patients from a clinical, multicentric trial. A report from the Mexican IBS Working Group. *Rev Gastroenterol Mex*. 2010;75:427–438.
56. Kuipers EJ, Grady WM, Lieberman D, et al. Colorectal cancer. *Nat Rev Dis Primers*. 2015;1:15065.
57. Sánchez-Barriga JJ. Mortality trends and risk of dying from colorectal cancer in the seven socioeconomic regions of Mexico, 2000–2012. *Rev Gastroenterol Mex*. 2017;82:217–225.
58. Ulanja MB, Rishi M, Beutler BD, et al. Colon cancer sidedness, presentation, and survival at different stages. *J Oncol*. 2019;2019:4315032.