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Title:

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ORIGINAL ARTICLE

Split-dose administration of a dual-action, low-volume bowel cleanser for colonoscopy: the SEE CLEAR I study

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Background: New bowel cleansers for colonoscopy that lead to improved efficacy, safety, and tolerability are needed.

Objective: This study evaluated a nonphosphate, dual-action, low-volume, orange-flavored preparation containing sodium picosulfate and magnesium citrate (P/MC).

Design: Multicenter, assessor-blinded, randomized, noninferiority study.

Setting: University hospitals, academic medical centers, and private clinics across the United States.

Patients: Adults preparing for colonoscopy.

Interventions: P/MC versus 2 L of polyethylene glycol solution (2L PEG-3350) and two 5-mg bisacodyl tablets.

Main Outcome Measurements: This phase 3 study investigated the efficacy, safety, and tolerability of split-dose administration of P/MC versus day-before dosing of 2L PEG-3350 and two 5-mg bisacodyl tablets (SEE CLEAR I study). Efficacy was evaluated by using the Aronchick and Ottawa scales; noninferiority and superiority analyses were performed. Safety was assessed by monitoring adverse events (AEs). Tolerability was measured via a patient questionnaire.

Results: The intent-to-treat population consisted of 601 patients who self-administered P/MC (n = 304) or 2L PEG-3350 and bisacodyl tablets (n = 297). P/MC was superior to 2L PEG-3350 and bisacodyl tablets in overall colon cleansing (84.2% vs 74.4%; 1-sided 97.5% confidence interval [CI], 3.4) (Aronchick scores of excellent or good) and in cleansing of the ascending (89.5% vs 78.8%; 1-sided 97.5% CI, 4.9), mid (transverse and descending) (92.4% vs 85.9%; 1-sided 97.5% CI, 1.6), and rectosigmoid (92.4% vs 87.2%; 1-sided 97.5% CI, 0.4) segments of the colon (Ottawa scores of excellent, good, or fair). Commonly reported AEs related to the bowel preparations were nausea, vomiting, headache, and chills. Patient-reported tolerability, including ease of consumption and taste, was significantly higher for P/MC than 2L PEG-3350 and bisacodyl tablets ($P < .0001$).

Limitations: Because of differences in administration and volume of the bowel preparations, the study was designed to be a single-assessor, blinded study.

Conclusions: The bowel-cleansing effects and patient acceptability of split-dose P/MC were superior to day-before dosing with 2L PEG-3350 and bisacodyl tablets. (Gastrointest Endosc 2013;■:1-10.)

Abbreviations: AE, adverse event; CI, confidence interval; ECG, electrocardiogram; ITT, intent to treat; P/MC, sodium picosulfate and magnesium citrate; PP, per-protocol; SAE, serious adverse event; TEAE, treatment-emergent adverse event; 2L PEG-3350, 2 L of polyethylene glycol solution.

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(footnotes continued on last page of article)

An ideal bowel preparation is effective, safe, and tolerable. Ineffective preparation results in lower detection rates of polyps^{1,2} and increased costs associated with repeat colonoscopy procedures.³ Safe bowel cleansers are important as evidenced by the recent reduction in the use of phosphate-containing preparations because of a risk of acute kidney damage.⁴ Furthermore, poor tolerability may prevent complete ingestion of the preparation and may hinder a patient's willingness to undergo both screening colonoscopy and repeat procedures.⁵ However, based on currently approved products, no preparation is considered to be superior with regard to efficacy, safety, and tolerability.

A nonphosphate, dual-action, low-volume, naturally orange-flavored preparation containing sodium picosulfate and magnesium citrate (P/MC) (Prepopik; Ferring Pharmaceuticals, Inc, Parsippany, NJ) was recently approved in the United States for bowel preparation before colonoscopy (based on the SEE CLEAR I and II studies [Safety and Efficacy of a Dual-Action, Low-Volume Preparation: An Evaluation of Colon Cleansing in Day Before and Split-Dose Regimens]). P/MC includes a stimulant prodrug (sodium picosulfate) with a well-established osmotic laxative (magnesium citrate). The combined effect stimulates peristalsis and draws water into the lumen, creating a softer stool and a "wash-out" effect.⁶ The bowel-cleansing effects of the combination of ingredients in P/MC have been demonstrated in clinical practice for more than 3 decades outside the United States⁷⁻¹⁰ with more than 28 million exposures worldwide.

Results from the SEE CLEAR II study demonstrating the noninferiority of day-before P/MC dosing compared with day-before 2 L of polyethylene glycol solution (2L PEG-3350) dosing were recently published.¹¹ This report summarizes the results from the SEE CLEAR I study, a phase 3, randomized, multicenter, assessor-blinded, noninferiority, head-to-head study that evaluated the efficacy, safety, and tolerability of a split-dose administration of P/MC versus a previously approved day-before dosing regimen of 2L PEG-3350 and two 5-mg bisacodyl tablets (Half-Lytely and Bisacodyl Tablets Bowel Prep Kit; Braintree Laboratories, Inc, Braintree, Mass). During the study, bisacodyl was administered as two 5-mg tablets, which is twice the dose strength of the currently marketed product (ie, one 5-mg bisacodyl tablet). Two 5-mg bisacodyl tablets was the approved dose in the bowel prep kit at the time of study initiation.

METHODS

Patients

Individuals eligible for inclusion in the study were men and women aged 18 to 80 years with at least 3 spontaneous bowel movements per week for 1 month before a scheduled elective outpatient colonoscopy. Patients with acute

Take-home Message

- Split-dose administration of a low-volume, dual-action bowel preparation containing sodium picosulfate and magnesium citrate provides superior colon cleansing with greater patient tolerability and equivalent short-term safety compared with 2 L of polyethylene glycol 3350 solution and bisacodyl tablets.

surgical abdominal conditions; active inflammatory bowel disease; colon disease including toxic megacolon, toxic colitis, idiopathic pseudo-obstruction, and hypomotility syndrome; ascites; GI disorders such as active ulcers, gastric outlet obstruction, retention, gastroparesis, and ileus; uncontrolled angina and/or myocardial infarction within the past 3 months; congestive heart failure or uncontrolled hypertension; or patients with known renal insufficiency who had abnormal creatinine or serum potassium levels at screening were excluded from the study. A history of colorectal surgery (excluding appendectomy, hemorrhoid surgery, or previous endoscopic procedures) or upper GI surgery (including gastric resection, banding, or bypass) also precluded patients from entering the study. Concomitant use of lithium, laxatives, constipating drugs, antidiarrheal agents, or oral iron preparations was not permitted in the study, and their use must have been suspended before administration of the bowel preparation.

Study design and treatment

This was a phase 3, randomized, multicenter, assessor-blinded, active-control, noninferiority study in adult patients preparing for colonoscopy. Patients were randomly assigned to 1 of 2 fixed-dose treatment arms, either split-dose P/MC or day-before 2L PEG-3350 and bisacodyl tablets. Randomization numbers were allocated sequentially by an interactive voice response system; study participants were assigned numbers in the order in which they were enrolled. Randomization assignment for each patient was known only to a prespecified unblinded coordinator and the patient. Both the patient and unblinded coordinator were instructed not to disclose the bowel preparation to which the patient had been assigned. The gastroenterologist who performed the colonoscopy and assessed the efficacy of the bowel preparation and all assistants were blinded to the study drug. After colonoscopy, patients were monitored at 24- to 48-hour, 7-day, and 4-week follow-up visits.

The exact hour of bowel preparation administration for both treatment arms was given at the direction of the unblinded coordinator according to the scheduled time for the colonoscopy. To mimic the naturalistic setting of clinical practice, scheduling of the colonoscopy was determined independently by each study site according to their usual scheduling practices. Patients received written instructions on when to begin self-administration of their

assigned study drug; patients were not provided instructions or information regarding the timing, volume, or taste of the study drug assigned to patients in the other treatment arm. Beginning 24 hours before the procedure, all patients were limited to a clear liquid diet. Patients receiving split-dose P/MC were instructed to reconstitute the first of 2 packets in 5 oz of water and drink the contents between 5:00 PM and 9:00 PM the evening before the colonoscopy. This was to be followed by drinking five 8-oz glasses of clear liquids of their choice over the next several hours, without forced-time drinking requirements. On the day of colonoscopy, at least 5 hours but not more than 9 hours before the procedure, the second packet was to be mixed in 5 oz of water and consumed followed by three 8-oz glasses of clear liquids. Patients randomized to receive day-before 2L PEG-3350 were instructed to begin treatment by ingesting two 5-mg bisacodyl tablets in the afternoon on the day before colonoscopy. Then, after the first bowel movement or 6 hours after taking the bisacodyl tablets, whichever occurred first, patients were instructed to drink the 2L PEG-3350 solution at a rate of one 8-oz glass every 10 minutes as required by the product labeling; patients were given an option to either flavor the PEG-3350 solution with a lemon-lime flavor packet or leave the PEG-3350 solution unflavored. Diary cards were used by patients to record whether all of the bowel preparation was ingested within the specified time period and whether the correct number of glasses of clear liquids was consumed.

The study, registered at ClinicalTrials.gov under the identifier NCT01073930, was conducted at 10 clinical sites directed by a board-certified gastroenterologist in the United States between May 2010 and October 2010; 52 colonoscopists who were board certified or under the supervision of the board-certified director participated in the study. The study received institutional review board approval at each site and was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice, and applicable regulatory requirements. All patients provided written informed consent.

Assessments

Overall colon cleansing was rated by using a modified version of the Aronchick scale, a validated graded assessment describing the visual appearance of the colon.¹² The scale was the primary efficacy variable for the study. Endoscopists, blinded to the bowel preparation used by patients, rated the cleanliness of the colon as follows: excellent (>90% of mucosa seen, mostly liquid stool, minimal suctioning needed for adequate visualization), good (>90% of mucosa seen, mostly liquid stool, significant suctioning needed for adequate visualization), fair (>90% of mucosa seen, mixture of liquid and semisolid stool, could be suctioned and/or washed), or inadequate (<90% of mucosa seen, mixture of semisolid and solid stool that could not be suctioned or washed).

Cleansing of the colon was considered successful after administration of the bowel preparation if the rating was excellent or good on a 4-point scale.

Efficacy was also evaluated by using the validated Ottawa scale¹³ as a secondary endpoint. The quality of cleansing of the ascending, mid (transverse and descending), and rectosigmoid segments of the colon was rated by endoscopists as follows: excellent: 0 (mucosal detail clearly visible; if fluid is present, it is clear; almost no stool residue), good: 1 (some turbid fluid or stool residue but mucosal detail still visible; washing and suctioning not necessary), fair: 2 (turbid fluid or stool residue obscuring mucosal detail; however, mucosal detail becomes visible with suctioning; washing not necessary), poor: 3 (presence of stool obscuring mucosal detail and contour; however, with suctioning and washing, a reasonable view is obtained), or inadequate: 4 (solid stool obscuring mucosal detail and contour despite aggressive washing and suctioning). Colon cleansing for a patient was considered successful after administration of the bowel preparation if the colon segment was scored excellent, good, or fair. If the endoscopist was unable to reach the colon segment because of poor quality of bowel preparation, the segment was automatically scored as inadequate. The endoscopist also rated the overall fluid amount on a 3-point scale (0, small; 1, medium; or 2, large). This fluid assessment score was then added to the scores obtained for each colon segment to derive a cumulative Ottawa scale score ranging from 0 (best) to 14 (worst).

Endoscopists were trained in the use of the scales during a face-to-face training session held before patient enrollment and had access to poster-sized images with standard examples of ratings for reference.

Patients were also required to complete a questionnaire to assess their acceptability and tolerability of the bowel preparation before any preliminary sedation for colonoscopy. The items read as follows: (1) "How easy or difficult was it to consume the study drug?" (2) "Were you able to consume the entire prep as instructed?" (3) "Please describe your overall experience with the bowel preparation." (4) "The taste of this bowel preparation was. . . ." (5) "Would you ask your doctor for this preparation again if you needed another colonoscopy in the future?" (6) "Would you refuse the same preparation again if it were to be prescribed to you in the future?" and (7) "Have you had a colonoscopy before (within the past 3 years)?" Patient responses to the questionnaire consisted of either yes or no answers (items 2, 5, 6, and 7) or ordinal scale answers (very easy, easy, tolerable, difficult, or very difficult [item 1] and excellent, good, fair, poor, or bad [items 3 and 4]).

Safety was assessed by the incidence of adverse events (AEs), findings on physical examinations, orthostatic vital sign measurements, laboratory test results (hematology, coagulation, blood chemistry, and urinalysis), and 12-lead electrocardiograms (ECGs). Data on AEs were collected

throughout the study by a patient's responses to questions about his or her health, spontaneous reports, and clinically relevant changes and abnormalities observed by the investigator. These AEs were coded by using version 13.0 of the Medical Dictionary for Regulatory Activities. The severity and causal relationship of AEs to the bowel preparation were assessed by the investigator based on clinical judgment. AEs were recorded from the time of the procedure until the patient completed the study. A complete physical examination was conducted at screening, and a directed physical examination was performed at all subsequent study visits. Orthostatic vital sign measurements were collected at all study visits. Laboratory tests and electrocardiography were performed at all study visits with the exception of the randomization visit. A patient's complete medical history was obtained at screening, and concomitant medication use was reported at multiple study visits.

Statistical analysis

Assuming an estimated successful cleansing rate of 85% for the treatment arms, a 9.0% noninferiority margin, and a 1-sided significance level of 0.025 powered at 85%, it was determined that 287 patients were necessary for each treatment arm. The safety population, by definition, included all randomized patients who received treatment. The intent-to-treat (ITT) population included all randomized patients who received treatment and produced efficacy assessments for the Aronchick and/or Ottawa scales. Patients who met the criteria for the ITT population and did not have a protocol deviation during the study were included in the per-protocol (PP) population.

The categorical efficacy endpoints, the Aronchick and Ottawa scales, were summarized by the percentage of patients successfully cleansed for each outcome. Noninferiority was demonstrated for these endpoints if the 1-sided 97.5% confidence interval (CI) for the treatment difference (P/MC minus 2L PEG-3350 and bisacodyl tablets) was greater than -9.0% . If the noninferiority criteria were satisfied, superiority could be demonstrated if the lower bound of the CI for the treatment difference was greater than 0% . A Wilcoxon rank sum test was used to compare the fluid assessment between treatment arms. Results from the patient acceptability and tolerability questionnaire were compared between treatment arms by using a χ^2 test for pooled responses. Unless otherwise noted, efficacy and acceptability/tolerability endpoints were summarized by using the ITT population. Descriptive statistics were used to summarize demographics, AEs, and serious AEs (SAEs) from the safety analysis population.

RESULTS

A total of 608 patients were randomized to receive split-dose P/MC or day-before 2L PEG-3350 and bisacodyl tablets dosing. Five patients were not treated and were excluded

from all analyses. Thus, the safety population consisted of 305 and 298 patients in the P/MC and 2L PEG-3350 and bisacodyl tablets treatment arms, respectively. The majority of patients completed the study; 4 patients discontinued (1 patient in the P/MC arm and 3 patients in the 2L PEG-3350 and bisacodyl tablets arm). One patient in each of the treatment arms failed to have an efficacy assessment performed. Therefore, the ITT population consisted of 304 patients in the P/MC treatment arm and 297 patients in the 2L PEG-3350 and bisacodyl tablets treatment arm. Fifty patients had protocol deviations during the study that led to exclusion from the PP population. For the P/MC arm, protocol deviations excluding patients from the PP population included inclusion/exclusion violations ($n = 18$), exclusionary medications taken ($n = 8$), incomplete efficacy assessments ($n = 2$), and incorrect randomization ($n = 1$). Two patients in the P/MC arm had 2 protocol deviations that led to exclusion (inclusion/exclusion violation and exclusionary medication taken for 1 patient and exclusionary medication and incomplete efficacy assessment for the other patient). For the 2L PEG-3350 and bisacodyl tablets arm, protocol deviations excluding patients from the PP population included inclusion/exclusion violations ($n = 13$), exclusionary medication taken ($n = 7$), incomplete efficacy assessments ($n = 2$), and incorrect randomization ($n = 1$). Violations of inclusion/exclusion criteria in both treatment arms were primarily screening laboratory values outside the normal range. The PP population included 277 patients in the P/MC treatment arm and 274 patients in the 2L PEG-3350 and bisacodyl tablets treatment arm.

Demographics and baseline characteristics were similar among patients, and no significant difference was observed between treatment arms (Table 1). The median age of patients was 55.0 years (range 19 to 80 years), 88.4% were white, and more than half were women (58.9%).

Nearly all of the patients receiving P/MC were able to consume the split-dose of P/MC the day before (100%) and the day of the colonoscopy (99.7%). Complete colonoscopy (ie, cecal intubation) was achieved for the majority of patients (99.3%). The small number of incomplete colonoscopies resulted from the quality of preparation in 1 patient and a structural abnormality that resulted in blocked visualization at the hepatic flexure in 1 patient. Compared with P/MC, 91.4% of patients receiving 2L PEG-3350 and bisacodyl tablets were able to ingest all of the bowel preparation. Complete colonoscopy was achieved for the majority of patients (98.7%). Incomplete colonoscopies in the 2L PEG-3350 and bisacodyl tablets treatment arm resulted from the quality of preparation in 3 patients and a redundant rectosigmoid colon in 1 patient.

Efficacy

A higher proportion of patients in the P/MC treatment arm had overall colon cleansing that was successful per the Aronchick scale (ie, excellent or good), compared with the proportion of patients with successful cleansing

TABLE 1. Demographics and baseline characteristics

Parameter	P/MC (n = 305)	2L PEG-3350 and bisacodyl tablets (n = 298)
Age, y, mean (range)	54.8 (22-77)	55.7 (19-80)
Age range, y, no. (%)		
18-64	253 (83.0)	250 (83.9)
≥ 65	52 (17.0)	48 (16.1)
Sex, no. (%)		
Female	181 (59.3)	174 (58.4)
Male	124 (40.7)	124 (41.6)
Race, no. (%)		
White	265 (86.9)	268 (89.9)
Black/African American	36 (11.8)	27 (9.1)
American Indian/ Alaska Native	1 (0.3)	1 (0.3)
Asian	0	1 (0.3)
Native Hawaiian/ Other Pacific Islander	0	1 (0.3)
Other	3 (1.0)	0
Mean body mass index (range), kg/m ²	29.4 (18.3-49.8)	29.6 (16.6-54.4)

P/MC, sodium picosulfate and magnesium citrate; 2L PEG-3350, polyethylene glycol solution.

in the 2L PEG-3350 and bisacodyl tablets treatment arm (84.2% vs 74.4%) (Table 2). P/MC was noninferior and superior to 2L PEG-3350 and bisacodyl tablets in overall cleansing of the colon for patients in the ITT (Fig. 1 and Table 2) and PP (Table 3) populations. Segmental cleansing was also noninferior and superior in all colonic segments for P/MC compared with 2L PEG-3350 and bisacodyl tablets (Tables 2 and 3 and Fig. 2). The largest segmental difference in the proportion of patients with successful cleansing was in the ascending colon (89.5% vs 78.8% for patients in the P/MC and 2L PEG-3350 and bisacodyl tablets treatment arms, respectively).

There was no significant difference in the quantity of fluid between patients in the treatment arms ($P = .247$). The majority of patients in the P/MC and 2L PEG-3350 and bisacodyl tablet treatment arms had a small or moderate quantity of fluid (93.4% and 93.9%, respectively). The total Ottawa score was significantly lower for patients in the P/MC treatment arm compared with patients in the 2L PEG-3350 and bisacodyl tablets treatment arm (4.6 vs 5.5; $P = .0002$).

Acceptability and tolerability

Overall, the distribution of patient-reported acceptability and tolerability responses was significantly higher for P/MC compared with 2L PEG-3350 and bisacodyl tablets ($P < .0001$). Important differences between the 2 treatment arms are summarized in Figure 3. Briefly, a greater proportion of patients receiving P/MC rated the treatment regimen as very easy or easy to consume (89.4% vs 29.1%) and as having an excellent or good taste (73.9% vs 21.5%) compared with patients in the 2L PEG-3350 and bisacodyl tablets treatment arm. Also, compared with patients receiving 2L PEG-3350 and bisacodyl tablets, patients in the P/MC treatment arm rated the overall treatment experience as excellent or good (92.0% vs 59.5%) and would use the same regimen for a future colonoscopy (96.0% vs 54.7%).

Overall, a greater proportion of patients in the P/MC treatment arm were able to consume the entire preparation as instructed compared with patients receiving 2L PEG-3350 and bisacodyl tablets (99.0% vs 89.9%; $P < .0001$). Compared with patients receiving P/MC, a larger proportion of patients in the 2L PEG-3350 and bisacodyl tablets treatment arm would refuse the preparation if another colonoscopy were needed in the future (1.7% vs 13.5%; $P < .0001$). Only a small percentage of patients receiving P/MC and 2L PEG-3350 and bisacodyl tablets had undergone a colonoscopy within the past 3 years (14.9% vs 19.5%; $P = .0793$).

Safety

The overall incidence of treatment-emergent AEs (TEAEs) was similar between the 2 treatment arms (69.2% for the P/MC group and 72.8% for the 2L PEG-3350 and bisacodyl tablets group). TEAEs considered possibly or probably related to the bowel preparation and reported by more than 1% of patients are summarized in Table 4. The majority of TEAEs reported were of mild or moderate intensity, with 2 patients in the P/MC treatment arm and 6 patients in the 2L PEG-3350 and bisacodyl tablets treatment arm reporting severe TEAEs. One patient in the 2L PEG-3350 and bisacodyl tablets treatment arm reported a severe TEAE of abdominal pain that was considered possibly or probably related to the bowel preparation; all other severe TEAEs were deemed unrelated or unlikely related to the study drug.

No patients receiving P/MC experienced a TEAE that led to discontinuation. Conversely, 2 patients (0.7%) receiving 2L PEG-3350 and bisacodyl tablets discontinued the study because of vomiting and chills or nausea.

The incidence of SAEs experienced during the study was low (<1%). SAEs included acute pancreatitis (1 patient, P/MC), noncardiac chest pain, (1 patient, 2L PEG-3350 and bisacodyl tablets), and, per findings during colonoscopy, colon cancer (1 patient, 2L PEG-3350 and bisacodyl tablets). None of the SAEs were considered related to the bowel preparations. No deaths were reported.

TABLE 2. Efficacy of bowel cleansing in patients undergoing colonoscopy (intent-to-treat population)

Colon segment	Patients successfully cleansed, n (%)		Treatment difference*	1-sided 97.5% CI†
	P/MC (n = 304)	2L PEG-3350 and bisacodyl tablets (n = 297)		
Aronchick scale‡				
Overall	256 (84.2)	221 (74.4)	9.8	3.4
Ottawa scale§				
Ascending	272 (89.5)	234 (78.8)	10.7	4.9
Mid	281 (92.4)	255 (85.9)	6.6	1.6
Rectosigmoid	281 (92.4)	259 (87.2)	5.2	0.4
Overall	264 (86.8)	224 (75.4)	11.4	5.2

CI, Confidence interval; P/MC, sodium picosulfate and magnesium citrate; 2L PEG-3350, polyethylene glycol solution.

*Treatment difference was calculated by subtracting the percentage of patients successfully cleansed in the 2L PEG-3350 and bisacodyl tablets treatment group from the percentage of patients successfully cleansed in the P/MC treatment group.

†Noninferiority was demonstrated if the 1-sided 97.5% CI for the treatment difference was greater than -9.0% ; superiority was achieved if the 1-sided 97.5% CI for the treatment difference was greater than 0% .

‡Patients were considered successfully cleansed after administration of prescribed treatment regimen if overall colon cleansing on the Aronchick scale was rated excellent or good.

§Patients were considered successfully cleansed after administration of prescribed treatment regimen if colon cleansing on the Ottawa Scale was rated excellent, good, or fair.

||Mid colon refers to the transverse and descending segments of the colon.

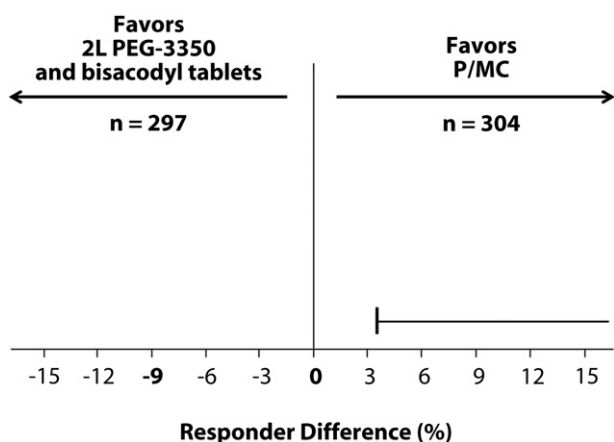


Figure 1. Sodium picosulfate and magnesium citrate (P/MC) is superior to 2 L of polyethylene glycol solution (2L PEG-3350) and bisacodyl tablets in overall cleansing of the colon, as measured by the Aronchick scale (intent-to-treat population). A patient was considered successfully cleansed after administration of the preparation if colon cleansing was rated excellent or good on a 4-point scale. The lower bound of the 1-sided 97.5% confidence interval for the treatment difference between P/MC and 2L PEG-3350 and bisacodyl tablets in overall colon cleansing met the a priori criteria for noninferiority ($> -9.0\%$) and superiority ($> 0\%$); thus, noninferiority and superiority of P/MC were established.

Mean changes from visit to visit in orthostatic vital sign measurements and in hematology, coagulation, blood chemistry, and urinalysis values were generally small and similar between treatment arms. Patients receiving P/MC were more likely to have an increase in magnesium values on the day of colonoscopy compared with patients in the 2L PEG-3350 and bisacodyl tablets treatment arm

(11.3% vs 0%; mean concentration [range], 0.979 [0.70-1.25] mmol/L vs 0.858 [0.60-1.05] mmol/L). Additionally, abnormal urine pH developed in a greater proportion of patients in the P/MC treatment arm compared with patients in the 2L PEG-3350 and bisacodyl tablets treatment arm (23.4% vs 7.6%; mean pH [range], 6.74 [5.5-8.5] vs 6.24 [5.0-8.0]). At the 48-hour follow-up visit, shifts in these parameters were resolved or resolving. The shifts in magnesium values and urine pH were generally comparable between the treatment arms at the 7-day and 28-day follow-up visits and had returned to normal thresholds by the end of the study.

After treatment with either P/MC or 2L PEG-3350 and bisacodyl tablets, no findings noted during physical examinations were considered clinically significant. Data collected from ECGs in patients receiving P/MC and 2L PEG-3350 and bisacodyl tablets were reviewed centrally by experienced cardiologists and indicated no effect on AV conduction or cardiac depolarization, as measured by PR and QRS interval durations, and no significant effect on cardiac repolarization as measured by QTcF.

DISCUSSION

When administered as a split dose, P/MC was superior to day-before dosing with 2L PEG-3350 and bisacodyl tablets in overall cleansing and in cleansing the individual segments, including the ascending colon, as assessed by the Aronchick and Ottawa scales. Split-dose P/MC was better tolerated than day-before 2L PEG-3350 and bisacodyl tablets dosing based on ease of consumption, overall

TABLE 3. Efficacy of bowel cleansing in patients undergoing colonoscopy (per-protocol population)

Colon segment	Patients successfully cleansed, n (%)		Treatment difference*	1-sided 97.5% CI†
	P/MC (n = 277)	2L PEG-3350 and bisacodyl tablets (n = 274)		
Aronchick scale‡				
Overall	235 (84.8)	207 (75.5)	9.3	2.7
Ottawa scale§				
Ascending	250 (90.3)	217 (79.2)	11.1	5.1
Mid¶	257 (92.8)	237 (86.5)	6.3	1.2
Rectosigmoid	256 (92.4)	240 (87.6)	4.8	-0.2
Overall	—	—	—	—

CI, Confidence interval; P/MC, sodium picosulfate and magnesium citrate; 2L PEG-3350, polyethylene glycol solution.

*Treatment difference was calculated by subtracting the percentage of patients successfully cleansed in the 2L PEG-3350 and bisacodyl tablets treatment group from the percentage of patients successfully cleansed in the P/MC treatment group.

†Noninferiority was demonstrated if the 1-sided 97.5% CI for the treatment difference was greater than -9.0%; superiority was achieved if the 1-sided 97.5% CI for the treatment difference was greater than 0%.

‡Patients were considered successfully cleansed after administration of prescribed treatment regimen if overall colon cleansing on the Aronchick scale was rated excellent or good.

§Patients were considered successfully cleansed after administration of prescribed treatment regimen if colon cleansing on the Ottawa scale was rated excellent, good, or fair.

¶Mid colon refers to the transverse and descending segments of the colon.

||Treatment difference and 1-sided 97.5% CI was not calculated overall for the per-protocol population.

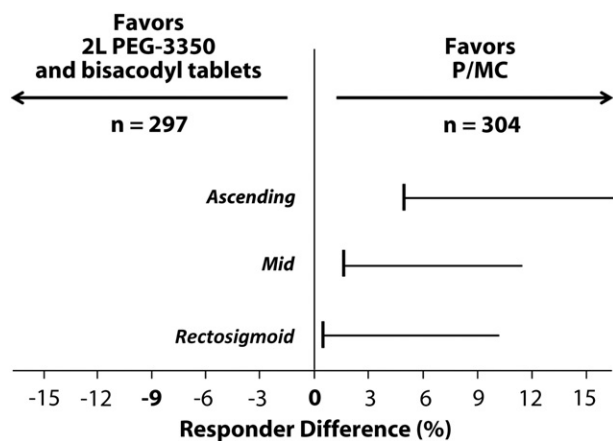


Figure 2. Sodium picosulfate and magnesium citrate (P/MC) is superior to 2 L of polyethylene glycol solution (2L PEG-3350) and bisacodyl tablets in cleansing the ascending, mid (transverse and descending), and rectosigmoid segments of the colon, as measured by the Ottawa scale (intent-to-treat population). A patient was considered successfully cleansed after administration of the preparation if colon cleansing was rated excellent, good, or fair on a 5-point scale. The lower bound of the 1-sided 97.5% confidence interval for the treatment difference between P/MC and 2L PEG-3350 and bisacodyl tablets in the ascending, mid, and rectosigmoid segments of the colon met the a priori criteria for noninferiority ($> -9.0\%$) and superiority ($> 0\%$); thus, noninferiority and superiority of P/MC were established.

experience, taste, and preference to receive the preparation again in the future. Split-dose P/MC was a safe preparation with an incidence of related AEs that was similar to

AEs experienced by patients using day-before 2L PEG-3350 and bisacodyl tablets dosing. During the study, there were no clinically relevant findings on physical examinations, vital sign measurements, laboratory test results, or ECGs after treatment with P/MC. There were shifts in the concentration of magnesium and urine pH observed on the day of colonoscopy, but these were not deemed clinically significant. These biochemical shifts, which returned to the normal range by the end of the study and resolved without sequelae, were likely caused by the magnesium component in the bowel preparation. The results of this study are consistent with the findings of efficacy, safety, and tolerability in the literature for the ingredients of P/MC.⁷⁻¹⁰ Administered in a split-dose or day-before regimen, P/MC is an effective, well-tolerated, and safe bowel preparation for colonoscopy.

Limitations of the study included the exclusion of patients with serious comorbidities, such as renal insufficiency (elevated serum creatinine and potassium values) and cardiovascular concerns (uncontrolled angina and/or myocardial infarction, congestive heart failure, or uncontrolled hypertension), and those younger than 18 years. Additionally, given the differences in administration and volume of the bowel preparations, the study was designed to be a single-assessor, blinded study. Although this may introduce a potential source of bias, the study used commonly accepted measures to ensure that the endoscopists remained blinded to the bowel preparation. It is possible that patients who had undergone previous

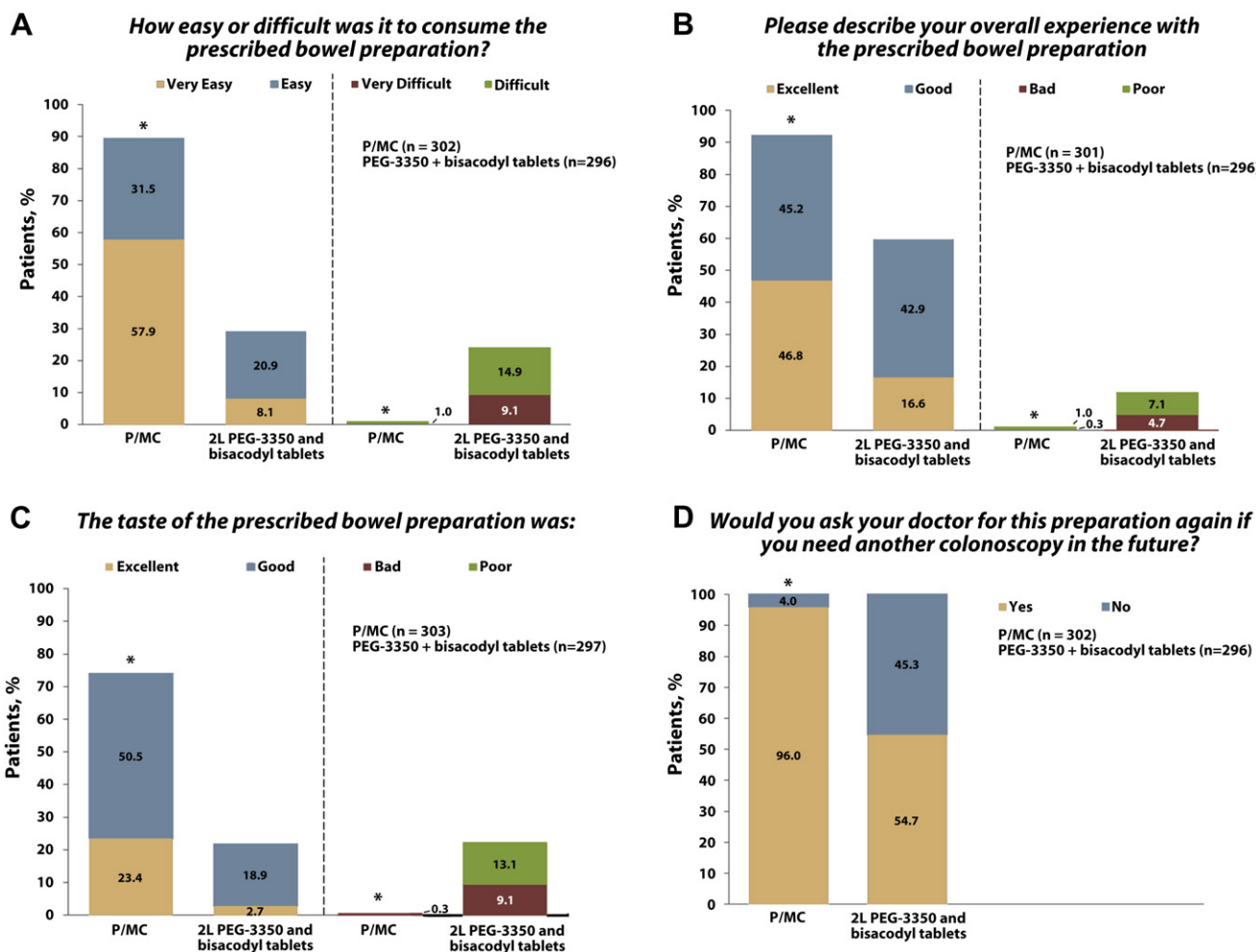


Figure 3. Sodium picosulfate and magnesium citrate (P/MC) was rated, accepted, and tolerated more favorably by patients than was 2 L of polyethylene glycol solution (2L PEG-3350) and bisacodyl tablets (intent-to-treat population). A questionnaire administered before any preliminary sedation for the colonoscopy summarized patients' reactions to the bowel preparation. Highlights from the questionnaire include patients' perspectives on the consumption of the preparation (A), patients' overall experience with the preparation (B), the taste of the preparation (C), and patients' preference on receiving the preparation again in the future (D). * $P < .0001$.

colonoscopy who were randomized to the P/MC treatment arm could have had knowledge of the differences in the timing, volume, and flavor of the 2L PEG-3350 and bisacodyl tablets preparation. The effects of this knowledge, if any, on the patients' experience is unknown. This knowledge may have affected their willingness to complete their preparation, although more patients in the 2L PEG-3350 and bisacodyl tablets treatment arm failed to consume the preparation as instructed than patients in the P/MC treatment arm. At the time of this study, P/MC was not available to patients in the United States; thus, patients receiving 2L PEG-3350 and bisacodyl tablets would not have had knowledge of the differences in the timing, volume, and flavor between the 2 preparations.

In other studies with similar patient populations, day-before 2L PEG-3350 and bisacodyl tablets dosing has demonstrated a wide range of efficacy (56%¹⁴-82%¹⁵ good/excellent cleansing). Superior cleansing of the colon in

this study with split-dose P/MC compared with day-before dosing with 2L PEG-3350 and bisacodyl tablets is most likely the result of split-dose administration. Nonetheless, the overall rate of successful cleansing for split-dose P/MC was greater than that reported for split dosing of a similar PEG-based solution.¹⁶ For this study, it was necessary to administer 2L PEG-3350 and bisacodyl tablets per the approved product label (ie, the preparation was given the evening before colonoscopy). At the time that this study was performed, split-dose regimens were not universally accepted. A day-before regimen of P/MC was determined to be noninferior to day-before dosing of 2L PEG-3350 and bisacodyl tablets (SEE CLEAR II study).¹¹

CONCLUSION

A split-dose regimen of a low-volume bowel preparation composed of sodium picosulfate and magnesium citrate

TABLE 4. Treatment-emergent adverse events (> 1%) possibly or probably related to treatment (safety population)

Adverse event	Patients	
	P/MC (n = 305)	2L PEG-3350 and bisacodyl tablets (n = 298)
Nausea		
Mild	6 (2.0)	5 (1.7)
Moderate	2 (0.7)	6 (2.0)
Severe	0	0
Vomiting		
Mild	2 (0.7)	8 (2.7)
Moderate	1 (0.3)	2 (0.7)
Severe	0	0
Headache		
Mild	3 (1.0)	3 (1.0)
Moderate	2 (0.7)	2 (0.7)
Severe	0	0
Chills		
Mild	0	3 (1.0)
Moderate	0	0
Severe	0	0

P/MC, Sodium picosulfate and magnesium citrate; 2L PEG-3350, polyethylene glycol solution.

Values are expressed as number (%) unless otherwise indicated. Patients with multiple incidences of a given adverse event are counted only once as having experienced that adverse event.

(P/MC) provided superior colon cleansing in patients preparing for colonoscopy with greater patient tolerability and equivalent short-term safety compared with day-before dosing of 2L PEG-3350 and bisacodyl tablets. Considering the results of this study and another study that compared day-before dosing of P/MC with day before 2L PEG-3350 and bisacodyl tablets, split dosing is the optimal regimen for administering P/MC. The authors anticipate P/MC to be a valuable addition to the armamentarium of bowel preparations available in the United States.

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