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# A Dual-Action, Low-Volume Bowel Cleanser Administered the Day Before Colonoscopy: Results From the SEE CLEAR II Study

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OBJECTIVES: **Optimal bowel preparation is vital for the efficacy and safety of colonoscopy. The inconvenience, discomfort, required consumption of large volumes of product, and potential adverse effects associated with some bowel preparations deter patients from colonoscopy and may provide inadequate cleansing. A dual-action, non-phosphate, natural orange-flavored, low-volume preparation containing sodium picosulfate and magnesium citrate (P/MC) is currently being reviewed for bowel cleansing.**

METHODS: **This was a phase 3, randomized, multicenter, assessor-blinded, prespecified non-inferiority, head-to-head study to investigate the efficacy, safety, and tolerability of day-before administration of P/MC vs. 2L polyethylene glycol solution and two 5-mg bisacodyl tablets (2L PEG-3350 and bisacodyl tablets (HalfLytely and Bisacodyl Tablets Bowel Prep Kit)) in adult patients preparing for colonoscopy (SEE CLEAR II Study). The primary objective of the study was to demonstrate the non-inferiority of P/MC to 2L PEG-3350 and bisacodyl tablets in overall colon cleansing using a modified Aronchick scale. In addition, efficacy in the ascending, mid (transverse and descending), and recto-sigmoid segments of colon was evaluated using a modified Ottawa scale. Patient acceptability and tolerability of the bowel preparations were assessed via a standard questionnaire. Safety was assessed based on the monitoring of adverse events (AEs) and meaningful findings on clinical evaluations including physical examinations, vital sign measurements, and electrocardiograms (ECGs).**

RESULTS: **A total of 603 patients were randomized to receive either P/MC ($n=300$) or 2L PEG-3350 and bisacodyl tablets ($n=303$). Based on the Aronchick scale, successful overall cleansing was similar in patients receiving P/MC (83.0%) and patients receiving 2L PEG-3350 and bisacodyl tablets (79.7%). P/MC demonstrated non-inferiority to 2L PEG-3350 and bisacodyl tablets in overall cleansing of the colon, as measured by the Aronchick scale. Similarly, the efficacy of P/MC, as measured by the Ottawa scale, was non-inferior to 2L PEG-3350 and bisacodyl tablets in cleansing the ascending, mid, and recto-sigmoid segments of the colon. Patient-reported acceptability and tolerability for each item examined on the questionnaire was significantly greater for P/MC compared with 2L PEG-3350 and bisacodyl tablets ($P<0.0001$).Treatment-emergent AEs related to the bowel preparation reported by 1% of patients receiving P/MC or 2L PEG-3350 and bisacodyl tablets were nausea (3.0% vs. 4.3%), vomiting (1.4% vs. 2.0%), and headache (2.7% vs. 1.7%). No clinically meaningful changes were noted in either treatment arm in data collected from physical examinations, vital sign measurements, and ECGs.**

CONCLUSIONS: **When administered as a day-before dose, the bowel cleansing effects of P/MC were non-inferior compared with 2L PEG-3350 and bisacodyl tablets using the clinician-rated Aronchick and Ottawa scales. Treatment acceptability was significantly more favorable in patients receiving P/MC than in patients receiving 2L PEG-3350 and bisacodyl tablets.**

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## INTRODUCTION

Surveillance research from the American Cancer Society has indicated that there were nearly 142,000 new cases of colorectal cancer and 50,000 deaths due to the disease during 2011 in the United States alone (1). Screening for colorectal cancer may decrease the incidence of colorectal cancer by 80% (2) and reduce the number of deaths associated with the disease by ~50% (3). Nonetheless, the use of colorectal screening continues to remain low despite the increase in endoscopy screening during the past decade (4). A recent national survey determined that ~63% of adults age 50 years and older underwent colorectal endoscopy for screening purposes (5); however, this screening rate falls short of the American Cancer Society's goal to achieve a 75% screening rate in adults age 50 years and older by 2015 (6).

A bowel preparation that adequately cleanses the colon is essential in exposing abnormalities in the colonic mucosa (7). An ideal preparation would empty the colon of all fecal material quickly with no alteration to the colonic mucosa, no patient discomfort, and no shift in fluids or electrolytes (8). Despite a large body of published literature on bowel cleansers, in some studies, nearly one in four preparations do not provide adequate cleansing for colonoscopy (9–12).

Historically, colon cleansing has been routinely performed with solutions containing polyethylene glycol (PEG) and until recently, sodium phosphate (13). PEG-based preparations preserve the histological features of the colonic mucosa (14), and have been shown to have an acceptable safety profile in patients with comorbidities, including serum electrolyte imbalances, inflammatory bowel disease, hepatic dysfunction, renal failure, and congestive heart failure (13,15,16). PEG is typically administered as a 2- or 4-l solution to achieve an adequate cathartic effect. This required consumption of large volumes of product has been shown to reduce patient tolerability and compliance (17). Despite superior patient tolerability and similar efficacy compared with PEG (18), the longstanding use of sodium phosphate preparations has declined in recent years. This is largely due to the number of serious adverse effects associated with these preparations. One rare but serious adverse effect in particular, acute phosphate nephropathy, has resulted in a black box warning in the label of all sodium phosphate laxatives (13).

Bowel cleansing preparations containing sodium picosulfate, citric acid, and magnesium oxide have been used outside the United States for nearly four decades with ~28 million exposures worldwide (19), and the efficacy, safety, and tolerability of the active ingredients have been well-demonstrated in clinical practice (20,21). A dual-action bowel cleansing preparation containing sodium picosulfate and magnesium citrate (P/MC; Ferring Pharmaceuticals, Parsippany, NJ) was recently approved in the United States (July 2012) for bowel preparation before colonoscopy (SEE CLEAR I and II studies (**S**afety and **E**fficacy of a Dual-Action, Low-Volume Preparation: An **E**valuation of **Col**on Cleansing in Day B**e**fore **a**nd Split-dose **R**egimens)). This combination of P/MC acts as both stimulant and osmotic laxative to clear the colon and rectum of fecal material. Magnesium citrate, which is formed during the dissolution of citric acid and magnesium oxide, draws water into the lumen creating a softer stool and a "wash-out" effect, while sodium picosulfate directly stimulates peristalsis in the colon (22).

This report summarizes the results from a phase 3, randomized, multicenter, assessor-blinded, prespecified non-inferiority, head-to-head study that investigated the efficacy, safety, and tolerability of a day-before administration of P/MC vs. 2L polyethylene glycol solution and two 5-mg bisacodyl tablets (2L PEG-3350 and bisacodyl tablets, HalfLytely and Bisacodyl Tablets (During the study bisacodyl was administered as two 5-mg tablets, which is twice the dose strength of the currently marketed product (i.e., one 5-mg bisacodyl tablet). Two 5-mg bisacodyl tablets was the approved dosage in the Bowel Prep Kit at the time of study initiation). Bowel Prep Kit, Braintree Laboratories, Braintree, MA).

## METHODS

### Patients

Men and women aged 18–80 years with at least three spontaneous bowel movements per week for 1 month before a scheduled elective colonoscopy were eligible for inclusion. Patients were excluded from the study if they had acute surgical abdominal conditions; active inflammatory bowel disease; or colon disease, including toxic megacolon, toxic colitis, idiopathic pseudo-obstruction, hypomotility syndrome, or ascites. Other exclusions included patients with gastrointestinal disorders such as active ulcers, gastric outlet obstruction, retention, gastroparesis, or ileus. Patients with uncontrolled angina and/or myocardial infarction within the last 3 months, congestive heart failure or uncontrolled hypertension, or renal insufficiency (with elevated serum creatinine accompanied with electrolyte abnormalities) were also excluded from the study. A history of colorectal surgery (excluding appendectomy, hemorrhoid surgery, or prior endoscopic procedures) or upper gastrointestinal surgery (including gastric resection, banding, or bypass) precluded patients from entering the study. Patients were also excluded if any clinically significant abnormalities in screening laboratory values were identified. The following drugs were not permitted to be used in combination with the bowel preparations and must have been suspended before administration: lithium, laxatives, constipating drugs, antidiarrheals, and oral iron preparations.

### Study design and treatment

This was a phase 3, randomized, multicenter, assessor-blinded, active-control, non-inferiority study in adult patients preparing for colonoscopy (SEE CLEAR II). Patients were randomly assigned to one of two fixed-dose treatment arms, P/MC or 2L PEG-3350 and bisacodyl tablets, and self-administered the bowel preparation the day before the colonoscopy. Randomization numbers were allocated sequentially to participants by an interactive voice response system; study participants were assigned numbers in the order in which they were enrolled. After colonoscopy was completed, patients were monitored at 48-h, 7-day, and 4-week follow-up visits.

Preparations were given at the direction of the unblinded coordinator. On the day before the procedure, all patients were

limited to a clear liquid diet. Patients receiving P/MC were instructed to reconstitute the first of two preparation sachets in 5 ounces of water and drink the contents between 1,600 and 1,800 hours on the day before colonoscopy followed by five 8-ounce glasses of clear liquids of the patient's choice over the next several hours, without forced-time drinking requirements. Approximately 6 h later, the second pouch was to be mixed in water and consumed between 2200 and 0000 hours followed by three 8-ounce glasses of clear liquids. Patients randomized to receive 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 h after taking the bisacodyl tablets, whichever occurred first, patients were instructed to drink the 2L PEG-3350 solution at a rate of one 8-ounce glass every 10 min as required by the product labeling. Patients recorded compliance with treatment on a diary card that tracked if all of the bowel preparation was ingested within the specified time period and if the correct number of glasses of clear liquids was consumed. Patients were deemed compliant if dosing occurred within 30 min of the time provided by the coordinator.

The first patient entered the study on 10 May 2010, with the last patient completing the study on 18 October 2010. The study was performed at 12 clinical sites in the United States. The study received institutional review board approval at each site and was conducted in accordance with the Declaration of Helsinki Principles, Good Clinical Practice, and applicable regulatory requirements. All participants provided written informed consent. The study was registered at ClinicalTrials.gov under the identifier NCT01073943.

### Assessments

Bowel cleansing was scored by endoscopists who were blinded to the preparation method. The primary efficacy variable was colon cleansing based on a modified version of the Aronchick scale (23), a validated assessment that describes the visual appearance of the colon on a four-point graded scale. Cleanliness was reported by describing the overall preparation 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). Based on the Aronchick scale, a patient was considered successfully cleansed following administration of the bowel preparation if overall colon cleansing was rated "excellent" or "good" on the four-point scale.

Efficacy was also assessed in the ascending, mid (transverse and descending), and recto-sigmoid segments of the colon using another validated instrument, the Ottawa scale (24). Cleanliness of the colon segments was reported by endoscopists who assigned a score based on a five-point scale 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). If the endoscopist was unable to reach any of the colon segments due to poor quality of bowel preparation, that segment was automatically scored as "inadequate". Training was provided to the endoscopists to aid in the assessment of each colon segment. For the Ottawa scale, a patient was considered successfully cleansed following administration of the bowel preparation if the respective segment of the colon was scored "excellent", "good", or "fair". Overall fluid amount, as graded by the endoscopist on a three-point scale (0, small; 1, medium; or 2, large), was also reported. To further describe the cleansing effects of the bowel preparation, the total Ottawa scale score was calculated. The total score was determined by adding the score for each of the three colon segments along with the overall fluid assessment score to arrive at a cumulative total cleanliness score ranging from 0 (best) to 14 (worst).

The acceptability and tolerability of the bowel preparation was assessed via a standardized questionnaire administered to patients on the day of the colonoscopy, before receiving any preliminary sedation for the procedure. Patient responses to the questionnaire consisted of either "yes" or "no" answers (four items) or ordinal scale answers ("very easy", "easy", "tolerable", "difficult", or "very difficult" (one item) and "excellent", "good", "fair", "poor", or "bad" (two items)). The items read as follows: (i) "How easy or difficult was it to consume the study drug?", (ii) "Were you able to consume the entire prep as instructed?", (iii) "Please describe your overall experience with the bowel preparation.", (iv) "The taste of this bowel preparation was . . .", (v) "Would you ask your doctor for this preparation again if you need another colonoscopy in the future?", (vi) "Would you refuse the same preparation again if it were to be prescribed to you in the future?", and (vii) "Have you had a colonoscopy before (within the past 3 years)?".

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). AEs were collected throughout the study by a patient's positive response to questions about his or her health, spontaneous reports, and clinically relevant changes and abnormalities observed by the investigator. These AEs were coded using version 13.0 of the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by MedDRA-preferred terms within the system organ class, severity, and relationship to treatment. The severity and casual relationship of AEs to 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. As P/MC is considered a new chemical entity

in the United States, laboratory tests and ECGs were performed; these assessments occurred at all study visits with the exception of the randomization visit. A patient's complete medical history was obtained at screening and concomitant medications were reported at multiple study visits.

### Statistical analysis

The sample size of the study was determined assuming an estimated rate of 85% for successful cleansing in the treatment arms, a 9.0% non-inferiority margin, and a one-sided significance level of 0.025 powered at 85%. Based on these assumptions, it was determined that 287 patients were required for each treatment arm. By definition, all randomized patients who received treatment were included in the safety population. Randomized patients who received treatment and produced efficacy assessments via the Aronchick scale and/or Ottawa scale were included in the intent-to-treat (ITT) population. 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 population.

The categorical efficacy end points, the Aronchick and Ottawa scales, were summarized by the percentage of patients successfully cleansed for each outcome. Non-inferiority was demonstrated for these end points if the one-sided 97.5% confidence interval for the treatment difference (P/MC minus 2L PEG-3350 and bisacodyl tablets) was greater than −9.0%. The fluid assessment was compared between treatment arms using a Wilcoxon rank sum test. Acceptability and tolerability of the bowel preparation, as assessed by a standardized patient questionnaire, were compared between treatment arms using a $\chi^2$ test for pooled responses. Unless otherwise noted, efficacy and acceptability/tolerability end points were summarized using the ITT population. Descriptive statistics were used to summarize demographics, AEs, and serious AEs from the safety analysis population.

## RESULTS

A total of 603 patients were screened and randomized to receive P/MC ($n=300$) or 2L PEG-3350 and bisacodyl tablets ($n=303$). Five patients were not treated and were excluded from all analyses; of these, three patients randomized to the P/MC withdrew consent, one patient could not tolerate the bowel preparation, and one patient randomized to 2L PEG-3350 and bisacodyl tablets withdrew consent. Accordingly, 296 patients receiving P/MC and 302 patients receiving 2L PEG-3350 and bisacodyl tablets were included in the safety analysis population. Two patients in each treatment arm failed to have an efficacy assessment performed; therefore, the ITT population consisted of 294 patients receiving P/MC and 300 patients receiving 2L PEG-3350 and bisacodyl tablets. Fifty-four patients had protocol deviations during the study. Therefore, the per protocol population included 540 patients; of these, 260 patients and 280 patients comprised the P/MC and 2L PEG-3350 and bisacodyl tablets treatment arms, respectively. The majority of patients, 97.3%, completed the study. The predominant reason for study discontinuation was withdrawal of consent (1.0%) followed by protocol violation (0.5%), other event (0.5%), AE (0.3%), and lost to follow-up (0.3%).

Demographics and baseline characteristics were similar among patients, and no significant difference was observed between treatment arms (**Table 1**). The median age was 56.0 years (range 18–79 years), and the majority of patients were female (63.7%) and white (90.6%).

One patient receiving P/MC (0.3%) and fourteen patients receiving 2L PEG-3350 and bisacodyl tablets (4.8%) were not able to consume all of the bowel preparation. The majority of patients in both treatment arms had a complete colonoscopy (i.e., cecal intubation), 98.6% for P/MC and 100% for 2L PEG-3350 and bisacodyl tablets. The small percentage of incomplete colonoscopies in the P/MC treatment arm resulted from three AEs and one incidence of inadequate bowel preparation.

### Efficacy

Using the Aronchick scale, overall colon cleansing in preparation for colonoscopy was similar in those patients who received P/MC compared with those who received 2L PEG-3350 and bisacodyl tablets (**Tables 2** and **3**). The lower bound of the one-sided 97.5% confidence interval for treatment difference in overall colon cleansing between the bowel preparations was greater than −9.0%; therefore, the efficacy of P/MC was determined to be non-inferior to 2L PEG-3350 and bisacodyl tablets (**Figure 1**).

**Tables 2** and **3** highlight the proportion of patients who were successfully cleansed for three segments of the colon as assessed via the Ottawa scale. Similar to that observed with the Aronchick scale, the lower bound of the one-sided 97.5% confidence interval for treatment difference between the bowel preparations was greater than −9.0%, demonstrating non-inferiority of P/MC to 2L PEG-3350 and bisacodyl tablets in all segments of the colon using the Ottawa scale (**Figure 2**).

Fluid quantity was comparable between patients in the treatment arms ($P=0.710$). The majority of patients had a "small" or "moderate" fluid quantity; 95.5% and 94.3% in patients receiving P/MC and 2L PEG-3350 and bisacodyl tablets, respectively. The total Ottawa scale score for patients in the P/MC treatment arm was significantly lower than the score for patients in the 2L PEG-3350 and bisacodyl tablets treatment arm (4.2 vs. 4.8, $P=0.0086$).

### Patient acceptability and tolerability

Overall, the distribution of patient rating of acceptability and tolerability for P/MC was significantly superior to 2L PEG-3350 and bisacodyl tablets ($P<0.0001$). Important differences between the treatment arms are illustrated in **Figure 3**. Briefly, a greater proportion of patients receiving P/MC rated the treatment regimen as "very easy" or "easy" to consume (87.4% vs. 37.2%) and as having an "excellent" or "good" taste (73.7% vs. 27.8%) 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" (89.3% vs. 67.8%) and would use the same regimen for a future colonoscopy (93.2% vs. 59.4%).

**Table 1. Demographics and baseline characteristics (safety population)**

| Parameter | P/MC, *N*=296 | 2L PEG-3350 and bisacodyl tablets, *N*=302 |
|---|---|---|
| Mean age, years (range) | 56.8 (21–78) | 56.2 (18–79) |
| *Age range,* n *(%)* | | |
| 18–64 years | 236 (79.7) | 247 (81.8) |
| ≥65 years | 60 (20.3) | 55 (18.2) |
| *Sex,* n *(%)* | | |
| Male | 104 (35.1) | 113 (37.4) |
| Female | 192 (64.9) | 189 (62.6) |
| *Race,* n *(%)* | | |
| White | 274 (92.6) | 268 (88.7) |
| Black/African American | 22 (7.4) | 32 (10.6) |
| American Indian/Alaska Native | 0 | 1 (0.3) |
| Asian | 0 | 1 (0.3) |
| Native Hawaiian/Other Pacific Islander | 0 | 0 |
| Other | 0 | 0 |
| Mean body mass index, kg/m$^2$ (range) | 29.19 (17.53–45.46)[a] | 29.54 (16.80–51.32) |

P/MC, sodium picosulfate and magnesium citrate; 2L PEG-3350, polyethylene glycol solution.
[a]n=295 patients as one patient was missing an assessment to calculate body mass index at baseline.

**Table 2. Efficacy of bowel cleansing in patients undergoing colonoscopy (ITT population)**

| Colon segment | Patients successfully cleansed: P/MC, *n*=294 | Patients successfully cleansed: 2L PEG-3350 and bisacodyl tablets, *n*=300 | Treatment difference[a] | One-sided 97.5% CI[b] |
|---|---|---|---|---|
| *Aronchick scale*[c] | | | | |
| Overall | 244 (83.0) | 239 (79.7) | 3.3 | −2.9 |
| *Ottawa scale*[d] | | | | |
| Ascending | 239 (81.3) | 252 (84.0) | −2.7 | −8.8 |
| Mid[e] | 274 (93.2) | 266 (88.7) | 4.5 | −0.1 |
| Recto-sigmoid | 271 (92.2) | 267 (89.0) | 3.2 | −1.5 |
| Overall | 232 (78.9) | 234 (78.0) | 0.9 | −5.7 |

CI, confidence interval; ITT, intent to treat; P/MC, sodium picosulfate and magnesium citrate; 2L PEG-3350, polyethylene glycol solution.
[a]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.
[b]Non-inferiority was demonstrated if the one-sided 97.5% CI for the treatment difference was greater than –9.0%.
[c]Patients were considered successfully cleansed following administration of prescribed treatment regimen, if overall colon cleansing on the Aronchick scale was rated "excellent" or "good".
[d]Patients were considered successfully cleansed following administration of prescribed treatment regimen, if colon cleansing on the Ottawa Scale was rated "excellent", "good", or "fair".
[e]Mid colon refers to the transverse and descending segments of the colon.

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 (99.7% vs. 92.3%). 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 was necessary in the future (4.8% vs. 14.4%). More than three-quarters of patients receiving P/MC (84.3%) and 2L PEG-3350 and bisacodyl tablets (85.9%) had not undergone a colonoscopy within the past 3 years ($P=0.6442$).

## Safety

The overall incidence of treatment-emergent AEs (TEAEs) was similar in patients receiving P/MC (73.6%). and 2L PEG-3350 and bisacodyl tablets (79.8%). Nausea, headache, and vomiting were the most common TEAEs not associated with colonoscopy findings. TEAEs considered possibly or probably related to the bowel preparation reported by >1% of patients are displayed in **Table 4**. The majority of TEAEs reported in patients receiving P/MC (98.3%) and 2L PEG-3350 and bisacodyl tablets (98.0%) were of mild or moderate intensity. All TEAEs considered to be of severe intensity were unrelated or unlikely related to the bowel preparations, with the exception of one event in the P/MC (headache) and 2L PEG-3350 and bisacodyl tablets treatment arms (dizziness).

Less than 1% of patients in either treatment arm experienced serious AEs during the study and none were considered related to the bowel preparations. Adenocarcinoma was revealed in one patient receiving P/MC; following colon resection, the patient experienced an anastomotic complication and dehydration, and recovered. Another patient receiving P/MC, with a history of hypertension and hypercholesterolemia, experienced acute coronary syndrome post colonoscopy. The patient was hospitalized for treatment and recovered with sequelae. Ileus was identified in one patient who received 2L PEG-3350 and bisacodyl tablets. Following study participation, a patient receiving P/MC was noted to have adenocarcinoma with extensive necrosis that was considered unlikely related to the bowel preparation.

In this study, discontinuation relating to AEs was low. Vomiting, gastritis, and esophagitis led to discontinuation in one patient receiving P/MC; only vomiting was deemed possibly related to the bowel preparation. Vomiting, dizziness, migraine, and syncope led to discontinuation in one patient receiving 2L PEG-3350 and bisacodyl tablets; vomiting, dizziness, and migraine were possibly related to the bowel preparation.

Overall, no clinically significant findings were noted during physical examinations or in orthostatic vital sign measurements following

**Table 3. Efficacy of bowel cleansing in patients undergoing colonoscopy (PP population)**

| Colon segment | Patients successfully cleansed | | Treatment difference[a] | One-sided 97.5% CI[b] |
|---|---|---|---|---|
| | P/MC, *n*=260 | 2L PEG-3350 and bisacodyl tablets *n*=280 | | |
| *Aronchick scale*[c] | 216 (83.1) | 222 (79.3) | 3.8 | −2.8 |
| Overall | | | | |
| *Ottawa scale*[d] | | | | |
| Ascending | 211 (81.2) | 237 (84.6) | −3.5 | −9.8 |
| Mid[e] | 247 (95.0) | 249 (88.9) | 6.1 | 1.5 |
| Recto-sigmoid | 243 (93.5) | 251 (89.6) | 3.8 | −0.8 |
| Overall[f] | — | — | — | — |

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

[a]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.

[b]Non-inferiority was demonstrated if the one-sided 97.5% CI for the treatment difference was greater than –9.0%.

[c]Patients were considered successfully cleansed following administration of prescribed treatment regimen if overall colon cleansing on the Aronchick scale was rated "excellent" or "good".

[d]Patients were considered successfully cleansed following administration of prescribed treatment regimen if colon cleansing on the Ottawa scale was rated "excellent", "good", or "fair".

[e]Mid colon refers to the transverse and descending segments of the colon.

[f]Treatment difference and one-sided 97.5% CI was not calculated overall for the PP population.

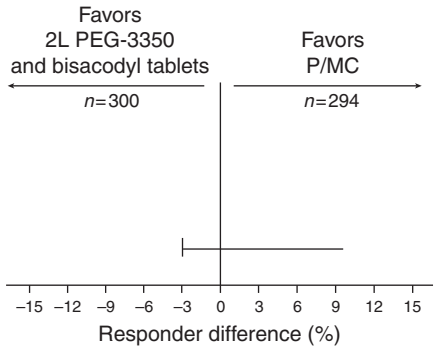


**Figure 1.** Sodium picosulfate and magnesium (P/MC) is non-inferior to 2L PEG-3350 (polyethylene glycol solution) and bisacodyl tablets in overall cleansing of the colon, as measured by the Aronchick scale (intent-to-treat population). A patient was considered successfully cleansed following administration of the preparation if colon cleansing was rated "excellent" or "good" on a four-point scale. The lower bound of the one-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 (>−9.0%); thus, non-inferiority of P/MC was established.

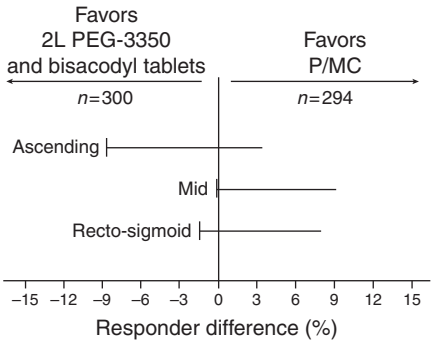


**Figure 2.** Sodium picosulfate and magnesium citrate (P/MC) is non-inferior to 2L PEG-3350 (polyethylene glycol solution) and bisacodyl tablets in cleansing the ascending, mid (transverse and descending), and recto-sigmoid segments of the colon, as measured by the Ottawa scale (intent-to-treat population). A patient was considered successfully cleansed following administration of the preparation if colon cleansing was rated "excellent", "good", or "fair" on a five-point scale. The lower bound of the one-sided 97.5% confidence interval for the treatment difference between P/MC and 2L PEG-3350 and bisacodyl tablets in the ascending, mid, and recto-sigmoid segments of the colon met the *a priori* criteria (>−9.0%); thus, non-inferiority of P/MC was established.

treatment with P/MC or 2L PEG-3350 and bisacodyl tablets. Data collected from ECGs in patients receiving P/MC and 2L PEG-3350 and bisacodyl tablets indicated no significant effect on cardiac repolarization, as measured by QTcF. Mean changes from baseline to scheduled visits in hematology, coagulation, blood chemistry, and urinalysis values were generally small and similar between the treatment arms. On the day of the procedure, the incidence of increased magnesium levels was higher in patients receiving P/MC compared with patients in the 2L PEG-3350 and bisacodyl tablets treatment arm (8.7% vs. 0.3%; mean concentration (range), 0.979 (0.75–1.20) mmol/l vs. 0.850 (0.45–1.10) mmol/l). In addition, the P/MC treatment arm tended to have a greater proportion of patients who developed abnormal urine pH compared with patients receiving 2L PEG-3350 and bisacodyl tablets (29.4% vs. 5.9%; mean pH (range), 6.76 (5.5–8.5) vs. 6.18 (5.0–8.0)). The shifts in these parameters were likely due to the magnesium component in the bowel preparation. The changes in magnesium levels and urine pH levels were transient, and values returned to normal thresholds by the end of the study.

## DISCUSSION

The inability of patients to tolerate the bowel preparation, including ingestion of a large volume preparation, is of concern for

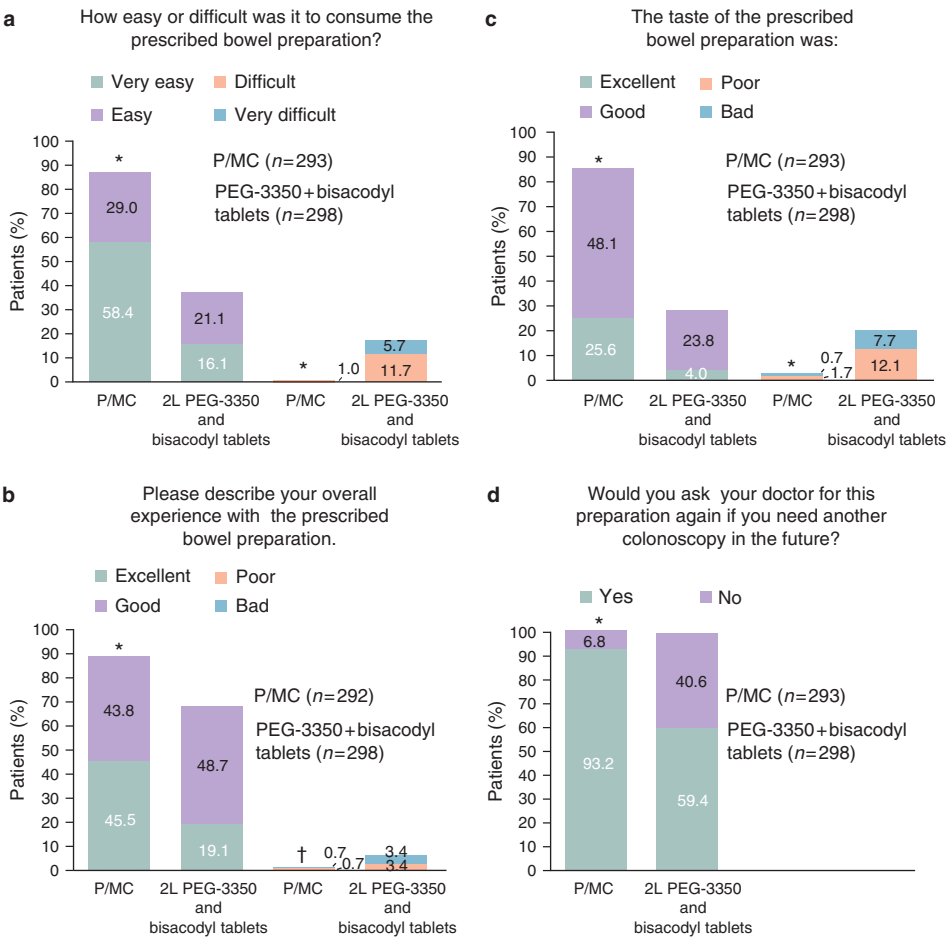


**Figure 3.** Higher proportion of patients rated, accepted, and tolerated sodium picosulfate and magnesium citrate (P/MC) than 2L PEG-3350 (polyethylene glycol solution) and bisacodyl tablets (intent-to-treat population). Administered before any preliminary sedation for the colonoscopy, the questionnaire summarized the patients' reactions to the prescribed treatment regimen. Highlights from the questionnaire include (**a**) perspective on the consumption of the preparation, (**b**) the overall experience with the preparation, (**c**) the taste of the preparation, and (**d**) preference on receiving the preparation again in the future (*$P<0.0001$; †$P=0.001$).

endoscopists because inadequate preparation of the bowel is known to influence the effectiveness of a colonoscopy. Poor palatability and the inability to consume a large volume of purgative may deter patients from completing the bowel preparation as instructed (25). An inadequately prepared bowel may increase procedure time, complications, and patient expense (10,26) and decrease the detection rate for lesions and adenomas (12). This is of particular concern given that adenomatous polyps have been suggested as the precursor for the majority of colon and rectal cancers (27).

There also appears to be a direct relationship between the quality of bowel preparation and the time interval between the last dose of preparation and colonoscopy start time (11,28). Therefore, timing for administration of a bowel preparation before colonoscopy is important. P/MC has demonstrated superiority to 2L PEG-3350 and bisacodyl tablets in colon cleansing when used in a split-dose regimen (29). Taken together with the results from this study, P/MC provides a flexible-dosing regimen, which may be advantageous for optimizing colonoscopy scheduling in busy clinical practices.

When administered as in a day-before regimen, P/MC was noninferior to 2L PEG-3350 and bisacodyl tablets in overall cleansing and in cleansing the individual segments of the colon, as assessed by the Aronchick and Ottawa scales. P/MC was rated as a patient-friendly preparation with a pleasant taste and low volume of solution to consume, 10 ounces compared with 68 ounces of 2L PEG-3350 solution required to be ingested at specific time intervals. P/MC was a safe bowel preparation with an incidence of related AEs that was similar to that found with 2L PEG-3350 and bisacodyl tablets. Despite the transient, yet anticipated, shifts in the concentration of magnesium and urine pH observed on the day of colonoscopy in patients receiving P/MC, there were no clinically significant trends in laboratory test results, physical examinations, vital sign measurements, or ECGs. The results of this study, the largest head-to-head comparison of bowel preparations to date, support the efficacy, safety, and tolerability profile for the ingredients of P/MC (20,21).

The study was designed to be single-blinded due to the differences in the administration of bowel preparations. Although this

**Table 4. TEAEs (>1%) possibly or probably related to treatment by intensity**

| | Patients, *n* (%) | |
|---|---|---|
| | P/MC, *N*=296 | 2L PEG-3350 and bisacodyl tablets, *N*=302 |
| Any possibly or probably related TEAEs | 33 (11.1) | 29 (9.6) |
| *Preferred term* | | |
| Nausea | | |
| Mild | 8 (2.7) | 12 (4.0) |
| Moderate | 1 (0.3) | 1 (0.3) |
| Severe | 0 | 0 |
| Vomiting | | |
| Mild | 4 (1.4) | 5 (1.7) |
| Moderate | 0 | 1 (0.3) |
| Severe | 0 | 0 |
| Headache | | |
| Mild | 7 (2.4) | 5 (1.7) |
| Moderate | 0 | 0 |
| Severe | 1 (0.3) | 0 |

P/MC, sodium picosulfate and magnesium citrate; TEAE, treatment-emergent adverse event; 2L PEG-3350, polyethylene glycol solution.
Patients with multiple incidences of a given adverse event are counted only once as having experienced that adverse event.

represents a potential source of bias, precautions were taken to ensure the endoscopists remained blinded to the bowel preparation. Patients with renal insufficiency (elevated serum creatinine and potassium values) and cardiovascular concerns (uncontrolled angina and/or myocardial infarction, congestive heart failure, or uncontrolled hypertension) were not eligible to participate; therefore, the results of this study should not be extrapolated to these high-risk populations. Although the active ingredients of P/MC have been investigated in children outside of the United States, further studies are warranted to examine the bowel cleansing effects of P/MC in a pediatric population.

In summary, day-before dosing of P/MC demonstrated non-inferior colon cleansing in preparation for colonoscopy and provided more favorable patient tolerability than 2L PEG-3350 and bisacodyl tablets.


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## CONFLICT OF INTEREST

**Guarantor of the article:** Philip O. Katz, MD.

**Specific author contributions:** Planning the study, interpreting data, and drafting the manuscript: Douglas K. Rex, Stephen Vanner, Lawrence C. Hookey, and Vivian Alderfer. Conducting the study, collecting and interpreting the data, and drafting the manuscript: Philip O. Katz, Michael Epstein, and Nav K. Grandhi. Approval of the final draft of the manuscript before submission: all authors.

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**Potential competing interests:** Philip O. Katz has received grant/research support, participated in speakers' bureaus, and/or acted as a consultant for Intec Pharma, Ironwood, Norvartis Consumer, and Takeda. Douglas K. Rex has received grant/research support, participated in speakers' bureaus, and/or acted as a consultant for Ferring Pharmaceuticals and Braintree Laboratories. Michael Epstein has received grant/research support, participated in speakers' bureaus, and/or acted as a consultant for Abbott Laboratories, Ostsuka Pharmaceuticals, Promethius, and Sucampo. Nav K. Grandhi declares no conflict of interest. Stephen Vanner has received grant/research support, participated in speakers' bureaus, and/or acted as a consultant for Ferring Pharmaceuticals in Canada and the United States. Lawrence C. Hookey has received grant/research support from Ferring Pharmaceuticals in Canada and has participated in speakers' bureaus and/or acted as a consultant for Ferring Pharmaceuticals in Canada and the United States. Vivian Alderfer is an employee of ICON Clinical Research, the organization contracted on behalf of Ferring Pharmaceuticals to maintain the database and perform statistical analyses for the study. Raymond Joseph is a full-time employee of Ferring Pharmaceuticals.

## Study Highlights

### WHAT IS CURRENT KNOWLEDGE

- ✓ A bowel preparation is essential for diagnostic and therapeutic evaluation of the colon.
- ✓ Colon cleansing with large-volume preparations are often poorly tolerated by patients, which may result in reduced efficacy and reluctance to undergo subsequent colonoscopies as part of surveillance screening programs.
- ✓ The optimum bowel preparation should provide excellent cleansing, have a good safety profile, and be well tolerated by patients—although this has yet to be demonstrated in currently available preparations.

### WHAT IS NEW HERE

- ✓ A low-volume, dual-action bowel preparation containing sodium picosulfate and magnesium citrate, administered in a day-before dose, provides non-inferior colon cleansing and greater patient tolerability than 2L PEG-3350 and bisacodyl tablets.

## REFERENCES


1. Siegel R, Ward E, Brawley O *et al.* Cancer statistics, 2011: the impact of eliminating socioeconomic and racial disparities on premature cancer deaths. CA Cancer J Clin 2011;61:212–36.
2. Rex DK, Johnson DA, Anderson JC *et al.* American College of Gastroenterology guidelines for colorectal cancer screening 2009 [corrected]. Am J Gastroenterol 2009;104:739–50.
3. Zauber AG, Winawer SJ, O'Brien MJ *et al.* Colonoscopic polypectomy and long-term prevention of colorectal-cancer deaths. N Engl J Med 2012;366:687–96.

4. Swan J, Breen N, Graubard BI *et al.* Data and trends in cancer screening in the United States: results from the 2005 National Health Interview Survey. Cancer 2010;116:4872–81.
5. Centers for Disease Control and Prevention (CDC-). Vital signs: colorectal cancer screening among adults aged 50-75 years -- United states, 2008. MMWR Morb Mortal Wkly Rep 2010;59:808–12.
6. Centers for Disease Control and Prevention (CDC). Cancer screening - United States, 2010. MMWR Morb Mortal Wkly Rep 2012;61:41–5.
7. Cohen LB. Split dosing of bowel preparations for colonoscopy: an analysis of its efficacy, safety, and tolerability. Gastrointest Endosc 2010;72:406–12.
8. Wexner SD, Beck DE, Baron TH *et al.* A consensus document on bowel preparation before colonoscopy: prepared by a Task Force from the American Society of Colon and Rectal Surgeons (ASCRS), the American Society for Gastrointestinal Endoscopy (ASGE), and the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES). Surg Endosc 2006;20:1161.
9. Harewood GC, Sharma VK, de Garmo P. Impact of colonoscopy preparation quality on detection of suspected colonic neoplasia. Gastrointest Endosc 2003;58:76–9.
10. Froehlich F, Wietlisbach V, Gonvers JJ *et al.* Impact of colonic cleansing on quality and diagnostic yield of colonoscopy: the European Panel of Appropriateness of Gastrointestinal Endoscopy European multicenter study. Gastrointest Endosc 2005;61:378–84.
11. Di Palma JA, Rodriguez R, McGowan J *et al.* A randomized clinical study evaluating the safety and efficacy of a new, reduced-volume, oral sulfate colon-cleansing preparation for colonoscopy. Am J Gastroenterol 2009;104:2275–84.
12. Lebwohl B, Kastrinos F, Glick M *et al.* The impact of suboptimal bowel preparation on adenoma miss rates and the factors associated with early repeat colonoscopy. Gastrointest Endosc 2011;73:1207–14.
13. Adamcewicz M, Bearelly D, Porat G *et al.* Mechanism of action and toxicities of purgatives used for colonoscopy preparation. Expert Opin Drug Metab Toxicol 2011;7:89–101.
14. Pockros PJ, Foroozan P. Golytely lavage versus a standard colonoscopy preparation. Effect on normal colonic mucosal histology. Gastroenterology 1985;88:545–8.
15. Lichtenstein G. Bowel preparations for colonoscopy: a review. Am J Health Syst Pharm 2009;66:27–37.
16. Belsey J, Epstein O, Heresbach D. Systematic review: adverse event reports for oral sodium phosphate and polyethylene glycol. Aliment Pharmacol Ther 2009;29:15–28.
17. Shawki S, Wexner SD. Oral colorectal cleansing preparations in adults. Drugs 2008;68:417–37.
18. Hookey LC, Depew WT, Vanner S. The safety profile of oral sodium phosphate for colonic cleansing before colonoscopy in adults. Gastrointest Endosc 2002;56:895–902.
19. Periodic safety report for Picolax/Picoprep/Picosalax/Pico-Salax/Cilaxoral. Ferring Pharmaceuticals A/S (Denmark); February 16 2012.
20. Hoy SM, Scott LJ, Wagstaff AJ. Sodium picosulfate/magnesium citrate: a review of its use as a colorectal cleanser. Drugs 2009;69:123–36.
21. Hookey LC, Vanner SJ. Pico-salax plus two-day bisacodyl is superior to pico-salax alone or oral sodium phosphate for colon cleansing before colonoscopy. Am J Gastroenterol 2009;104:703–9.
22. Parente F, Marino B, Crosta C. Bowel preparation before colonoscopy in the era of mass screening for colo-rectal cancer: a practical approach. Dig Liver Dis 2009;41:87–95.
23. Aronchick CA, Lipshutz WH, Wright SH *et al.* A novel tableted purgative for colonoscopic preparation: efficacy and safety comparisons with Colyte and Fleet Phospho-Soda. Gastrointest Endosc 2000;52:346–52.
24. Rostom A, Jolicoeur E. Validation of a new scale for the assessment of bowel preparation quality. Gastrointest Endosc 2004;59:482–6.
25. Atreja A, Nepal S, Lashner BA. Making the most of currently available bowel preparations for colonoscopy. Cleve Clin J Med 2010;77:317–26.
26. Rex DK, Imperiale TF, Latinovich DR *et al.* Impact of bowel preparation on efficiency and cost of colonoscopy. Am J Gastroenterol 2002;97: 1696–700.
27. Burke CA, Church JM. Enhancing the quality of colonoscopy: the importance of bowel purgatives. Gastrointest Endosc 2007;66:565–73.
28. Parra-Blanco A, Nicolas-Perez D, Gimeno-Garcia A *et al.* The timing of bowel preparation before colonoscopy determines the quality of cleansing, and is a significant factor contributing to the detection of flat lesions: a randomized study. World J Gastroenterol 2006;12:6161–6.
29. Rex DK, Katz P, Bertiger G *et al.* Split-dose administration of a novel, dual-action, low-volume bowel cleanser for colonoscopy: efficacy and safety results from the SEE CLEAR I study. Am J Gastroenterol 2012; 107(Suppl 1):S746.