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Efficacy and safety of a ready-to-drink bowel preparation for colonoscopy: a randomized, controlled, non-inferiority trial

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Abstract

Background: We performed a randomized, controlled, assessor-blinded, multicenter, non-inferiority (NI) study to compare the safety and efficacy of a ready-to-drink formulation of sodium picosulfate, magnesium oxide, and citric acid (SPMC oral solution) with a powder formulation (P/MC powder) for oral solution.

Methods: Eligible participants (adults undergoing elective colonoscopy) were randomized 1:1 to split-dose SPMC oral solution or P/MC powder. The primary efficacy endpoint assessed overall colon-cleansing quality with the Aronchick Scale (AS), and the key secondary efficacy endpoint rated quality of right colon cleansing with the Boston Bowel Preparation Scale (BBPS). Assessments were performed by a treatment-blinded endoscopist. Tolerability was assessed using the Mayo Clinic Bowel Prep Tolerability Questionnaire. Safety assessments included adverse events and laboratory evaluations.

Results: The study included 901 participants: 448 for SPMC oral solution; 453 for P/MC powder. SPMC oral solution demonstrated non-inferiority to P/MC powder {87.7% (393/448) responders *versus* 81.5% (369/453) responders [difference (95% confidence interval): 6.3% (1.8, 10.9)]}. The key secondary efficacy objective assessing the right colon was also met. According to the prespecified hierarchical testing, after meeting the primary and key secondary objectives, SPMC oral solution was tested for superiority to P/MC powder for the primary endpoint ($p = 0.0067$). SPMC oral solution was well tolerated. Most common adverse events were nausea (3.1% *versus* 2.9%), headache (2.7% *versus* 3.1%), hypermagnesemia (2.0% *versus* 5.1%), and vomiting (1.3% *versus* 0.7%) for SPMC oral solution and P/MC powder, respectively.

Conclusions: Ready-to-drink SPMC oral solution showed superior efficacy of overall colon cleansing compared with P/MC powder, with similar safety and tolerability.

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Keywords: bowel preparation, colon cleansing, inadequate bowel preparation, oral solution, screening colonoscopy

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Introduction

Regular colorectal cancer (CRC) screening, most often performed in the United States (US) and Canada by screening colonoscopy, is recommended to reduce the risk of death from CRC, which is considered the most preventable cancer.[1] Effective bowel preparation is essential for an optimal screening colonoscopy.[2] An estimated 20–30% of bowel preparations are inadequate, with almost 10% being too poor to allow complete evaluation.[3–5]

Inadequate bowel preparation can result from poorly tolerated cleansing agents, which may

hinder the patient from fully ingesting the agent, leading to negative outcomes.[3,6] Failure to follow preparation instructions is cited as an independent predictor of inadequate bowel preparation.[7] Additionally, low health literacy is a strong predictive factor of inadequate bowel preparation for screening colonoscopy in the average-risk population.[8,9] Poor bowel preparation can lead to longer procedure times, incomplete colonoscopy, missed lesions at colonoscopy, and early repeated colonoscopies.[2,10–12]

Improved tolerability, ease of use, and ease of completion of the bowel preparation can lead to a more favorable patient experience and better colonoscopy outcomes.[3,6,13] Taste and convenience directly impact acceptance and tolerability of the bowel preparation.[13] The convenience and ease of the bowel preparation is a concern for both patients and physicians.[14–16] To increase patient adherence, new bowel preparations should be developed to be more tolerable and convenient, thus improving the success rate of the colonoscopy.[3,7]

Sodium picosulfate, magnesium oxide, and citric acid (P/MC) powder was developed as a step in the process of making bowel preparation more tolerable and convenient. The efficacy of colon cleansing with low-volume P/MC powder for oral solution was established in two randomized controlled trials *versus* polyethylene glycol (PEG)-3350 with bisacodyl tablets.[17,18]

The objective of this study was to evaluate the safety and efficacy of a new ready-to-drink, low-volume formulation of sodium picosulfate, magnesium oxide, and citric acid (SPMC oral solution). As opposed to P/MC powder, the active ingredients in SPMC oral solution are already fully dissolved, with no mixing or stirring required. This further improves the product profile while adding another level of convenience to the patient experience and diminishing the potential for inadequate bowel preparation due to confusion regarding mixing directions. No other oral solution ready-to-drink formulation of low-volume bowel preparation for colonoscopy is approved in the US. In this report, we describe a non-inferiority (NI) study comparing the safety and efficacy of SPMC oral solution with P/MC powder.

The study was designed to assess colon cleansing using two highly validated scales. The Aronchick Scale (AS) allows the quality of colon cleansing to be measured without the influence of any washing or suctioning by the endoscopist, thereby giving a more direct measure of the efficacy of the bowel preparation agent on the colon cleansing.[19] The Boston Bowel Preparation Scale (BBPS) aligns more closely with clinical practice and real-world outcomes as it allows the endoscopist to wash and aspirate the mucosa, though the results are also more user dependent.[20,21]

Materials and methods

Study design

We conducted a phase III, randomized, assessor-blinded, multicenter, NI study comparing split-dose, low-volume SPMC oral solution (Clenpiq™, Ferring Pharmaceuticals Inc., Parsippany, NJ) with split-dose, low-volume P/MC powder for oral solution (Prepopik®, Ferring Pharmaceuticals Inc., Parsippany, NJ) [ClinicalTrials.gov identifier: NCT03017235]. The study was conducted at 12 sites (hospitals, academic medical centers, and private clinics) in the US, and 2 in Canada. The study was conducted in accordance with the principles set forth in the Declaration of Helsinki and in compliance with ICH-GCP standards. The study protocol was approved by Schulman IRB (protocol #000253).

Eligibility criteria

Eligible participants included females and males, 18–80 years of age, who were undergoing elective colonoscopy. Females of childbearing potential must have agreed to use adequate contraception during the study and could not be pregnant or lactating at the time of enrollment.

Eligible participants must have had an average of at least three spontaneous bowel movements per week for 1 month prior to the colonoscopy, and be willing, able, and competent to complete the procedure and comply with study instructions. Written informed consent was obtained at screening.

Exclusion criteria included known or suspected major gastrointestinal (GI) disorder, including GI obstruction, perforation, ileus, severe acute inflammatory bowel disease, or diverticulitis; chronic nausea and vomiting; participants who were undergoing colonoscopy for foreign body removal or decompression; prior upper GI

surgery; prior colorectal surgery (excluding appendectomy, hemorrhoid surgery, or endoscopic procedures); severely reduced renal function (<30 ml/min/1.73m^2); or uncontrolled angina or myocardial infarction within the last 3 months, congestive heart failure, uncontrolled hypertension, or ascites.

Use of certain medications was prohibited during the study: lithium (potential constipating agent); laxatives (within 24 h prior to colonoscopy), constipating drugs such as opiates, anticholinergics, calcium-channel blockers, and clonidine (within 48 h prior to colonoscopy); antidiarrheals such as loperamide (within 72 h prior to colonoscopy); or oral iron preparations (within 1 week prior to colonoscopy).

Participants eligible to participate in this study met similar inclusion/exclusion criteria to those eligible for two randomized controlled trials that established the efficacy of P/MC powder *versus* PEG-3350 with bisacodyl tablets for colon cleansing before colonoscopy.[17,18]

Randomization

Participants were randomized according to a list that was computer generated by an independent, unblinded statistician prior to the first participant's enrollment. Participants were randomized 1:1 to receive either SPMC oral solution or P/MC powder, and stratified by study site and whether or not they participated in the pharmacokinetic subgroup. Randomization numbers were allocated sequentially to participants at each site, in the order of enrollment.

An unblinded study coordinator enrolled participants electronically, distributed the assigned drug, and instructed the participant and caregiver(s) about the use of the bowel preparation, including dietary restrictions. The endoscopist performing the colonoscopy and assessing efficacy was blinded to the participant's treatment group.

Interventions

For both treatment groups, the colon-cleansing regimen was a split-dose preparation (one dose the evening before and one dose the same day as colonoscopy, within 5 to 9 h prior to the procedure; see Supplementary Table 1 for the schedule of visits and assessments).

SPMC oral solution (two 5.4-oz doses) is a ready-to-drink formulation and was consumed as supplied (without mixing, stirring, or dilution), followed by five or more 8-oz glasses of clear liquid within 5 h of the first dose, and four or more 8-oz glasses of clear liquid within 4 h of the second dose. P/MC powder was reconstituted in approximately 5 oz of cold water and stirred for a full 2–3 min before consuming. After the first dose, participants were asked to consume five or more 8-oz glasses of clear liquids within 5 h. After the second dose, participants were asked to consume three 8-oz glasses of clear liquids within 5 h.

In both cases, participants were instructed to maintain a diet of clear liquids from 24 h before the colonoscopy and to stop taking anything by mouth 2 h before. Immediately prior to the colonoscopy, participants returned the Mayo Clinic Bowel Prep Tolerability Questionnaire,[22] and chemistry and hematology laboratory samples were obtained. Following the colonoscopy, participants returned for visits at 1–2 days, 7 days, and 4 weeks.

Endpoints

The primary efficacy endpoint was overall quality of colon cleansing as measured by the validated AS prior to irrigation of the colon (AS; Supplementary Table 2), assessed by the treatment-blinded endoscopist during the procedure. The same primary endpoint was used in two previous studies that established P/MC powder was as effective as or more effective than PEG-3350 with bisacodyl tablets.[17,18]

Secondary efficacy endpoints were the quality of cleansing of the right colon, transverse colon, and left colon, as assessed by the BBPS (Supplementary Table 3); as well as the findings on the Mayo Clinic Bowel Prep Tolerability Questionnaire. The key secondary efficacy endpoint was the quality of cleansing in the right colon by BBPS.

Safety assessments included adverse events (AEs), laboratory evaluations, and electrocardiograms. AEs were classified according to the Medical Dictionary for Regulatory Activities (MedDRA) version 20.1.

The endoscopist noted the number of lesions found during the colonoscopy (recorded as an AE) and removed polyps when possible and appropriate. Lesion biopsies were sent for histological analysis. All malignancies found during the study

period, including colonic lesions that were determined to be cancerous, were reported as a serious AE. Polyp and adenoma findings were not a key efficacy endpoint in the study.

Statistical analyses

The assumed true response rate for both treatments was 84% by AS.[17,18] A NI margin of 8% was chosen to ensure no more than a 10% relative decrease in efficacy of SPMC oral solution from P/MC powder. The trial was designed to enroll 900 participants, approximately 450 per treatment group, to maintain at least 90% power to demonstrate NI of SPMC oral solution to P/MC powder at a one-sided 0.025 significance level.

Analysis populations included modified intent to treat (mITT; all participants who were randomized and received at least one dose of treatment); per protocol [PP; all mITT participants except those with major protocol deviations (e.g., those not taking medication at prescribed intervals)]; and safety (all subjects who received any medication). The mITT and safety populations were identical in this study.

Descriptive statistics [e.g., mean, standard deviation (SD)] were derived as appropriate, including for baseline and demographic characteristics. The primary efficacy endpoint ('responders') by AS was the proportion of participants with 'excellent' or 'good' ratings (mITT). The difference between the responder rates for overall colon cleansing using SPMC oral solution or P/MC powder was assessed with a two-sided 95% confidence interval (CI). This primary analysis CI adjusts for the stratification factor of site, where the stratification weights are based on Cochran–Mantel–Haenszel weights.[23]

The key secondary efficacy rate by BBPS was the proportion of participants with a segmental score of '3' or '2' in the right colon. The difference between the responder rates in right colon cleansing using SPMC oral solution or P/MC powder was assessed similarly to the primary endpoint, that is, with a two-sided 95% CI that adjusts for stratification factor of site. Responder rates for the left and transverse colon by BBPS were also calculated (mITT).

The prespecified NI margin for both efficacy endpoints (responders by AS; responders by BBPS in right colon) was −8% (comparison of SPMC oral solution *versus* P/MC powder). If both primary and key secondary efficacy endpoints met NI (the lower limit of the 95% CI was greater than −8%), then prespecified superiority testing for the primary efficacy endpoint was performed. If the lower bound of the 95% CI for the superiority test was above 0%, then superiority could be declared.

Adenoma detection rate (ADR) and polyp detection rate (PDR) were *ad hoc* analyses, calculated as the ratio of number of participants who had at least one adenoma or polyp, respectively : number of participants in the treatment group.

Results

The trial was conducted between 20 February 2017 (first enrollment) and 12 October 2017 (last follow-up visit). The trial ended after the expected number of participants had enrolled and completed.

Demographics

A total of 901 participants underdoing colonoscopy were treated and included in the analysis (Figure 1). The mean (SD) age was 57.2 (10.9) years and 55.7% were female (Table 1). The treatment groups had similar demographic characteristics.

Efficacy

The primary efficacy objective was met, with SPMC oral solution demonstrating NI to P/MC powder for responders by AS. The responder rate by AS was 87.7% (393/448) for SPMC oral solution and 81.5% (369/453) for P/MC powder [difference (95% CI): 6.3% (1.8, 10.9); Table 2; Figure 2].

The key secondary efficacy objective was also met, with SPMC oral solution demonstrating NI to P/MC powder for responders by BBPS in the right colon. The response rate by BBPS in the right colon was 94.2% (422/448) for SPMC oral solution and 89.6% (406/453) for P/MC powder [difference (95% CI): 4.6% (1.1, 8.0); Table 3].

After the prespecified criteria of NI were met for both primary efficacy and key secondary efficacy endpoints, a subsequent prespecified superiority test of the primary efficacy endpoint was

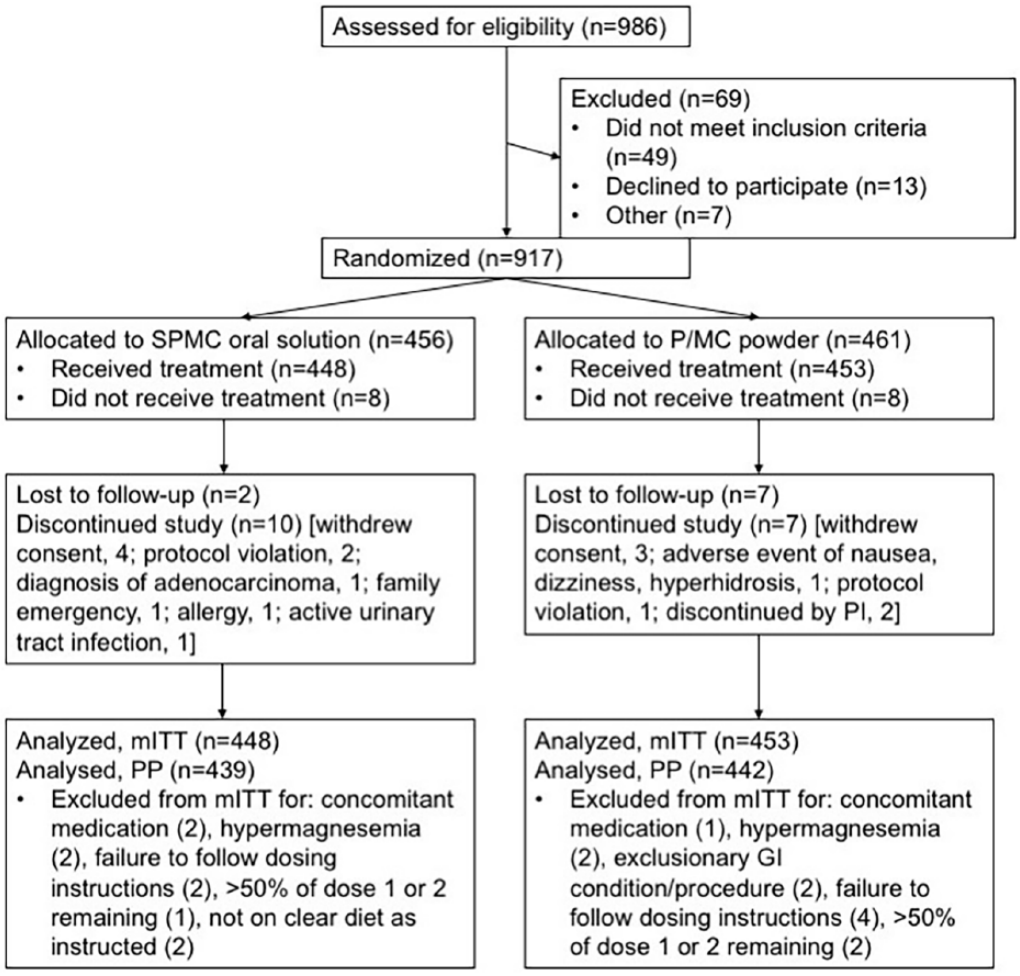

Figure 1. CONSORT diagram of study population.
GI, gastrointestinal; mITT, modified intent to treat; PP, per protocol; PI, prinicipal investigator; P/MC, sodium picosulfate, magnesium oxide, and citric acid; SPMC, sodium picosulfate, magnesium oxide, and citric acid.

performed. Superiority for the primary efficacy endpoint by AS was met at a two-sided significance level of 5% ($p = 0.0067$).

The mean (SD) total score on BBPS was 7.7 (1.4) for participants receiving SPMC oral solution ($n = 440$) and 7.3 (1.7) for those receiving P/MC powder ($n = 447$). Responder rates were calculated by BBPS in the transverse colon: 96.0% (430/448) for SPMC oral solution and 94.0% (426/453) for P/MC powder [difference (95% CI): 1.9% (−0.9, 4.7)]. The responder rate by BBPS in the left colon was 94.6% (424/448) for SPMC oral solution and 91.2% (413/453) for P/MC powder [difference (95% CI): 3.5% (0.2, 6.7)].

Inadequate bowel preparation by AS was seen in 0.9% (4/448) of the SPMC oral solution group and 2.2% (10/453) of the P/MC powder group (Table 2).

Compliance and tolerability

The majority of participants tolerated SPMC oral solution well. A sum of 98.9% of participants in both treatment groups completed most of the bowel preparation ($p = 0.67$). In the SPMC oral solution arm, 2/447 (0.4%) had at least 25% of the bowel preparation left, compared with 3/452 (0.7%) in the P/MC powder group. No data were available for 2/447 (0.4%) and 1/452 (0.2%) of participants in the SPMC oral solution and P/MC powder groups.

For SPMC oral solution and P/MC powder, 89.5% (400/447) and 95.8% (433/453) of

Table 1. Demographic characteristics, mITT population.

	SPMC oral solution ($n = 448$)	P/MC powder ($n = 453$)	Total ($n = 901$)
Age (years), mean (SD)	57.2 (11.0)	57.1 (10.9)	57.2 (10.9)
<65 years, *n* (%)	324 (72.3)	340 (75.1)	664 (73.7)
Female, *n* (%)	252 (56.3)	250 (55.2)	502 (55.7)
Race, *n* (%)			
White	376 (83.9)	394 (87.0)	770 (85.5)
Black/African American	49 (10.9)	41 (9.1)	90 (10.0)
Asian	13 (2.9)	5 (1.1)	18 (2.0)
Other	7 (1.6)	8 (1.8)	15 (1.7)
BMI, kg/m^2; mean (SD)	29.7 (6.1)	29.9 (5.4)	29.8 (5.8)

BMI, body mass index; mITT, modified intent to treat; P/MC, sodium picosulfate, magnesium oxide, and citric acid; SD, standard deviation; SPMC, sodium picosulfate, magnesium oxide, and citric acid.

Table 2. Primary efficacy endpoint, Aronchick Scale, mITT population.

% (*n*)	SPMC oral solution ($n = 448$)	P/MC powder ($n = 453$)	Total ($n = 901$)
Excellent	53.8 (241)	46.4 (210)	50.1 (451)
Good	33.9 (152)	35.1 (159)	34.5 (311)
Fair	9.6 (43)	15.0 (68)	12.3 (111)
Inadequate	0.9 (4)	2.2 (10)	1.6 (14)
No rating	1.8 (8)	1.3 (6)	1.6 (14)
Responders [95% CI]	87.7 (393) [84.3, 90.6]	81.5 (369) [77.6, 84.9]	84.6 (762) [82.0, 86.9]
Difference [95% CI][a]	6.3 [1.8, 10.9] $p = 0.0067$[b]		

[a]The CI for treatment difference was calculated using stratified (by site) proportion difference, where the weights are Cochran–Mantel–Haenszel weights for site.
[b]*p* value associated with the test of superiority.
CI, confidence interval; mITT, modified intent to treat; P/MC, sodium picosulfate, magnesium oxide, and citric acid; SPMC, sodium picosulfate, magnesium oxide, and citric acid.

participants, respectively, stated that the bowel preparation tolerability was 'easy' or 'acceptable' [Figure 3(a)]. Almost all participants were 'mostly willing' or 'somewhat willing' to use the study bowel preparation in the future [97.5% (436/448) SPMC oral solution *versus* 98.7% (446/453) P/MC powder; Figure 3(b)]. The majority of participants were not bothered or only mildly bothered by a bad taste in their mouth [83.2% (371/448) SPMC oral solution *versus* 94.0% (426/453) P/MC powder; Figure 3(c)].

For 58.3% (261/447) of participants in the SPMC oral solution group and 62.0% (281/453) of participants in the P/MC group, the study colonoscopy was not their first colonoscopy. In this subgroup, 72.8% (190/261) and 74.4% (209/281) of participants in the SPMC oral solution group

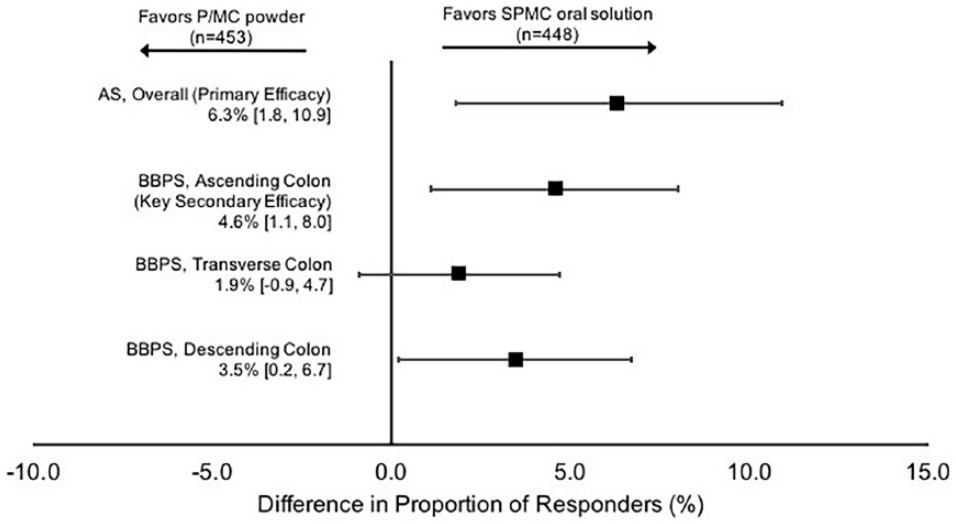

Figure 2. Forest plots showing the treatment difference between SPMC oral solution and P/MC powder bowel preparations on several efficacy endpoints in the mITT population.
Error bars depict the 95% CI, given in brackets. The CI for treatment difference was calculated using stratified (by site) proportion difference, where the weights are Cochran–Mantel–Haenszel weights for site.
AS, Aronchick Scale; BBPS, Boston Bowel Preparation Scale; CI, confidence interval; mITT, modified intent to treat; P/MC, picosulfate, magnesium oxide, and citric acid powder; SPMC, sodium picosulfate, magnesium oxide, and citric acid.

Table 3. Key secondary efficacy endpoint, BBPS in right colon, mITT population.

% (*n*)	SPMC oral solution (*n* = 448)	P/MC powder (*n* = 453)	Total (*n* = 901)
3	51.6 (231)	44.4 (201)	47.9 (432)
2	42.6 (191)	45.3 (205)	44.0 (396)
1	4.0 (18)	8.4 (38)	6.2 (56)
0	0	0.7 (3)	0.3 (3)
No rating	1.8 (8)	1.3 (6)	1.6 (14)
Responders [95% CI]	94.2 (422) [91.6, 96.2]	89.6 (406) [86.4, 92.3]	91.9 (828) [89.9, 93.6]
Difference [95% CI][a]	4.6 [1.1, 8.0] $p = .0099$[b]		

[a]The CI for treatment difference was calculated using stratified (by site) proportion difference, where the weights are Cochran–Mantel–Haenszel weights for site.
[b]*p* value associated with the test of superiority.
BBPS, Boston Bowel Preparation Scale; CI, confidence interval; mITT, modified intent to treat; P/MC, sodium picosulfate, magnesium oxide, and citric acid; SPMC, sodium picosulfate, magnesium oxide, and citric acid.

and P/MC group, respectively, stated that the tolerability of the study bowel preparation was better compared with previous bowel preparation(s) [Figure 3(d)]. Only 1.9% (5/261) and 1.8% (5/281) of participants, respectively, reported the study bowel preparation as worse than their previous preparation(s).

Lesion detection

All endoscopic findings during the colonoscopy were classified as AEs, and any malignancies were classified as serious AEs (AEs as incidental findings of the procedure, not AEs related to the study drug). A *post hoc* analysis was conducted to determine PDR, as well as associated pathology.

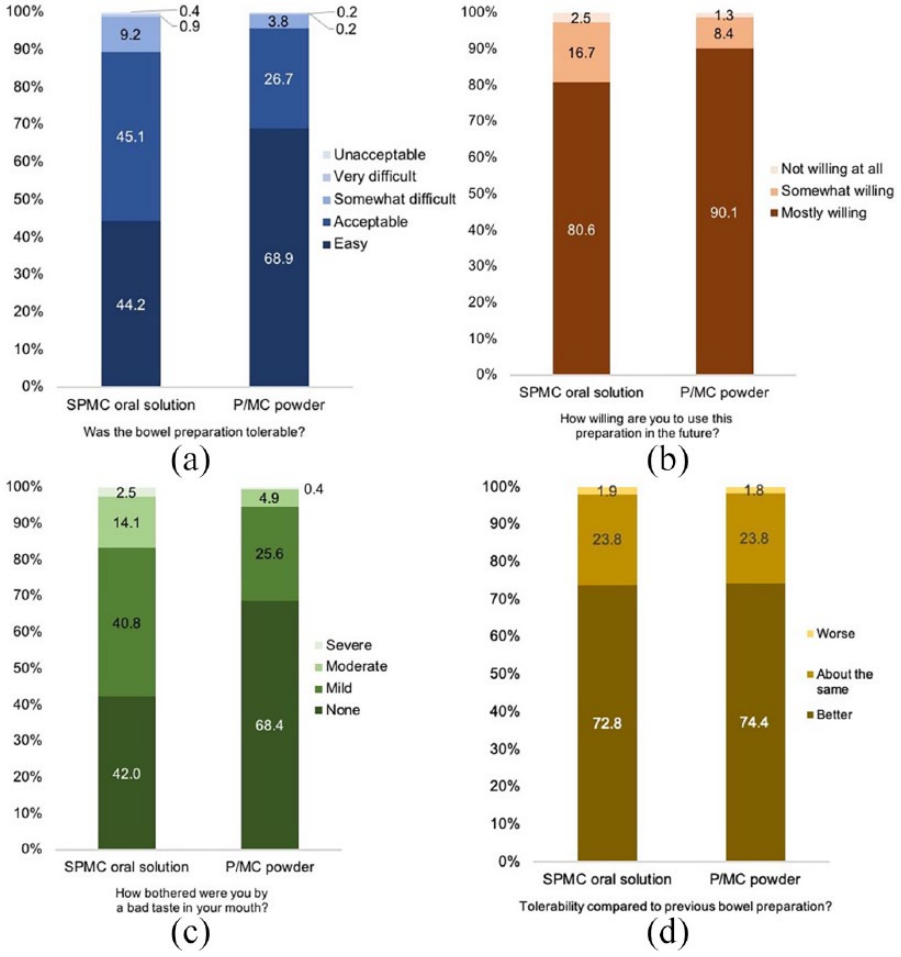

Figure 3. Responses to the Mayo Clinic Bowel Prep Tolerability Questionnaire for the mITT population.
Participants tolerated SPMC oral solution well, with most (a) saying that the bowel preparation was 'easy' or 'acceptable', (b) willing to use this preparation again, and (c) not bothered or only mildly bothered by a bad taste; (d) of the participants who had a previous screening colonoscopy ($n = 261$ for SPMC oral solution, $n = 281$ for P/MC powder), most stated that the tolerability of the study bowel preparation was better than the previous bowel preparation.
mITT, modified intent to treat; P/MC, picosulfate, magnesium oxide; SPMC, sodium picosulfate, magnesium oxide, and citric acid.

Overall, the PDR was 45.3% (203/448) for SPMC oral solution and 45.7% (207/453) for P/MC powder (Table 4). Approximately half of all polyps were found to be adenomas. The ADR was 31.5% (141/448) for SPMC oral solution and 28.7% (130/453) for P/MC powder. Females receiving SPMC oral solution had an ADR of 26.2% (66/252) and a PDR of 40.1% (101/252), and males had an ADR of 38.3% (75/196) and a PDR of 52.0% (102/196).

Safety

Serious treatment-emergent AEs (TEAEs) were reported for 2.0% (9/448) of participants receiving SPMC oral solution and 1.3% (6/453) of those receiving P/MC powder (Table 5). None was reported as related to the study drug. For SPMC oral solution, serious TEAEs reported were atrial fibrillation (one), ascites (one), post-procedural hemorrhage (one), and neoplasm (seven). For P/MC powder, serious TEAEs reported were GI hemorrhage (one), influenza (one), neoplasm (three), and aspiration pneumonia (one).

There were no deaths in either group. Three participants experienced severe TEAEs possibly related to the study drug: one participant experienced hyperhidrosis, nausea, and dizziness after the first dose of P/MC powder and discontinued the study drug; one participant receiving SPMC

Table 4. Colonoscopy polyp and adenoma findings, mITT population.

	SPMC oral solution	P/MC powder	Total
Participants, *n*	448	453	901
Participants with polyps, *n*	203	207	410
PDR, %	45.3	45.7	45.5
Total number of polyps	448	425	873
Histology of polyps, *n* (%)[a]			
Adenoma	251 (56.0)	208 (48.9)	459 (52.6)
Hyperplastic	136 (30.4)	116 (27.3)	252 (28.9)
Serrated	18 (4.0)	17 (4.0)	35 (4.0)
Unknown	28 (6.3)	59 (13.9)	87 (10.0)
Not applicable	14 (3.1)	23 (5.4)	37 (4.2)
Missing	1 (0.2)	2 (0.5)	3 (0.3)
Morphology of polyps, *n* (%)[a]			
Sessile	255 (56.9)	227 (53.4)	482 (55.2)
Flat	64 (14.3)	70 (16.5)	134 (15.3)
Pedunculated	34 (7.6)	26 (6.1)	60 (6.9)
Unknown	95 (21.2)	98 (23.1)	193 (22.1)
Not applicable	0	4 (0.9)	4 (0.5)
Participants with ⩾1 adenoma, *n*	141	130	271
ADR, %[b]	31.5	28.7	30.1

[a]The total number of polyps per each category is presented. Percentage is calculated as the proportion of the total number polyps.
[b]ADR is calculated as the percentage of participants who had an adenoma.
ADR, adenoma detection rate; mITT, modified intent to treat; PDR, polyp detection rate; P/MC, sodium picosulfate, magnesium oxide, and citric acid; SPMC, sodium picosulfate, magnesium oxide, and citric acid.

oral solution experienced nausea and dizziness, which resolved without treatment; and one participant receiving P/MC powder experienced left bundle branch block, which resolved without treatment.

For SPMC oral solution and P/MC powder, respectively, headache was reported in 2.7% (12/448) of participants and 3.1% (14/453) of participants, and hypermagnesemia was reported in 2.0% (9/448) of participants and 5.1% (23/453) of participants. Hypermagnesemia was transient in nature, with elevated levels typically returning to baseline within 24–48 h without sequela. The most commonly reported drug-related TEAEs involved the GI system and were reported by 4.9% (22/448) of participants receiving SPMC oral solution and 4.9% (22/453) of participants receiving P/MC powder (Table 6). Participants taking SPMC oral solution or P/MC powder reported nausea (3.1% *versus* 2.9%), vomiting (1.3% *versus* 0.7%), abdominal distension (0.4% *versus* 0.7%), and abdominal pain (0.7% *versus* 0.2%). None of the drug-related TEAEs were reported as serious. No other clinically significant differences were seen from baseline in hematology, clinical chemistry, or urinalysis.

Table 5. Treatment-emergent adverse events, safety population.

% (*n*)	SPMC oral solution (*n* = 448)	P/MC powder (*n* = 453)	Total (*n* = 901)
Any TEAE	84.4 (378)	84.8 (384)	84.6 (762)
Deaths	0	0	0
Serious TEAEs	2.0 (9)	1.3 (6)	1.7 (15)
TEAEs leading to study discontinuation	0	0	0
Severe TEAEs	2.5 (11)	2.2 (10)	2.3 (21)
Adverse drug reactions	13.2 (59)	16.8 (76)	15.0 (135)
Serious adverse drug reaction	0	0	0

P/MC, sodium picosulfate, magnesium oxide, and citric acid; SPMC, sodium picosulfate, magnesium oxide, and citric acid; TEAE, treatment-emergent adverse event.

Table 6. Treatment-emergent, drug-related gastrointestinal AEs, safety population.

% (*n*)	SPMC oral solution (*n* = 448)	P/MC powder (*n* = 453)	Total (*n* = 901)
Gastrointestinal system	4.9 (22)	4.9 (22)	4.9 (44)
Nausea	3.1 (14)	2.9 (13)	3.0 (27)
Vomiting	1.3 (6)	0.7 (3)	1.0 (9)
Abdominal distention	0.4 (2)	0.7 (3)	0.6 (5)
Abdominal pain	0.7 (3)	0.2 (1)	0.4 (4)

AE, adverse event; P/MC, sodium picosulfate, magnesium oxide, and citric acid; SPMC, sodium picosulfate, magnesium oxide, and citric acid.

Discussion

Ready-to-drink SPMC oral solution met the primary efficacy criteria of NI and further demonstrated superior efficacy of overall colon cleansing by AS compared with P/MC powder. Evaluation by AS was chosen as the primary efficacy endpoint for this NI study to align with the pivotal studies of P/MC powder *versus* PEG-3350 with bisacodyl, which used the same endpoint.[17,18] Additionally, the split-dose, low-volume SPMC oral solution bowel preparation was efficacious in cleaning the right, transverse, and left colon segments, as assessed by BBPS. BBPS is a highly validated and frequently used measure for quality of colon cleansing, and is recommended for use in the clinic.[20,21] The superior efficacy of SPMC oral solution may be attributed to the ready-to-drink formulation that required no mixing or stirring and ensured a fully dissolved solution. Another factor could be that SPMC oral solution dosing instructions specified at least four 8-oz glasses of clear liquid after the second dose compared with the three 8-oz glasses specified for P/MC powder, allowing for more hydration.

High-quality bowel preparations improve the detection rate of adenomas, including small lesions and those with advanced histology.[24] High-quality bowel preparations are also associated with greater detection of sessile serrated polyps.[25] Increased ADRs were observed in participants with tolerable bowel preparation experiences.[26] Increased ADRs are directly associated with a decrease in CRC occurrence and death due to CRC.[1]

In this study, SPMC oral solution demonstrated an overall ADR of 31.5%, which exceeds the guideline-directed target of ⩾25% ADR.[12] However, the study was not designed with ADR as an efficacy endpoint. An ADR of 31.5% is well

within or above the range of values seen in other studies of bowel preparation quality and screening colonoscopy.[1,27]

A recent meta-analysis of bowel preparation quality and ADR in screening colonoscopy showed that patients with adequate bowel preparation by AS (defined as those with 'excellent,' 'good,' or 'fair' ratings) had sufficient ADR for follow up at guideline-recommended intervals, and only patients with inadequate bowel preparation should have earlier repeat-screening colonoscopy.[27] In this study, 87.7% of patients met the predefined criteria for responder (only patients with 'excellent' or 'good' ratings by AS). Using the criteria defined in the aforementioned meta-analysis, 97.3% of those in the SPMC oral solution group (responders plus those with a 'fair' rating, i.e., 9.6% of the group) had an adequate quality of colon cleansing, sufficient for follow up at guideline-recommended intervals. In this study, only 0.9% of patients in the SPMC oral solution group had an 'inadequate' rating by AS.

SPMC oral solution showed good tolerability in this study, with most participants willing to repeat the preparation, and preferring SPMC oral solution over previous bowel preparation(s). Previous studies of P/MC powder show that it has historically been very tolerable.[17,18,28–30] SPMC oral solution has several properties that likely contribute to its good tolerability, including a favorable taste profile, low volume of active drug solution to ingest (160 ml), and ability to supplement with clear liquids of the patient's choice. This is especially highlighted by the fact that almost all patients were able to complete the SPMC oral solution bowel preparation.

The AE profiles of SPMC oral solution and P/MC powder were comparable, with the most common drug-related AEs being nausea (3.1% *versus* 2.9%, respectively), headache (2.7% *versus* 3.1%, respectively), and hypermagnesemia (2.0% *versus* 5.1%, respectively).

Possible limitations of the study include a patient population that may not reflect the general population[31] (e.g., excluding certain GI disorders or prior procedures) and unknown adherence to mixing instructions for P/MC powder (stirring for full 2–3 min). The impact of these variables on the outcomes is unknown.

Advantages of the study include the large population; the randomized, controlled trial design; multicenter study with several types of participating sites, representing a wide spectrum of study drug use; efficacy was measured using two validated scales that measure colon cleansing on colonoscope insertion and withdrawal; and the prespecified type 1 control *via* the hierarchical evaluation of the hypothesis tests associated with the primary and key secondary endpoints. This enabled us to conclude that the primary NI and superiority criteria and the key secondary NI criteria were met without inflating the type 1 error rate.

The ideal bowel preparation is one that is highly effective, safe, convenient, and tolerable enough that participants are not deterred from completing the preparation and following through with the procedure.[5] Bowel preparations that are more tolerable and easier to complete are viewed favorably by participants.[3,6,13] Low-volume bowel preparations are shown to be more tolerable compared with high-volume preparations.[3] Bowel preparations that are easier to complete should contribute to increased likelihood of an effective preparation, with an associated increase in adenoma detection and CRC prevention.

At present, there are no other commercially available, ready-to-drink formulations of low-volume bowel preparation for colonoscopy in the US. The ready-to-drink formulation of SPMC oral solution offers participants a convenient bowel preparation that requires no mixing, stirring, or dilution. With simplified instructions to follow compared with liquid bowel preparations that require mixing or diluting, participants may have a lower barrier to adhering to dosing instructions.

Conclusion

Ready-to-drink SPMC oral solution showed superior efficacy of overall colon cleansing compared with P/MC powder. In this robust study, both primary and secondary efficacy endpoints were met, and SPMC oral solution efficacy was demonstrated on two different measurement scales. SPMC oral solution had a similar safety and tolerability profile to P/MC powder. SPMC oral solution should be preferentially considered for all bowel preparations for colonoscopy.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

Prior publication

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Supplemental material

Supplemental material for this article is available online.

References

1. Corley DA, Jensen CD, Marks AR, *et al.* Adenoma detection rate and risk of colorectal cancer and death. *N Engl J Med* 2014; 370: 1298–1306.
2. Jang JY and Chun HJ. Bowel preparations as quality indicators for colonoscopy. *World J Gastroenterol* 2014; 20: 2746–2750.
3. Johnson DA, Barkun AN, Cohen LB, *et al.* Optimizing adequacy of bowel cleansing for colonoscopy: recommendations from the US Multi-Society Task Force on Colorectal Cancer. *Gastroenterology* 2014; 147: 903–924.
4. Saltzman JR, Cash BD, Pasha SF, *et al.* Bowel preparation before colonoscopy. *Gastrointest Endosc* 2015; 81: 781–794.
5. Harrison NM and Hjelkrem MC. Bowel cleansing before colonoscopy: balancing efficacy, safety, cost and patient tolerance. *World J Gastroenterol Endosc* 2016;8:4–12.
6. Hautefeuille G, Lapuelle J, Chaussade S, *et al.* Factors related to bowel cleansing failure before colonoscopy: results of the PACOME study. *United Eur Gasteroenterol J* 2014; 2: 22–29.
7. Wexner SD, Beck DE, Baron TH, *et al.* Consensus document on bowel preparation for colonoscopy. *Gastrointest Endosc* 2006; 63: 894–909.
8. Nguyen DL and Weiland M. Risk factors predictive of poor quality preparation during average risk colonoscopy screening: the importance of health literacy. *J Gastrointest Liver Dis* 2010; 19: 369–372.
9. Smith SG, Von Wagner C, McGregor LM, *et al.* The influence of health literacy on comprehension of a colonoscopy preparation information leaflet. *Dis Colon Rectum* 2012; 55: 1074–1080.
10. Lebwohl B, Kastrinos F, Glick M, *et al.* The impact of suboptimal preparation on adenoma miss rates and the factors associated with early repeat colonoscopy. *Gastrointest Endosc* 2011; 73: 1207–1214.
11. Romero RV and Mahadeva S. Factors influencing quality of bowel preparation for colonoscopy. *World J Gastroenterol* 2013; 5: 39–46.
12. Rex DK, Schoenfeld PS, Cohen J, *et al.* Quality indicators for colonoscopy. *Gastrointest Endosc* 2015; 81: 31–53.
13. Bechtold ML, Mir F, Puli SR, *et al.* Optimizing bowel preparation for colonoscopy: a guide to enhance quality of visualization. *Ann Gastroenterol* 2016; 29: 137–146.
14. Horton N, Garber A, Hasson H, *et al.* Impact of single- vs. split-dose low-volume bowel preparations on bowel movement kinetics, patient

inconvenience, and polyp detection: a prospective trial. *Am J Gastroenterol* 2016; 111: 1330–1337.

15. Munsterman ID, Cleeren E, van der Ploeg T, *et al*. 'Pico–Bello–Klean study': effectiveness and patient tolerability of bowel preparation agents sodium picosulphate–magnesium citrate and polyethylene glycol before colonoscopy. A single-blinded randomized trial. *Eur J Gastroenterol Hepatol* 2015; 27: 29–38.
16. Rex DK. Optimal bowel preparation - a practical guide for clinicians. *Nat Rev Gastroenterol Hepatol* 2014; 11: 419–425.
17. Katz PO, Rex DK, Epstein M, *et al*. A dual-action, low-volume bowel cleanser administered the day before colonoscopy: results from the SEE CLEAR II study. *Am J Gastroenterol* 2013; 108: 401–409.
18. Rex DK, Katz PO, Bertiger G, *et al*. Split-dose administration of a dual-action, low-volume bowel cleanser for colonoscopy: the SEE CLEAR I study. *Gastrointest Endosc* 2013; 78: 132–141.
19. 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: 346–352.
20. Parmar R, Martel M, Rostom A, *et al*. Validated scales for colon cleansing: a systematic review. *Am J Gastroenterol* 2016; 111: 197–204.
21. Kastenberg D, Bertiger G and Brogadir S. Bowel preparation quality scales for colonoscopy. *World J Gastroenterol* 2018; 24: 2833–2843.
22. Patel M, Staggs E, Thomas CS, *et al*. Development and validation of the Mayo Clinic Bowel Prep Tolerability Questionnaire. *Dig Liver Dis* 2014; 46: 808–812.
23. Kim Y and Won S. Adjusted proportion difference and confidence interval in stratified randomized trials. Paper SP04. *PharmaSUG* 2013.
24. Sherer EA, Imler TD and Imperiale TF. The effect of colonoscopy preparation quality on adenoma detection rates. *Gastrointest Endosc* 2012; 75: 545–553.
25. Clark BT and Laine L. High-quality bowel preparation is required for detection of sessile serrated polyps. *Clin Gastroenterol Hepatol* 2016; 14: 1155–1162.
26. Holt EW, Yimam KK, Ma H, *et al*. Patient tolerability of bowel preparation is associated with polyp detection rate during colonoscopy. *J Gastrointest Liver Dis* 2014; 23: 135–140.
27. Clark BT, Rustagi T and Laine L. What level of bowel prep quality requires early repeat colonoscopy: systematic review and meta-analysis of the impact of preparation quality on adenoma detection rate. *Am J Gastroenterol* 2014; 109: 1714–1724.
28. Sacks NC, Sharma A, Cyr PL, *et al*. Real-world comparison of the effectiveness and safety of different bowel preparation agents. *Clin Experim Gastroenterol* 2018; 11: 289–299.
29. Kojecky V, Dolina J, Kianicka B, *et al*. A single or split dose picosulphate/magnesium citrate before colonoscopy: comparison regarding tolerance and efficacy with polyethylene glycol. A randomized trial. *J Gastrointest Liver Dis* 2014; 23: 141–146.
30. Kim HG, Huh KC, Koo HS, *et al*. Sodium picosulfate with magnesium citrate (SPMC) plus laxative is a good alternative to conventional large volume polyethylene glycol in bowel preparation: a multicenter randomized single-blinded trial. *Gut Liver* 2015; 9: 494–501.
31. Wang C, Yang R and Hookey LC. Does it work in clinical practice? A comparison of colonoscopy cleansing effectiveness in clinical practice versus efficacy from selected prospective trials. *J Can Assoc Gastroenterol*. Epub 12 February 2019. DOI: 10.1093/jcag/gwy070