Ther Adv Gastroenterol
2021, Vol. 14: 1–12
DOI: 10.1177/17562848211024458


# Safety and efficacy of sodium picosulfate, magnesium oxide, and citric acid bowel preparation in patients with baseline renal impairment or diabetes: subanalysis of a randomized, controlled trial

**Gautam N. Mankaney, Masakazu Ando, David N. Dahdal and Carol A. Burke**

***Abstract***

**Background:** Selecting a bowel preparation for patients with renal impairment or diabetes requires special consideration. We aimed to describe the effect of baseline renal impairment or diabetes on the safety, efficacy, and tolerability of low-volume sodium picosulfate, magnesium oxide, and citric acid (SPMC) ready-to-drink oral solution bowel preparation.

**Methods:** A *post hoc* secondary analysis was performed from a randomized, assessor-blinded study of SPMC oral solution bowel preparation in participants with mild or moderate baseline renal impairment or diabetes. Primary efficacy endpoint ('responders') was the proportion of participants with 'excellent' or 'good' ratings on a modified Aronchick Scale (AS). Secondary efficacy outcomes were the quality of ascending colon cleansing from the Boston Bowel Preparation Scale (BBPS), and selected results from the Mayo Clinic Bowel Prep Tolerability Questionnaire. Safety assessments included adverse events (AEs), adenoma detection, and laboratory evaluations.

**Results:** Similar overall colon cleansing was demonstrated in the subgroups, with >85% of participants in any subgroup rated as responders by the AS, and >92% of participant responders by the BBPS. Most participants reported a tolerable bowel preparation, regardless of baseline renal impairment or diabetes history. Safety of SPMC oral solution was similar between all subgroups and the overall cohort. For the mild renal impairment, moderate renal impairment, and diabetes subgroups, respectively, commonly reported, drug-related AEs were nausea (2.6%, 5.3%, 1.4%) and headache (2.2%, 2.6%, 4.3%).

**Conclusions:** Ready-to-drink SPMC oral solution demonstrated efficacious colon cleansing in patients with baseline mild/moderate renal impairment or diabetes, with a tolerable bowel preparation reported by most.

**Clinical Trial Registration:** ClinicalTrials.gov identifier: NCT03017235

***Keywords:*** bowel cleansing, colon cleansing, colonoscopy, diabetes, renal impairment

Received: 24 December 2020; revised manuscript accepted: 24 May 2021.

Correspondence to:
**Carol A. Burke**
Department of Gastroenterology, Hepatology and Nutrition, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195, USA
**burkec1@ccf.org**

**Gautam N. Mankaney**
Department of Gastroenterology, Hepatology and Nutrition, Cleveland Clinic, Cleveland, OH, USA

**Masakazu Ando**
**David N. Dahdal**
Ferring Pharmaceuticals Inc, Parsippany, NJ, USA

## Introduction

Adequate bowel preparation is necessary for effective colonoscopy. The consequences of poor bowel preparation can range from aborted examinations, need for early repeat colonoscopy with additional bowel preparation, missed adenomas, decreased efficiency in the endoscopy unit, increased adverse events (AEs), and other direct and indirect costs.[1–5] Effective bowel preparations have been associated with higher adenoma

detection, and recommendations for follow-up screening and surveillance colonoscopy at intervals according to guideline recommendations.[6–8]

While many bowel preparations are available for colonoscopy cleansing, the volume, taste, tolerability, and dosing regimens vary. Data have shown that tolerability, which can be influenced through lower volume and improved taste of the preparation agent, can improve the patient experience and colonoscopy outcomes.[9–11] Poor patient tolerability for bowel preparation is associated with lower rate of polyp detection.[12] Split-dose polyethylene glycol (PEG)-based bowel preparation significantly increased participant willingness to repeat their preparation compared with day-before PEG dosing, and is also associated with improved colon cleansing.[13–18]

Safety is an essential attribute of bowel preparation that must be considered when prescribed. While the majority of healthy patients undergo colonoscopy safely and effectively after the use of any commercial bowel preparation, certain patients, including those with chronic diseases such as renal disease or diabetes, require special consideration.[19,20] A low-volume bowel preparation that is safe and effective in high-risk populations, such as those with renal impairment or diabetes, would be welcomed.

Underlying chronic kidney disease may cause electrolyte imbalances, and volume shifts with bowel preparation need to be taken into consideration for patients with renal impairment.[10] Some bowel preparations are associated with renal side effects, such as sodium phosphate solution, which causes fluid and electrolyte shifts.[21] Though PEG is the standard of care for patients at risk of fluid or electrolyte shifts, PEG has been associated with transient electrolyte shifts, and a small, reversible risk of developing renal injury.[22] There are limited data available on the colon-cleansing efficacy of low-volume bowel preparation in individuals with renal dysfunction.[23]

Diabetes has been associated with poor bowel preparation.[24–26] Current clinical practice guidelines do not specifically address selecting a bowel preparation for patients with diabetes.[15,16]

While sodium picosulfate, magnesium oxide, and citric acid (SPMC) bowel preparation has been shown to induce electrolyte shifts, these shifts were transient in nature and not clinically significant.[27] A previous study in patients with baseline renal impairment demonstrated minor and transient elevations of serum magnesium that did not result in clinically significant consequences.[28] Our aim in this study was to describe the effect of baseline renal impairment or diabetes on the safety efficacy, tolerability, and of low-volume SPMC ready-to-drink oral solution bowel preparation in a *post hoc* secondary analysis from a phase III trial.

## Methods

A *post hoc* secondary analysis of a phase III study was performed to assess efficacy, safety, and tolerability in two subgroups from a cohort of 448 participants receiving SPMC ready-to-drink, low-volume oral solution bowel preparation. The participants had baseline renal impairment or diabetes. The phase III, randomized, assessor-blinded, multicenter, non-inferiority study compared split-dose, low-volume SPMC oral solution (Clenpiq®, Ferring Pharmaceuticals Inc., Parsippany, NJ) with split-dose, low-volume SPMC powder for oral solution (Prepopik®, Ferring Pharmaceuticals Inc., Parsippany, NJ) [ClinicalTrials.gov identifier: NCT03017235]. Details of the full study have been published previously.[29] The study was conducted in accordance with the principles set forth in the Declaration of Helsinki and in compliance with International Conference on Harmonisation-Good Clinical Practice (ICH-GCP) standards. The study protocol was approved by Schulman IRB (protocol #000253).

Eligible participants included females and males, 18–80 years of age, who were undergoing elective colonoscopy (screening, surveillance, or diagnostic). Patients with severe renal impairment [estimated glomerular filtration rate (eGFR) $<30$ ml/min/1.73 m$^2$] were excluded from enrollment. Written informed consent was obtained at screening. Full inclusion and exclusion criteria have been published previously.[29]

Renal function at baseline was classified according to National Kidney Foundation definitions (mild impairment: eGFR 60–89 ml/min/1.73 m$^2$; moderate impairment: eGFR 30–59 ml/min/1.73 m$^2$). eGFR was calculated from baseline serum creatinine levels (which were measured prior to administration of any study drug) using the Modification of Diet in Renal Disease study formula at the

central laboratory. Participants with diabetes were defined as those who reported a medical history of any diabetes (including type 1 diabetes mellitus and type 2 diabetes mellitus). During this study, participants with diabetes were instructed to continue taking all anti-diabetes medication, including insulin, as usual. Participants with diabetes were given a suggested list of acceptable clear fluids to ingest every hour (such as apple juice, flavored gelatin, and popsicles) that would help them meet their carbohydrate needs during the bowel preparation.

The analysis included all subgroup participants who were randomized and received at least one dose of the study drug [modified intent-to-treat (mITT) population]. Baseline and demographic characteristics were descriptively summarized.

The responder rates for overall colon cleansing on the Aronchick Scale (AS) and ascending colon cleansing on the Boston Bowel Preparation Scale (BBPS) were summarized with exact 95% confidence intervals (CIs), calculated by the Clopper–Pearson method. Responders by the AS were the proportion of participants with 'excellent' or 'good' ratings. Responders by the BBPS were the proportion of participants with a segmental score of '3' or '2' in the ascending colon. These two validated scales were used to assess quality of colon cleansing before washing/suctioning (AS) and after washing/suctioning (BBPS) to provide a more direct measure of bowel preparation efficacy and a more real-world practice situation, respectively.[30–32] The colon-cleansing assessment was performed locally by the endoscopist who was blinded to the treatment group. Investigators received training on properly using the scales at the Investigator Meeting prior to beginning the study.

Tolerability endpoints from the Mayo Clinic Bowel Prep Tolerability Questionnaire were descriptively summarized.[33] Safety assessments included AEs and laboratory evaluations. AEs were classified according to the Medical Dictionary for Regulatory Activities (MedDRA), version 20.1. A treatment-emergent adverse event (TEAE) was any AE that occurred or a pretreatment AE/medical condition that worsened in intensity after starting the study drug and within 30 days of last exposure to study drug and did not necessarily have a causal relationship with the study drug. All AEs were classified in intensity on a scale of mild, moderate, or severe. A severe TEAE was one that led to an inability to work or perform usual activities. A serious TEAE was one that resulted in death, was life threatening, required or prolonged an existing hospitalization, resulted in persistent or significant disability/incapacity, was a congenital anomaly, or was an important medical event (that jeopardized the participant or required intervention to prevent another outcome listed).

The endoscopist noted the number of polyps found during the colonoscopy, and resected polyps, when possible, which were then sent for histological analysis. Adenoma detection rate (ADR) and polyp detection rate was calculated as the proportion of participants who had at least one adenoma or polyp, respectively, in the subgroup. Polyp and adenoma findings were not a prespecified efficacy endpoint in the study. As required by the study protocol, following guidance from the International Conference on Harmonisation and US Food and Drug Administration, all endoscopic findings, including polyps, found during the study period were reported as an AE as an incidental finding (i.e. not related to the study drug), and all malignancies were reported as a serious AE.

## Results

Of the 448 participants who received SPMC oral solution, 61.2% (274/448) had mild renal impairment, 8.5% (38/448) had moderate renal impairment, 15.4% (69/448) had a history of diabetes, and 9.2% (41/448) had both renal impairment and diabetes (Table 1). Participants with moderate baseline renal impairment or diabetes history were slightly older, on average, than the overall cohort. The mean body mass index (BMI) was higher for the diabetes subgroup than the overall cohort. In the diabetes subgroup, the majority (59/69) had type 2 diabetes mellitus.

Consistent overall colon cleansing by AS was seen in the subgroups (Figure 1; Table 2). A total of 87.7% of the overall cohort were responders, including 88.0% and 86.8% of the mild and moderate renal impairment subgroups, respectively, and 85.5% of diabetes subgroup. There was a very low rate (<1%) of participants with an 'inadequate' rating in any subgroup.

Similarly, ratings for ascending colon cleansing by BBPS were consistent across renal and

**Table 1.** Demographic and baseline characteristics, mITT population.

| | Renal subgroup | | Diabetes subgroup | Overall cohort |
|---|---|---|---|---|
| | Mild impairment (*n* = 274) | Moderate impairment (*n* = 38) | (*n* = 69) | (*n* = 448) |
| Age, years, mean (SD) | 57.8 (9.9) | 63.8 (7.4) | 60.6 (8.7) | 57.2 (11.0) |
| Female, *n* (%) | 155 (56.6) | 23 (60.5) | 42 (60.9) | 252 (56.3) |
| Race, *n* (%) | | | | |
| White | 242 (88.3) | 33 (86.8) | 52 (75.4) | 376 (83.9) |
| Black/African American | 23 (8.4) | 4 (10.5) | 11 (15.9) | 49 (10.9) |
| Asian | 6 (2.2) | 1 (2.6) | 2 (2.9) | 13 (2.9) |
| Other | 3 (1.1) | 0 | 4 (5.8) | 7 (1.6) |
| BMI, kg/m$^2$, mean (SD) | 29.4 (5.9) | 31.6 (7.0) | 33.0 (6.7) | 29.7 (6.1) |

BMI, body mass index; mITT, modified intent-to-treat; SD, standard deviation.

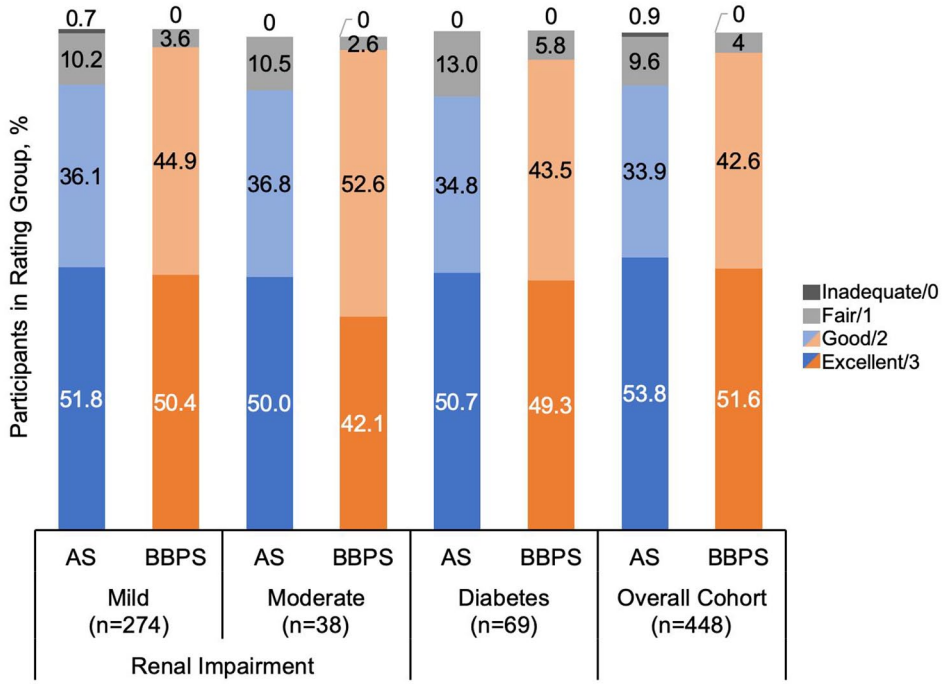


**Figure 1.** Colon-cleansing efficacy by AS and BBPS was consistent across renal impairment subgroups and the diabetes subgroup relative to the overall SPMC oral solution cohort.
Participants considered responders by AS (shown in blue; rating of 'excellent' or 'good') or BBPS (shown in orange; rating of '3' or '2') were similar across subgroups. The overall cohort represents all participants in the randomized, controlled trial who received SPMC oral solution.
AS, Aronchick Scale; BBPS, Boston Bowel Preparation Scale; SPMC, sodium picosulfate, magnesium oxide, and citric acid.

**Table 2.** Primary efficacy endpoint, overall colon cleansing by modified AS, mITT population.

| % (*n*) | Renal subgroup | | Diabetes subgroup | Overall cohort |
|---|---|---|---|---|
| | Mild impairment (*n* = 274) | Moderate impairment (*n* = 38) | (*n* = 69) | (*n* = 448) |
| Excellent | 51.8 (142) | 50.0 (19) | 50.7 (35) | 53.8 (241) |
| Good | 36.1 (99) | 36.8 (14) | 34.8 (24) | 33.9 (152) |
| Fair | 10.2 (28) | 10.5 (4) | 13.0 (9) | 9.6 (43) |
| Inadequate | 0.7 (2) | 0 | 0 | 0.9 (4) |
| No rating | 1.1 (3) | 2.6 (1) | 1.4 (1) | 1.8 (8) |
| Responders* [95% CI for proportion] | 88.0 (241) [83.5, 91.6] | 86.8 (33) [71.9, 95.6] | 85.5 (59) [75.0, 92.8] | 87.7 (393) [84.3, 90.6] |

*Responders were those rated 'excellent' or 'good' on the modified AS before suctioning/washing by an endoscopist blinded to the treatment group, and the 95% CI of the responder rate was calculated using the Clopper-Pearson method.
AS, Aronchick Scale; CI, confidence interval; mITT, modified intent-to-treat.

**Table 3.** Key secondary efficacy endpoint, ascending colon cleansing by BBPS, mITT population.

| % (*n*) | Renal subgroup | | Diabetes subgroup | Overall cohort |
|---|---|---|---|---|
| | Mild impairment (*n* = 274) | Moderate impairment (*n* = 38) | (*n* = 69) | (*n* = 448) |
| 3 | 50.4 (138) | 42.1 (16) | 49.3 (34) | 51.6 (231) |
| 2 | 44.9 (123) | 52.6 (20) | 43.5 (30) | 42.6 (191) |
| 1 | 3.6 (10) | 2.6 (1) | 5.8 (4) | 4.0 (18) |
| 0 | 0 | 0 | 0 | 0 |
| No rating | 1.1 (3) | 2.6 (1) | 1.4 (1) | 1.8 (8) |
| Responders* [95% CI for proportion] | 95.3 (261) [92.0, 97.4] | 94.7 (36) [82.3, 99.4] | 92.8 (64) [83.9, 97.6] | 94.2 (422) [91.6, 96.2] |

*Responders were those with a rating of '3' or '2' on the BBPS after suctioning/washing by an endoscopist blinded to the treatment group, and the 95% CI of the responder rate was calculated using the Clopper–Pearson method.
BBPS, Boston Bowel Preparation Scale; CI, confidence interval; mITT, modified intent-to-treat.

diabetes subgroups and similar to the overall cohort (Figure 1; Table 3). At least 92% of participants in each subgroup were responders by BBPS. No participants received the lowest rating of '0'; few participants received a rating of '1' in any subgroup. Colon cleansing by BBPS in the transverse and descending colon showed similar results (see Table, Supplemental Digital Content 1). Responder rates by AS ('excellent' or 'good' rating) or BBPS ('3' or '2' rating) were similar for participants who had a morning *versus* afternoon procedure in all subgroups, except for the diabetes subgroup that had a numerically higher responder rate by both AS and BBPS for the morning procedures (see Table, Supplemental Digital Content 2).

Most participants in each subgroup (>85%) reported a tolerable bowel preparation experience with SPMC oral solution, regardless of baseline renal impairment or diabetes history, similar to the overall cohort (Figure 2). For the

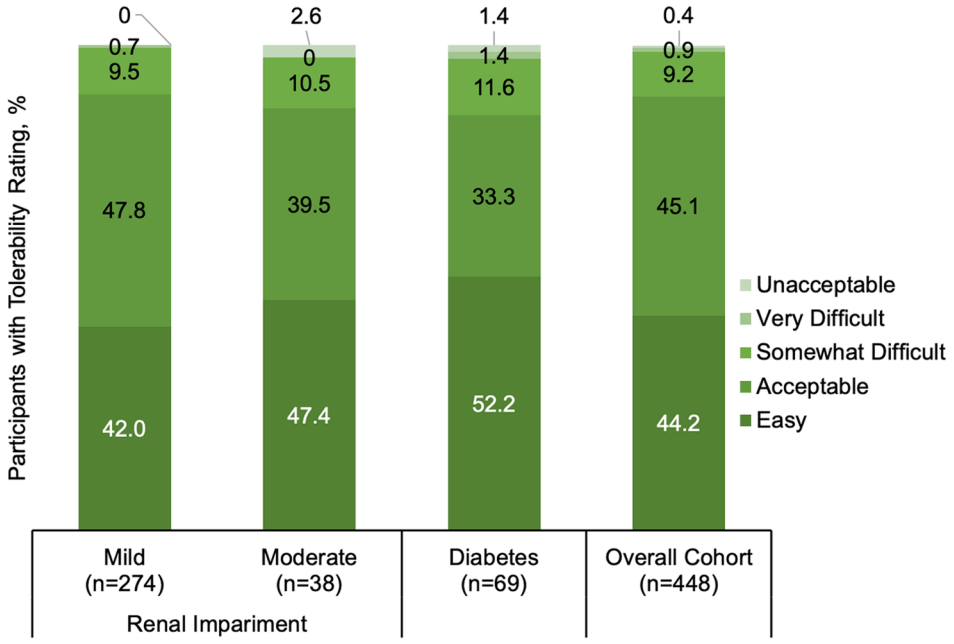


**Figure 2.** Participants in the renal and diabetes subgroups tolerated SPMC oral solution well, similarly to the overall cohort.
Participants were asked 'Was the bowel preparation tolerable?' The overall cohort represents all participants in the randomized, controlled trial who received SPMC oral solution.
SPMC, sodium picosulfate, magnesium oxide, and citric acid.

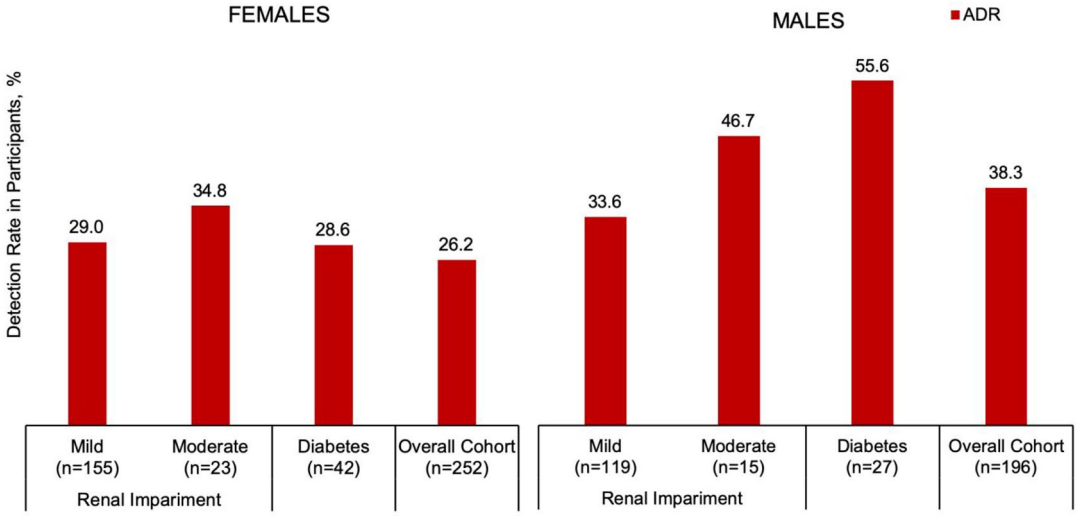


**Figure 3.** Adenoma detection rate (ADR) was above 28% for female subgroups and 33% for male subgroups.
ADR was calculated as the percentage of participants who had at least one adenoma. The overall cohort represents all participants in the randomized, controlled trial who received SPMC oral solution.
SPMC, sodium picosulfate, magnesium oxide, and citric acid.

mild renal impairment, moderate renal impairment, and diabetes subgroups, respectively, the ADR was 29.0% (45/155), 34.8% (8/23), and 28.6% (12/42) for females, and 33.6% (40/119), 46.7% (7/15), and 55.6% (15/27) for males (Figure 3).

There were no TEAEs leading to study discontinuation, deaths, or serious adverse drug reactions in any subgroup (Table 4). Rates of TEAEs were generally similar between subgroups and the overall cohort. Serious TEAEs were reported in 2.6% and 0% of the mild and moderate renal impairment groups, respectively, and 2.9% of the diabetes subgroup (see Table, Supplemental Digital Content 3). Likewise, severe TEAEs were reported by 3.6%, 0%, and 2.9% of participants in the mild and moderate renal impairment subgroups, and the diabetes subgroup, respectively. None of the serious TEAEs and only two severe TEAEs (i.e. dizziness and nausea) were considered related to the study drug.

A total of 41 participants had both diabetes and mild or moderate renal impairment, of which 80.5% (33/41) reported any TEAE, 2.4% (1/41) reported a serious TEAE, and 19.5% (8/41) reported a drug-related TEAE. No serious TEAEs were related to the study drug.

Drug-related TEAEs in each subgroup were generally similar to those reported in the overall cohort (Table 5). For the mild renal impairment, moderate renal impairment, and diabetes subgroups, respectively, nausea (2.6%, 5.3%, 1.4%) and headache (2.2%, 2.6%, 4.3%) were commonly reported drug-related AEs.

No renal AEs in any subgroup were considered related to the study drug; unrelated renal AEs were two participants (0.4%) reporting proteinuria, one participant (0.2%) reporting glycosuria and proteinuria, and one participant (0.2%) reporting worsening renal insufficiency. No AEs specific to diabetes (e.g. hyperglycemia, hypoglycemia) were considered related to the study drug in any subgroup.

Hypermagnesemia was transient with no clinically significant sequelae. Six participants reported hypermagnesemia (two participants in only the mild renal impairment group; three participants in only the diabetes group; one participant in both the mild renal impairment and diabetes subgroups). Peak elevations on the day of colonoscopy were slightly above the upper limit of normal (maximum value was 1.15 mmol/l). All magnesium elevations were transient and returned to normal limits by day 7, with four of five participants resolving by day 2 after colonoscopy. In patients aged $\geq$60 years, hypermagnesemia was defined as a serum level $>$0.98 mmol/l; in patients aged $<$60 years, hypermagnesemia was defined as a serum level $>$1.05 mmol/l. No other patterns of clinically significant changes from baseline laboratory values were noted, including electrolytes. Drug-related, electrolyte-associated abnormalities that did not resolve by the end of the study were reported in three participants: one participant with diabetes reported hyperosmolar state on day 28; one participant with diabetes had a hyperosmolar state at baseline and also reported hyperosmolar state on day 3; and one participant with mild renal impairment reported hypokalemia of 3.1 mmol/l on day 2 (which returned to normal at day 7, and was slightly below normal at 3.4 mmol/l on day 28). There were no subsequent clinical sequelae as a result of the abnormalities.

## Discussion

SPMC oral solution bowel preparation showed consistent colon cleansing by AS and BBPS in participants with baseline mild or moderate renal impairment or diabetes. The efficacy, tolerability, and safety results in the renal impairment and diabetes subgroups were similar to those of the overall cohort receiving SPMC in the study. As the data were derived from a phase III, randomized, assessor-blinded study, the risk of bias in the data is lower than other study designs. Additionally, the study design allowed the investigators to specifically report AEs, including ones related to renal or glycemic changes, that could be analyzed in relation to the subgroups of interest. In addition to overall colon cleansing, efficacy was also measured specifically in the ascending colon separately, which is of concern as the location of origin for interval colorectal cancers. The conclusions of this study for patients with mild baseline renal impairment are strengthened by the relatively large subgroup.

Chronic kidney disease is present in 14.8% of US adults.[34] An estimated 13.0% of US adults have some form of diabetes.[35] It is important to use a bowel preparation in patients with chronic underlying conditions that is safe, tolerable, and effective.

A prospective multicenter study found that patients with diabetes were more likely to have an inadequate bowel preparation than patients without diabetes (11.9% *versus* 6.4%; $p<0.001$).[36] A meta-analysis of 24 studies covering more than

**Table 4.** Summary of treatment-emergent adverse events, safety population.

| % (*n*) | Renal subgroup | | Diabetes subgroup | Overall cohort |
|---|---|---|---|---|
| | Mild impairment (*n* = 274) | Moderate impairment (*n* = 38) | (*n* = 69) | (*n* = 448) |
| Any TEAE* | 84.3 (231) | 84.2 (32) | 84.1 (58) | 84.4 (378) |
| Deaths | 0 | 0 | 0 | 0 |
| Serious TEAE** | 2.6 (7) | 0 | 2.9 (2) | 2.0 (9) |
| TEAE leading to study discontinuation | 0 | 0 | 0 | 0 |
| Severe TEAE‡ | 3.6 (10) | 0 | 2.9 (2) | 2.5 (11) |
| Adverse drug reaction | 12.8 (35) | 15.8 (6) | 18.8 (13) | 13.2 (59) |
| Serious adverse drug reaction | 0 | 0 | 0 | 0 |

*A TEAE was any AE that occurred or a pretreatment AE/medical condition that worsened in intensity after starting the study drug and within 30 days of last exposure to study drug. Per study protocol, all endoscopic findings were reported as TEAEs; malignancies were reported as serious TEAEs. AEs were classified according to the MedDRA, version 20.1.
**Serious TEAEs were defined as ones that resulted in death, were life threatening, required new or prolonged an existing hospitalization, resulted in persistent or significant disability/incapacity, were a congenital anomaly, or were an important medical event (that jeopardized the participant or required intervention to prevent another outcome listed).
‡Severe TEAEs classified the intensity of an AE as ones that led to an inability to work or perform usual activities. All AEs were classified on a scale of mild, moderate, or severe.
AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event.

**Table 5.** Treatment-emergent, drug-related adverse events of interest, safety population.

| % (*n*) | Renal subgroup | | Diabetes subgroup | Overall cohort |
|---|---|---|---|---|
| | Mild impairment (*n* = 274) | Moderate impairment (*n* = 38) | (*n* = 69) | (*n* = 448) |
| Any drug-related AE* | 12.8 (35) | 15.8 (6) | 18.8 (13) | 13.2 (59) |
| Nausea | 2.6 (7) | 5.3 (2) | 1.4 (1) | 3.1 (14) |
| Vomiting | 1.1 (3) | 2.6 (1) | 0 | 1.3 (6) |
| Abdominal pain | 0.4 (1) | 2.6 (1) | 0 | 0.7 (3) |
| Headache | 2.2 (6) | 2.6 (1) | 4.3 (3) | 2.7 (12) |
| Hypermagnesemia | 1.1 (3) | 0 | 5.8 (4) | 2.0 (9) |

*A TEAE was any AE that occurred or a pretreatment AE/medical condition that worsened in intensity after starting the study drug and within 30 days of last exposure to study drug. TEAEs were deemed related to the study drug by the investigator. AEs were classified according to the MedDRA, version 20.1.
AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event.

49,000 patients, of which 19.9% had an inadequate preparation, demonstrated an odds ratio of 0.58 (95% CI: 0.43, 0.79) of an adequate bowel preparation for patients with diabetes.[37] Difficulty adhering to diet modifications during bowel preparation and changes in gastrointestinal motility may play a role in poorer outcomes of bowel preparation.[37,38] Glycemic control has not been identified as a risk factor of poor bowel preparation.[24,39]

In our study, SPMC oral solution did not display a tendency for poorer colon cleansing in patients with diabetes as compared with the overall cohort. A total of 92.8% of participants received a rating

of '3' or '2' on the BBPS for ascending colon cleansing regardless of glycemic control (not measured). This could be related to the formulation and taste of the bowel preparation. SPMC oral solution is a low-volume cranberry-flavored solution that also includes sucralose for palatability.[27] After ingesting the active drug, participants supplemented fluid intake with a clear liquid of their choice. The small size of the cohort with diabetes could have limited the size of any effect, and the status of glycemic control was unknown at baseline. A multifactorial approach for bowel preparation in patients with diabetes, which included split-dose PEG-based bowel preparation, educational intervention, low-fiber diet, and adjustment of blood-glucose-lowering medications, reduced the rate of inadequate bowel preparation from 20% to 7% ($n = 120$; $p = 0.014$).[38]

Participants with mild or moderate renal impairment demonstrated consistent overall and ascending colon cleansing compared with the entire cohort receiving SPMC oral solution. A search of the literature did not reveal any similar reports on colon-cleansing efficacy in participants with baseline renal impairment with which to compare these data. All participants in this study received SPMC oral solution as a split dose and were to ingest additional fluids over a 5 h period after each dose of SPMC oral solution, providing the ability to distribute the increased fluid load over a period of time. Participants were instructed to stop taking certain medications (calcium-channel blockers, clonidine, opioids, anticholinergics, anti-diarrheals, and oral iron preparations) for a period of time before the colonoscopy. There were no drug-related TEAEs related to renal impairment. The study excluded patients with severe renal impairment, a condition which is contraindicated according to SPMC oral solution labeling.

A recent meta-analysis determined that individuals with an overall colon-cleansing rating of 'fair' by AS had similar ADR to those with an 'excellent' or 'good' rating and may follow guideline-recommended surveillance intervals for an acceptable preparation, possibly because the endoscopist can obtain good visualization of the colon after washing/suctioning a minor amount of residual waste.[7] Accordingly, in this subgroup analysis, 98.2% (269/274) of participants with mild renal impairment, 97.4% (37/38) with moderate impairment, and 98.6% (68/69) with diabetes would be considered acceptable for recommended colonoscopy follow-up intervals, which aligns closely with the responders by BBPS, for which the endoscopist was allowed to suction before rating the colon cleansing.

SPMC oral solution showed similar safety outcomes in patients with mild or moderate baseline renal impairment compared with the overall cohort. A previous study of SPMC demonstrated minor and transient elevations of serum magnesium that did not result in clinically significant consequences in patients with baseline renal impairment.[28] Fluid shifts and toxicity from bowel preparation ingredients have been found with previous bowel preparations. Phosphate nephropathy is a known potential adverse effect of sodium-phosphate-based bowel in patients with renal impairment.[21,40] Acute electrolyte imbalances, including hypocalcemia or hypophosphatemia, can occur after bowel preparation with PEG-based solutions.[22]

SPMC oral solution showed similar safety outcomes in patients with diabetes compared with the overall cohort, with no significant glycemic changes. Limited data on the safety of other bowel preparation agents in patients with diabetes does not reveal any concerns.[38,41]

There were no notable differences for ADR in the subgroups with renal impairment or diabetes. ADR was greater than the national minimum benchmark of $\geqslant$20% in females and $\geqslant$30% in males in all subgroups.[42] The inclusion of surveillance and diagnostic colonoscopies in the calculation may have increased the ADR.

SPMC oral solution is a ready-to-drink, low-volume bowel preparation formulated with ingredients that are shown to be very tolerable.[29,43–45] Decreased bowel preparation tolerability has been associated with poorer quality of colon cleansing and lower rates of polyp detection.[11,12] SPMC oral solution was tolerated well by patients with diabetes or baseline renal impairment. Future studies would be needed to compare outcomes of patients with diabetes or baseline renal impairment to those without either condition.

## Conclusion

Ready-to-drink SPMC oral solution is safe, tolerable, and efficacious in individuals with mild renal impairment or diabetes and comparable

with the overall cohort receiving SPMC oral solution in a phase III randomized, controlled trial. Data suggest that it is also safe and efficacious in patients with moderate renal impairment, though more data are warranted, given the limited group size. These data demonstrate high rates of effective colon cleansing in these subgroups, without regard to timing of colonoscopy.

## Acknowledgements

Medical writing and editorial support were provided by Agnella Izzo Matic, PhD, CMPP (AIM Biomedical, LLC) and was funded by Ferring Pharmaceuticals Inc.

## Author contributions

MA assisted with data analysis. All authors interpreted the data, drafted, and critically revised the article for important intellectual content. All authors approved the final version of this article for publication.

## Conflict of interest statement

Dr Burke has received research support and consultant fees from Ferring Pharmaceuticals Inc. Dr Mankaney has received research support from Ferring Pharmaceuticals Inc. Drs Ando and Dahdal are employees of Ferring Pharmaceuticals Inc.

## Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: this study was funded by Ferring Pharmaceuticals Inc. (Parsippany, NJ).

## Prior publication

Portions of the data contained in this manuscript appeared in electronic presentation form at Digestive Disease Week 2020, 2–5 May 2020.

## ORCID iD

Carol A. Burke https://orcid.org/0000-0002-7225-0696

## Data availability

Data that support the findings of this study will be considered for release by the study sponsor upon reasonable request.

## Supplemental material

Supplemental material for this article is available online.

## References

1. Chokshi RV, Hovis CE, Hollander T, *et al.* Prevalence of missed adenomas in patients with inadequate bowel preparation on screening colonoscopy. *Gastrointest Endosc* 2012; 75: 1197–1203.
2. Clark BT and Laine L. High-quality bowel preparation is required for detection of sessile serrated polyps. *Clin Gastroenterol Hepatol* 2016; 14: 1155–1162.
3. 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.
4. Harrison NM and Hjelkrem MC. Bowel cleansing before colonoscopy: balancing efficacy, safety, cost and patient tolerance. *World J Gastroenterol* 2016; 8: 4–12.
5. 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.
6. Calderwood AH, Thompson K, Schroy PCI, *et al.* Good is better than excellent: bowel preparation quality and adenoma detection rates. *Gastrointest Endosc* 2015; 81: 691–699.
7. 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.
8. Harewood GC, Sharma VK and De Garmo P. Impact of colonoscopy preparation quality on detection of suspected colonic neoplasia. *Gastrointest Endosc* 2003; 58: 76–79.
9. 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.
10. 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.
11. Denters MJ, Schreuder M, Depla ACTM, *et al.* Patients' perception of colonoscopy: patients with inflammatory bowel disease and irritable bowel syndrome experience the largest burden. *Eur J Gastroenterol Hepatol* 2012; 25: 964–972.
12. 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.

13. Kilgore TW, Abdinoor AA, Szary NM, *et al.* Bowel preparation with split-dose polyethylene glycol before colonoscopy: a meta-analysis of randomized controlled trials. *Gastrointest Endosc* 2011; 73: 1240–1245.

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. Saltzman JR, Cash BD, Pasha SF, *et al.* Bowel preparation before colonoscopy. *Gastrointest Endosc* 2015; 81: 781–794.

16. Rex DK, Boland CR, Dominitz JA, *et al.* Colorectal cancer screening: recommendations for physicians and patients from the U.S. Multi-Society Task Force on colorectal cancer. *Am J Gastroenterol* 2017; 112: 1016–1030.

17. Singh S, Dhawan M, Chowdhry M, *et al.* Differences between morning and afternoon colonoscopies for adenoma detection in female and male patients. *Ann Gastroenterol* 2016; 29: 497–501.

18. Bucci C, Rotondano G, Hassan C, *et al.* Optimal bowel cleansing for colonoscopy: split the dose! A series of meta-analyses of controlled studies. *Gastrointest Endosc* 2014; 80: 566–576.

19. Garber A, Sarvepalli S, Burke CA, *et al.* Modifiable factors associated with quality of bowel preparation among hospitalized patients undergoing colonoscopy. *J Hosp Med* 2019; 14: 278–283.

20. Sharma P, Burke CA, Johnson DA, *et al.* The importance of colonoscopy bowel preparation for the detection of colorectal lesions and colorectal cancer prevention. *Endosc Int Open* 2020; 8: E673–E683.

21. Florentin M, Liamis G and Elisaf MS. Colonoscopy preparation-induced disorders in renal function and electrolytes. *World J Gastrointest Pharmacol Ther* 2014; 5: 50–54.

22. Cheng C-L, Liu N-J, Tang J-H, *et al.* Risk of renal injury after the use of polyethylene glycol for outpatient colonoscopy: a prospective observational study. *J Clin Gastroenterol2* 2019; 53: e44–e450.

23. Yoshida N, Naito Y, Murakami T, *et al.* Safety and efficacy of a same-day low-volume 1L PEG bowel preparation in colonoscopy for the elderly people and people with renal dysfunction. *Dig Dis Sci* 2016; 61: 3229–3235.

24. Taylor C and Schubert ML. Decreased efficacy of polyethylene glycol lavage solution (Golytely) in the preparation of diabetic patients for outpatient colonoscopy: a prospective and blinded study. *Am J Gastroenterol* 2001; 96: 710–714.

25. Romero RV and Mahadeva S. Factors influencing quality of bowel preparation for colonoscopy. *World J Gastroenterol* 2013; 5: 39–46.

26. Parra Pérez VF, Watanabe Yamamoto J, Nago Nago A, *et al.* Factors related to a suboptimal bowel preparation for colonoscopy. *Acta Gastroenterol Latinoam* 2015; 45: 24–30.

27. CLENPIQ (package insert). Parsippany, NJ: Ferring Pharmaceuticals Inc., 2019.

28. Bertiger G, Jones E, Dahdal DN, *et al.* Serum magnesium concentrations in patients receiving sodium picosulfate and magnesium citrate bowel preparation: an assessment of renal function and electrocardiographic conduction. *Clin Exp Gastroenterol* 2015; 8: 215–224.

29. Hookey L, Bertiger G, Johnson Kenneth Lee I, *et al.* Efficacy and safety of a ready-to-drink bowel preparation for colonoscopy: a randomized, controlled, non-inferiority trial. *Ther Adv Gastroenterol* 2019; 12: 1–13.

30. 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.

31. Parmar R, Martel M, Rostom A, *et al.* Validated scales for colon cleansing: a systematic review. *Am J Gastroenterol* 2016; 111: 197–204.

32. Kastenberg D, Bertiger G and Brogadir S. Bowel preparation quality scales for colonoscopy. *World J Gastroenterol* 2018; 24: 2833–2843.

33. 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.

34. United States Renal Data System. *2018 USRDS annual data report*. Bethesda, MD: United States Renal Data System, 2018.

35. Centers for Disease Control and Prevention. *National diabetes statistics report 2020: Estimates of diabetes and its burden in the United States*. Atlanta, GA: Centers for Disease Control and Prevention, 2020.

36. Hassan C, Fuccio L, Bruno M, *et al.* A predictive model identifies patients most likely to have inadequate bowel preparation for colonoscopy. *Clin Gastroenterol Hepatol* 2012; 10: 501–506.

37. Mahmood S, Farooqui SM and Madhoun MF. Predictors of inadequate bowel preparation for colonoscopy: a systematic review and meta-analysis. *Eur J Gastroenterol Hepatol* 2018; 30: 819–826.

38. Alvarez-Gonzalez MA, Flores-Le Roux JA, Seoane A, *et al*. Efficacy of a multifactorial strategy for bowel preparation in diabetic patients undergoing colonoscopy: a randomized trial. *Endoscopy* 2016; 48: 1003–1009.

39. Izzy M, Changela K, Alhankawi D, *et al*. Impact of glycemic control on colonoscopy outcomes: bowel preparation and polyp detection. *Ann Gastroenterol* 2016; 29: 332–335.

40. Hoffmanová I, Kraml P and Andel M. Renal risk associated with sodium phosphate medication: safe in healthy individuals, potentially dangerous in others. *Expert Opin Drug Saf* 2015; 14: 1097–1110.

41. Madhoun MF, Chaudrey KK, Chilsholm SS, *et al*. Efficacy and tolerability of various bowel preparations in diabetic patients: a randomized controlled trial. *Endosc Int Open* 2018; 6: E1157–E1163.

42. Rex DK, Schoenfeld PS, Cohen J, *et al*. Quality indicators for colonoscopy. *Gastrointest Endosc* 2015; 81: 31–53.

43. 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.

44. 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.

45. 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.