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A Safety and Efficacy Comparison of a New Sulfate-Based Tablet Bowel Preparation Versus a PEG and Ascorbate Comparator in Adult Subjects Undergoing Colonoscopy

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INTRODUCTION: A new tablet-based bowel prep for colonoscopy has been developed containing poorly absorbed sulfate salts which act to retain water within the intestinal lumen resulting in a copious diarrhea, thereby cleansing the bowel. This study evaluated the safety and efficacy of these oral sulfate tablets (OST) compared with a US FDA–approved bowel prep solution containing PEG3350, electrolytes, and ascorbate (polyethylene glycol and ascorbate [PEG-EA]).

METHODS: Five hundred fifteen adult patients (mean 57y) were enrolled in this single-blind, multicenter, noninferiority study. Subjects were assigned either PEG-EA or OST to be administered in a split-dose regimen starting the evening before colonoscopy. PEG-EA was taken according to its approved labeling (1 L of prep solution with 16 oz. of additional water) in the evening and again in the morning. OST patients took a total of 24 tablets. OST patients were administered 12 tablets in the evening, and the following morning. Patients consumed 16 ounces of water with each dose of 12 tablets and drank an additional 32 oz. of water with each dose. Colonoscopies were performed by blinded investigators. Cleansing efficacy was evaluated globally and segmentally using a 4-point scale (Excellent—no more than small bits of feces/fluid which can be suctioned easily; achieves clear visualization of the entire colonic mucosa. Good—feces and fluid requiring washing and suctioning, but still achieves clear visualization of the entire colonic mucosa. Fair—enough feces even after washing and suctioning to prevent clear visualization of the entire colonic mucosa. Poor—large amounts of fecal residue and additional bowel preparation required). Scores of Good or Excellent were considered to be a success. Safety was assessed by spontaneously reported adverse events, solicited ratings of expected prep symptoms, and laboratory testing.

RESULTS: A high rate of cleansing success was seen with OST (92%), which was noninferior to PEG-EA (89%). Only a small proportion of subjects rated their expected gastrointestinal symptoms as severe (<5% for both preps). No clinically significant differences were seen between preps for chemistry and hematology parameters. No serious adverse experiences were reported with OST.

DISCUSSION: Sulfate tablets achieved a high level of cleansing in the study, comparable with US FDA–approved preps. OST was noninferior to PEG-EA in this study and achieved significantly more Excellent preps overall and in the proximal colon. The OST prep was well-tolerated, with a similar rate of spontaneously reported adverse experiences to PEG-EA and a low rate of severe expected gastrointestinal symptoms.

INTRODUCTION

Colonoscopy has been established as the gold standard for colorectal cancer screening and detection (1). The success of the method is dependent on adequate cleansing of the colon. This requires that a large volume of fluid must pass through the intestinal tract thereby washing out fecal matter that can obscure visualization of the intestinal mucosa. Typically, 3 or more liters are needed; thus, early US FDA–approved preparations required ingestion of about 1 gallon of an isotonic solution of polyethylene glycol (PEG) and electrolytes. These solutions rely on the osmotic activity of poorly absorbed ingredients, such as PEG, to cause water to be retained within the lumen of the intestine rather than absorbed, thereby inducing a copious diarrhea.

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The PEG and added electrolytes are included in appropriate quantities to prevent significant gains or losses during the diarrheal process (2,3). These solutions have generally been recognized as the safest methods of bowel preparation (4). However, a well-known impediment to adequate cleansing is patient reluctance to complete their bowel preparation regimen because of the large volumes of poor tasting solution to be ingested. Various attempts have been made to improve patient compliance by reducing the required volume to be consumed. Recently, hypertonic reduced volume solutions have been introduced that rely either on the sulfate anion or a reformulated combination of PEG and ascorbate (5,6). In both cases, additional water must be supplied to compensate for diarrheal losses, and in the case of PEG and ascorbate, problems in formulation or labeling instructions may risk dehydration in some patients (7). A tablet-based preparation was first attempted with a sodium phosphate-based product. Unfortunately, sodium phosphate–based preparations became associated with rare cases of nephrocalcinosis because of excessive phosphate absorption (8,9). In addition, these first tableted sodium phosphate options had a high number of tablets (totals of 40 and 32) and included some formulations that resulted in reports of visualization issues during colonoscopy as a result of the use of cellulose (10).

Because sodium phosphate–based formulations are associated with substantial safety concerns, the development of alternative tablet formulations is desirable. Previous studies of a US FDA–approved hypertonic oral sulfate colon-cleansing solution (OSS) showed that OSS had similar safety and efficacy to a polyethylene glycol and ascorbate preparation (PEG-EA) (6) and was as safe as PEG-based preparations (including 4-L isotonic solutions) under real-world conditions (11). However, the high sulfate content of OSS imparted a pungent flavor that negatively impacted the OSS patient experience. As such, a sulfate salt tablet formulation such as oral sulfate tablets (OST) may be an attractive solution to the safety concerns associated with sodium phosphate tablet formulations, while removing the taste barriers of OSS.

This report describes a randomized, investigator-blinded comparison of a new tablet bowel preparation based on a formulation of sulfate salts (OST) to a traditional PEG-EA comparator for colonoscopy preparation. The tablet preparation is composed of sodium and magnesium sulfate salts with potassium chloride and is formulated into 24 tablets. The OST preparation was formulated to prevent losses or gains of electrolytes that could result after inducing about 3 liters of diarrhea. Additional water is required to prevent dehydration.

METHODS
Study design
This investigator-blinded, randomized, controlled, noninferiority study was sponsored and conducted by Braintree Laboratories, Inc., Braintree, MA. The study compared OST (Braintree Laboratories, Inc.) with PEG-EA (MoviPrep, Salix Pharmaceuticals, Morrisville, NC) in outpatients undergoing colonoscopy for routine indications. The trial was registered at Clinicaltrials.gov (identifier NCT03404401) and approved by respective facility Institutional Review Boards. Written informed consent was obtained for all participating study subjects. Enrollment began on January 11, 2018, and the last subject completed on July 10, 2018.

Study population
Male and female outpatients at least 18 years of age who required a colonoscopy for routine indications were enrolled. These indications included screening, polyp or neoplasm history, rectal or

gastrointestinal bleeding, abdominal pain, change in bowel habit, and inflammatory bowel diseases. Female patients of child-bearing potential were required to be taking an acceptable form of birth control and to have had a negative urine pregnancy test at screening. Patients had to be mentally competent in the investigators' judgment and willing to provide informed consent. Patients were excluded if they had dysphagia or an aversion to swallowing tablets, had known or suspected ileus, gastrointestinal obstruction, gastroparesis, gastric retention, bowel perforation, toxic colitis, or megacolon, ongoing severe acute inflammatory bowel disease, previous significant abdominal surgeries, uncontrolled pre-existing electrolyte abnormalities, and clinically significant electrolyte abnormalities based on baseline laboratory results. Use of diuretics, antihypertensive medications, including angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers, or chronic nonsteroidal anti-inflammatory drugs (NSAIDs) must have been stable for 30 days (however, NSAID use for occasional pain was not exclusionary). Patients with uncontrolled hypertension (systolic >170 mm Hg and diastolic >100 mm Hg) were excluded. Patients were also excluded if they had a history of severe renal, liver, or cardiac insufficiency; impaired consciousness; the indication of foreign-body removal or colonoscopic decompression; pregnancy; lactation; refusal (if of child-bearing potential) to undergo pregnancy testing; allergy to the preparation components; and patients withdrawing from alcohol or benzodiazepines. As part of the screening procedures, patients underwent a physical examination, had vital signs taken (including electrocardiogram), and provided blood and urine samples for laboratory testing.

Preparation kit assignment used an automated interactive web response system which randomly assigned subjects to the 2 preparation groups in a 1:1 ratio. Subjects were asked to keep a treatment diary to record food consumption, the date and time of preparation consumption, and the reasons the preparation could not be completed (if applicable). On arrival to the clinic after completing the preparation, before the colonoscopy, study subjects completed a preference questionnaire which included questions on their overall experience with their preparation, and their willingness to repeat the preparation in the future. Physical examination, vital signs, and laboratory sample collection were repeated. To ensure an unbiased evaluation of the study preparations, the blinded endoscopist did not perform any drug-related activities such as randomization, dispensing, or drug accountability. Study subjects were instructed to not discuss their study preparation with any staff member. Colonoscopies were performed according to each site's standard procedures, and cleansing was graded. A safety follow-up visit was performed for all subjects 24–48 hours after colonoscopy. Subjects with ongoing adverse events or abnormal laboratory values at this visit were asked to return for an additional follow-up 7 and 30 days after colonoscopy.

Study centers
Data were collected at 22 US study sites", all of which used the same investigational protocol. Enrollment was competitive, and subjects were recruited from hospital-based and stand-alone gastroenterology practices.

Administration of study agents
Subjects assigned to the OST tablet preparation were permitted a low residue breakfast on the day before colonoscopy, followed by clear liquids until 2 hours before the colonoscopy examination.

Table 1. Subject disposition

	OST, n (%)	PEG-EA, n (%)	All, n (%)
Subjects screened			634
Subjects randomized	314	306	620
Safety population	281 (89.5)	271 (88.6)	552 (89.0)
Efficacy population	278 (88.5)	270 (88.2)	548 (88.4)
Completing subjects (% ITT)	263 (83.8)	252 (82.4)	515 (83.1)
Subjects discontinued (% ITT)	51 (16.2)	54 (17.6)	105 (16.9)
Reasons for discontinuation[a]:			
Adverse event	1 (2.0)	3 (5.6)	4 (3.8)
Lost to follow-up	19 (37.3)	12 (22.2)	31 (29.5)
Physician decision	2 (3.9)	1 (1.9)	3 (2.9)
Subject withdrew consent	14 (27.5)	18 (33.3)	32 (30.5)
Other	15 (29.4)	20 (37.0)	35 (33.3)

ITT, intent-to-treat; OST, oral sulfate tablets; PEG-EA, polyethylene glycol and ascorbate.

[a]Percentages based on the number of subjects who discontinued in each treatment group.

Subjects took their first 12-tablet dose the evening before colonoscopy with a minimum of 16 ounces of water. The second 12-tablet dose (with 16 ounces of water) was to be taken 5–8 hours before the colonoscopy. Additional hydration consisting of 32 ounces of water was required with each dose.

Subjects assigned to PEG-EA were instructed to take the preparation according to manufacturer's labeling for split-dose administration. PEG-EA subjects were allowed a clear broth and plain yogurt dinner on the evening before colonoscopy. Subjects were instructed to ingest only clear liquids while they took PEG-EA and until after their colonoscopy.

To determine preparation compliance, study subjects were instructed to bring their used preparation components to the clinic when they returned for colonoscopy. Compliance was assessed by counting the number of used PEG-EA pouches or remaining OST tablets.

Efficacy and safety variables

A new "US FDA Bowel Prep Scoring Scale" for the quality of bowel cleansing was used that also accounted for the work of endoscopist cleansing. Cleansing efficacy was evaluated by colonoscopists unaware of the randomized preparation. Cleansing was evaluated globally and segmentally using the 4-point scale (Excellent—no more than small bits of feces/fluid which can be suctioned easily; achieves clear visualization of the entire colonic mucosa. Good—feces and fluid requiring washing and suctioning, but still achieves clear visualization of the entire colonic mucosa. Fair—enough feces even after washing and suctioning to prevent clear visualization of the entire colonic mucosa. Poor—large amounts of fecal residue and additional bowel preparation required). Each colon segment (proximal, mid, and distal) was graded for cleansing efficacy during withdrawal of the colonoscope factoring the amount of effort required during both insertion and withdrawal. A global cleansing score of the entire colon using the same four-point scale was determined after completion of the examination. The primary efficacy variable was global cleansing. Grades of Good and Excellent were considered successful, and grades of Poor and Fair were considered failures. Secondary efficacy endpoints included the number (percentage) of Excellent preparations (global score), segmental cleansing score, adequacy of cleansing and need for repreparation, adenoma detection rate (ADR), duration of colonoscopy, the volume of intraprocedural water needed to irrigate the colon, and cecal intubation rate. Colonoscopists completed a Colonoscopy Preparation Scoring Training video created by Signant Health. Procedures were
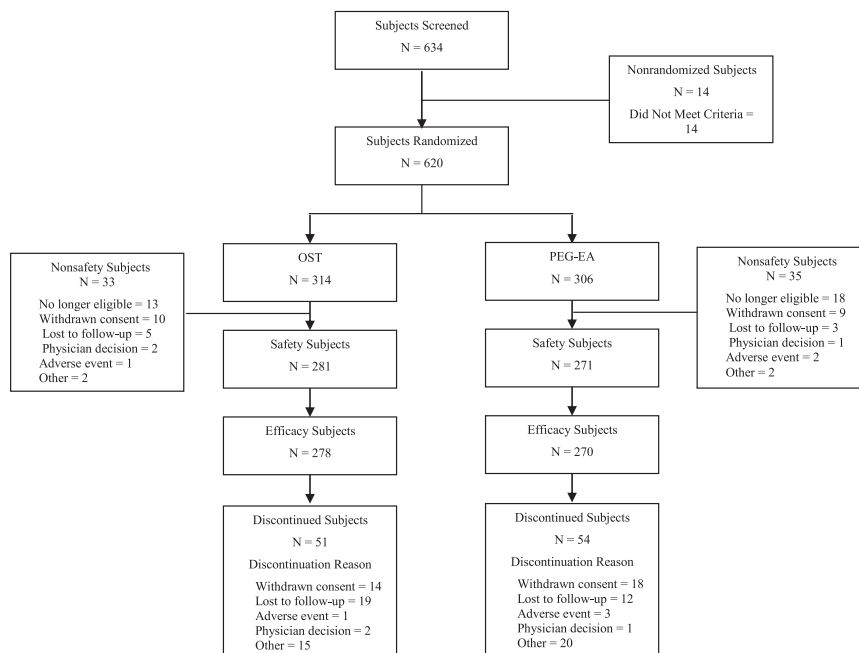
Figure 1. CONSORT diagram.

Table 2. Overall cleansing ratings

	OST (n = 278)	PEG-EA (n = 270)	95% CI[b]	P value[c,d]	P value[e]
Success (n %)[a]	257 (92.4)	241 (89.3)	−1.6 to 8.0	0.217	<**0.001**
Failure (n %)	21 (7.6)	29 (10.7)			
Grade (n %)					
Excellent	184 (66.2)	154 (57.0)		**0.034**	
Good	73 (26.3)	87 (32.2)			
Fair	11 (4.0)	15 (5.6)			
Poor	8 (2.9)	11 (4.1)			
Missing[f]	2 (0.7)	3 (1.1)			

Bold text was used for emphasis for P values < 0.05.
CMH, Cochran-Mantel-Haenszel; OST, oral sulfate tablets; PEG-EA, polyethylene glycol and ascorbate.
[a]Preparation success is defined as cleansing graded either Excellent or Good.
[b]Confidence interval (CI) for percent success difference between treatments is from a χ^2 test.
[c]P value for treatment difference (success) is from a CMH χ^2, controlling for site.
[d]P value for treatment difference (cleansing grade) is from a Fisher exact test.
[e]P value for testing the null hypothesis of inferiority using an equivalence margin of 10 percent.
[f]Five subjects (2 OST and 3 PEG-EA) were unable to complete their preparation and are included here as missing.

recorded using GI Hawkeye software and a subset underwent independent blinded central reading by GI Reviewers, LLC, Brookline, MA. At visit 2 (immediately before the scheduled colonoscopy), subjects were directly questioned about expected preparation-related symptoms (nausea, cramping, vomiting,

and bloating) and to rate them as mild, moderate, or severe. Each subject was also queried for occurrence of adverse events and changes in concomitant medications. Blood samples were collected at each study visit for analysis at a central laboratory.

Patient satisfaction

To evaluate the patients' perception of the preparation experience, subjects completed a questionnaire when they returned for colonoscopy (after completing both preparation doses). The following questions were asked: How easy or difficult was it to consume the study preparation (very difficult to very easy)?; Please describe your overall experience with the bowel preparation (bad to excellent); How did this bowel preparation experience compared with your prior experiences (worse to better)?; Would you ask your doctor for this preparation again if you need another colonoscopy in the future?; and Would you refuse the same preparation again if it were to be prescribed to you in the future?.

Table 3. Segmental cleansing assessment[a]

Segment grade	OST (n = 278)	PEG-EA (n = 270)	P value[b]
Proximal colon segment grade (n %)			0.115
Excellent	174 (63.7)	146 (55.1)	**0.034**
Good	78 (28.6)	91 (34.3)	
Fair	16 (5.9)	17 (6.4)	
Poor	5 (1.8)	11 (4.2)	
Mid-colon segment grade (n %)			0.372
Excellent	192 (70.3)	169 (63.5)	0.100
Good	67 (24.5)	77 (28.9)	
Fair	9 (3.3)	12 (4.5)	
Poor	5 (1.8)	8 (3.0)	
Distal colon segment grade (n %)			0.333
Excellent	183 (66.5)	158 (59.2)	0.066
Good	69 (25.1)	82 (30.7)	
Fair	16 (5.8)	18 (6.7)	
Poor	7 (2.5)	9 (3.4)	

Bold text was used for emphasis for P values < 0.05.
CMH, Cochran-Mantel-Haenszel; OST, oral sulfate tablets; PEG-EA, polyethylene glycol and ascorbate.
[a]Percents for each treatment group are based on the total number of responses. Missing values were not included.
[b]P value for difference between treatments is from a CMH χ^2, controlling for site.

Statistical methods

The primary efficacy endpoint was assessed based on an analysis of overall preparation success or failure and included all subjects randomized who took any portion of the study preparation. The definition of preparation success was a global cleansing assessment score by the colonoscopist of Excellent or Good (and which did not satisfy any of the failure criteria). Failed preparations were defined as global cleansing assessment scores of Fair or Poor, as well as any subject who did not have a colonoscopy because of the investigator's determination of insufficient fecal output, unclear fecal discharge, preparation-related adverse events preventing preparation, as well as any subject for whom cleaning was not adequate for evaluation by colonoscopy. Cleansing success rate was analyzed using Cochran-Mantel-Haenszel (CMH) χ^2 adjusting for the effect of investigator site. A margin of 10% was selected as the bar to establish noninferiority of the investigational preparation (OST) to the control preparation (PEG-EA). This noninferiority margin has been used in recent studies supporting US FDA approval of bowel preparations (6).

Table 4. Additional secondary endpoints

Endpoint	OST	PEG-EA	P value[a]
Preparation adequacy, n (%)	268 (96.8)	255 (94.8)	0.272
Cecal intubation rate, n (%)	271 (98.2)	261 (97.8)	0.824
Adenoma detection rate, n (%)	92 (33.1)	94 (34.8)	0.532
Procedure duration, mean (SD)	15.8 (9.6)	15.9 (8.1)	0.909
Intraprocedural water, mean (SD)	88.4 (128.1)	93.8 (126.2)	0.632

ANOVA, analysis of variance; CMH, Cochran-Mantel-Haenszel; OST, oral sulfate tablets; PEG-EA, polyethylene glycol and ascorbate.
[a] P value from a CMH test, controlling for site for categorical variables, and for treatment from an ANOVA with terms for treatment, site, and their interaction for continuous variables.

Secondary endpoints were analyzed in a like manner to the primary analysis using the Cochran-Mantel-Haenszel test and two-way analysis of variance with terms for treatment, site, and their interaction for continuous responses. No adjustment was made for multiplicity in testing of the secondary endpoints. Solicited symptom data were presented categorically and tested by the χ^2 test.

Adverse events were coded using the MedDRA classification (Version 19.1). Treatment-emergent adverse experiences were defined as adverse events that had an onset day and time on or after the day and time of the first dose of study drug. Any differences in adverse events between study treatment groups was tested by the Fisher exact test together with a 95% confidence interval (CI) for the treatment effect estimate.

The safety population included all subjects who took any portion of study preparation. The efficacy population included all subjects in the safety population with the exception of those who did not undergo a colonoscopy for a reason other than safety or efficacy (e.g. insurance coverage issue and lack of transportation to the clinic).

The protocol planned study size was approximately 540 subjects. Based on previous studies using a similar grading system, the success rate for PEG-EA was expected to be no greater than 94% (5). Assuming a similar success rate for OST, a two-sided asymptotic 95% CI for the difference in success rates between groups (BLI4700 − PEG-EA) will result in a lower CI bound greater than −10%, with probability 80%. This result would establish the noninferiority of OST to PEG-EA for a noninferiority margin of 10%.

RESULTS

Demographics

Twenty-two sites in the United States contributed 634 patients, and 620 were randomized and dispensed study preparation; 548 patients took their preparation and were included in the analysis (278 received OST and 270 received PEG-EA). The disposition of all study patients is shown in Table 1 along with the reasons for discontinuation. The proportion of patients discontinued was similar between the 2 preparation groups. Figure 1 presents the CONSORT diagram.

Demographic characteristics such as age, weight, and racial distribution of the 2 treatment groups were similar with no statistically significant differences detected. The average age of the study population was 57.9 years and included slightly more women (56%) than men (44%). Seventy-eight percent of patients identified as white, 16% identified as African American, and 11% identified as Hispanic or Latino.

Compliance with assigned bowel preparation was based on review of used drug materials and completed patient questionnaires. Preparation compliance was excellent across groups, with 96.5% of subjects in the study completing their entire preparation (OST = 98% and PEG-EA = 95%).

Efficacy

Global cleansing scores for the 2 preparations as rated by the local endoscopists are shown in Table 2. High rates of cleansing success (defined as scores of Excellent and Good) were seen with both preparations (92% for OST and 89% for PEG-EA), comparable with other US FDA–approved split-dose preparations. OST had significantly more Excellent preparations (66% vs 57%, respectively). Analysis of noninferiority (using the standard 10% margin) confirmed that OST was noninferior to PEG-EA (<0.001). No differences between the preparations in overall cleansing success were identified with respect to subject age, gender, or race. Independent central reading for a subset (27%) of colonoscopies showed excellent interobserver agreement between the local endoscopist and central reader (97%) with respect to global cleansing score.

The results of the segmental cleansing ratings were similar to the overall assessment discussed above and are shown in Table 3. OST tended to achieve a higher proportion of Excellent preparations in each colon segment, which was statistically significant for the proximal colon ($P = 0.034$).

Analysis of intraprocedural efficacy endpoints revealed no statistically significant differences between the 2 preparations.

Table 5. Overall preparation efficacy (success)[a] by subgroup

Subgroup	OST	PEG-EA	95% CI[b]	P value[c]	P value[d]

Hard to prep
  Hx of constipation
  Opioid use
  Failed colonoscopy
  BMI ≥35
	103 (89.6)	86 (82.7)	−2.3 to 16.0	0.121	<0.001

Afternoon colonoscopy	47 (95.9)	45 (91.8)	−5.4 to 13.5	0.216	0.002

BMI, body mass index; CMH, Cochran-Mantel-Haenszel; OST, oral sulfate tablets; PEG-EA, polyethylene glycol and ascorbate.
[a] Preparation success is defined as cleansing graded either Excellent or Good.
[b] Confidence interval (CI) for percent success difference between treatments is from a χ^2 test.
[c] P value for difference between treatments is from a CMH χ^2, controlling for site.
[d] P value for testing the null hypothesis of inferiority using an equivalence margin of 10 percent.

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Table 6. Number (%) of subjects with unsolicited treatment emergent adverse events[a] >1 by system organ class and preferred term

SOC/Preferred term[a]	OST (n = 281)	PEG-EA (n = 271)	95% CI[b]	P value[b]
No. of subjects with any event	77 (27.4)	75 (27.7)	−7.7 to 7.2	1.000
Total no. of events	120	118		
Blood and lymphatic system disorders	1 (0.4)	4 (1.5)	−2.7 to 0.5	0.209
Anemia	0	4 (1.5)	−2.9 to 0.0	0.057
Cardiac disorders	3 (1.1)	2 (0.7)	−1.2 to 1.9	1.000
Gastrointestinal disorders	14 (5.0)	12 (4.4)	−3.0 to 4.1	0.842
Abdominal pain	2 (0.7)	1 (0.4)	−0.9 to 1.6	1.000
Constipation	2 (0.7)	0	−0.3 to 1.7	0.499
Diarrhea	2 (0.7)	1 (0.4)	−0.9 to 1.6	1.000
Flatulence	2 (0.7)	2 (0.7)	−1.4 to 1.4	1.000
Proctitis	0	2 (0.7)	−1.8 to 0.3	0.241
Vomiting	2 (0.7)	4 (1.5)	−2.5 to 1.0	0.443
General disorders and administration site conditions	5 (1.8)	3 (1.1)	−1.3 to 2.7	0.725
Chills	4 (1.4)	1 (0.4)	−0.5 to 2.6	0.373
Pyrexia	1 (0.4)	2 (0.7)	−1.6 to 0.9	0.618
Infections and infestations	9 (3.2)	7 (2.6)	−2.2 to 3.4	0.801
Herpes zoster	2 (0.7)	0	−0.3 to 1.7	0.499
Upper respiratory tract infection	2 (0.7)	0	−0.3 to 1.7	0.499
Urinary tract infection	4 (1.4)	2 (0.7)	−1.0 to 2.4	0.686
Injury, poisoning, and procedural complications	5 (1.8)	2 (0.7)	−0.8 to 2.9	0.451
Procedural pain	2 (0.7)	0	−0.3 to 1.7	0.499
Investigations	42 (14.9)	46 (17.0)	−8.1 to 4.1	0.562
Blood creatine phosphokinase increased	3 (1.1)	3 (1.1)	−1.8 to 1.7	1.000
Blood creatinine increased	2 (0.7)	0	−0.3 to 1.7	0.499
Blood potassium decreased	2 (0.7)	1 (0.4)	−0.9 to 1.6	1.000
Blood pressure decreased	16 (5.7)	19 (7.0)	−5.4 to 2.8	0.601
Blood pressure increased	17 (6.0)	19 (7.0)	−5.1 to 3.2	0.731
Crystal urine present	0	3 (1.1)	−2.4 to 0.1	0.118
Hemoglobin decreased	1 (0.4)	2 (0.7)	−1.6 to 0.9	0.618
Metabolism and nutrition disorders	2 (0.7)	2 (0.7)	−1.4 to 1.4	1.000
Dehydration	0	2 (0.7)	−1.8 to 0.3	0.241
Musculoskeletal and connective tissue disorders	3 (1.1)	3 (1.1)	−1.8 to 1.7	1.000
Nervous system disorders	8 (2.8)	8 (3.0)	−2.9 to 2.7	1.000
Dizziness	1 (0.4)	4 (1.5)	−2.7 to 0.5	0.209
Headache	6 (2.1)	4 (1.5)	−1.6 to 2.9	0.752
Renal and urinary disorders	2 (0.7)	2 (0.7)	−1.4 to 1.4	1.000
Respiratory, thoracic, and mediastinal disorders	3 (1.1)	0	−0.1 to 2.3	0.249
Dysphonia	2 (0.7)	0	−0.3 to 1.7	0.499
Skin and subcutaneous tissue disorders	3 (1.1)	0	−0.1 to 2.3	0.249
Rash	2 (0.7)	0	−0.3 to 1.7	0.499

OST, oral sulfate tablets; PEG-EA, polyethylene glycol and ascorbate; SOC, system organ class.

[a]Subjects were counted once within each SOC and preferred term.

[b]95% confidence interval for difference in proportion and P value from the Fisher exact test.

Table 7. Solicited symptoms

Symptom[a]	OST (n = 281) (%)	PEG-EA (n = 271) (%)	P value[b]
Abdominal pain			
None	83	82	0.655
Mild	11	13	
Moderate	6	6	
Severe	0	0	
Abdominal distension			
None	70	78	0.052
Mild	21	16	
Moderate	9	6	
Severe	0	0	
Nausea[b]			
None	52	73	<0.001
Mild	35	20	
Moderate	13	6	
Severe	1	0	
Vomiting[b]			
None	77	94	<0.001
Mild	11	3	
Moderate	12	3	
Severe	0	0	

Bold text was used for emphasis for P values < 0.05.
OST, oral sulfate tablets; PEG-EA, polyethylene glycol and ascorbate.
[a] Mild: barely noticeable, does not influence functioning causing no limitations of usual activities; Moderate: makes participant uncomfortable, influences functioning causing some limitations of usual activities; Severe: severe discomfort, treatment needed, severe and undesirable, causing inability to carry out usual activities.
[b] P value from the Fisher exact test.

Investigators were able to attempt colonoscopy in greater than 98% of subjects across all preparation groups. Cecal intubation rates were also greater than 97% for each preparation group, in compliance with the recommended target, 90%–95% (12). The proportion of preparations that were considered clinically adequate by the investigators in both groups was approximately 97%. Secondary indicators of endoscopist effort were similar between groups and are shown in Table 4. These include the volume of irrigation water needed during the procedure (about 91 mL) and average procedure duration (approximately 16 minutes) ADRs were similar between the 2 preparations (OST 33.1%; PEG-EA 34.8%).

Analysis of 219 subjects with known predictors of suboptimal preparation, "hard to prep," with history of constipation, current opioid users, body mass index ≥35, failed previous preparation, and those subjects who had a planned afternoon colonoscopy are shown in Table 5. Both preparations achieved high rates of success in these subgroups. Similar to the general study population, the proportion of subjects with global cleansing scores rated as Excellent tended to favor OST (hard to prep—61% vs 51%, afternoon colonoscopy—74% vs 61%).

Safety and tolerance

No difference between the treatment groups was detected for spontaneously reported treatment emergent adverse events, shown in Table 6. There were 5 unrelated serious adverse events reported in 4 subjects; 2 occurred before bowel preparation was taken, and 3 occurred in the PEG-EA treatment group. For expected preparation symptoms, subjects were interviewed by site personnel at visit 2 after completing their preparation and were asked if they experienced any symptoms of abdominal cramping, bloating, nausea, or vomiting and to rate these symptoms as mild, moderate, or severe. As shown in Table 7, subjects in the OST group tended to report more nausea and vomiting compared with subjects in the PEG-EA group; however, only a small proportion (<5%) of ratings were severe.

Subjects completed a preference questionnaire at visit 2 to capture the subject's perceptions of the preparation

Table 8. Preference questionnaire[a]

	OST (n = 278) (n %)	PEG-EA (n = 270) (n %)	P value[b]
Experience consuming prep			
Very easy	73 (26.3)	39 (14.7)	<0.001
Easy	108 (38.8)	66 (24.8)	
Tolerable	73 (26.3)	106 (39.8)	
Difficult	16 (5.8)	36 (13.5)	
Very difficult	8 (2.9)	19 (7.1)	
Very easy + easy	181 (65.1)	105 (39.5)	<0.001
Overall experience			
Excellent	66 (23.7)	38 (14.3)	0.007
Good	133 (47.8)	121 (45.5)	
Fair	58 (20.9)	83 (31.2)	
Poor	11 (4.0)	16 (6.0)	
Bad	10 (3.6)	8 (3.0)	
Excellent + Good	199 (71.6)	159 (59.8)	0.004
Comparison with previous experience (n %)			
Better	121 (65.1)	84 (45.9)	<0.001
Same	37 (19.9)	77 (42.1)	
Worse	28 (15.1)	22 (12.0)	
Not applicable	92	82	
Would you request again?			
Yes	217 (78.1)	178 (67.2)	0.005
No	61 (21.9)	87 (32.8)	
Would you refuse?			
No	229 (82.4)	216 (81.2)	0.746
Yes	49 (17.6)	50 (18.8)	

Bold text was used for emphasis for P values < 0.05.
OST, oral sulfate tablets; PEG-EA, polyethylene glycol and ascorbate.
[a] Efficacy population.
[b] P value from the exact χ^2 test.

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Table 9. Mean (SD) chemistry values by visit

Analyte Normal range	Visit	OST (n = 281)	PEG-EA (n = 270)	P^a
ALT/SGPT 5–30 (U/L)	1	23.1 (25)	21.2 (14)	**0.044**
	2	22.8 (15)	23.0 (13)	
Anion gap 8–16 (mEq/L)	1	7.9 (2)	8.0 (2)	**0.008**
	2	9.8 (2)	9.3 (2)	
AST/SGOT 9–34 (U/L)	1	20.2 (14)	19.7 (9)	0.093
	2	22.0 (10)	22.8 (11)	
Bicarbonate 21–33 (mEq/L)	1	28.0 (3)	27.7 (3)	**<0.001**
	2	26.7 (3)	25.6 (3)	
Bilirubin 0.1–1.1 (mg/dL)	1	0.56 (0.2)	0.52 (0.2)	**0.048**
	2	0.81 (0.4)	0.76 (0.3)	
BUN 5–22 (mg/dL)	1	15.8 (5)	15.1 (5)	0.839
	2	12.4 (4)	11.7 (4)	
Calcium 8.5–10.5 (mg/dL)	1	9.33 (0.4)	9.25 (0.5)	0.139
	2	9.13 (0.4)	9.13 (0.4)	
Chloride 95–110 (mEq/L)	1	103.3 (2)	103.3 (2)	**<0.001**
	2	103.3 (2)	104.4 (3)	
Creatine phosphokinase 25–210 (U/L)	1	127.7 (105)	122.6 (99)	0.792
	2	135.3 (98)	133.2 (100)	
Creatinine (mg/dL) F 0.49–1.12 M 0.62–1.44	1	0.87 (0.2)	0.86 (0.2)	0.122
	2	0.86 (0.2)	0.87 (0.2)	
GFR (mL/min/1.73 m^2) 18–49y >60 ≥50y ≥49	1	83.2 (20)	83.6 (20)	0.261
	2	85.0 (20)	83.8 (20)	
GGT (U/L) F 7–38 M 11–52	1	32.4 (31)	31.5 (32)	0.558
	2	30.2 (25)	31.1 (31)	
Magnesium 1.8–2.4 (mEq/Lmg/dL)	1	2.20 (0.2)	2.19 (0.2)	**<0.001**
	2	2.34 (0.2)	2.16 (0.2)	
Osmolality 276–295 (mOsm/kg)	1	300.2 (5)	299.3 (6)	0.791
	2	298.5 (7)	297.6 (5)	
Phosphorus 2.5–4.8 (mg/dL)	1	3.53 (0.5)	3.48 (0.5)	**<0.001**
	2	3.18 (0.5)	3.38 (0.5)	
Potassium 3.5–5.1 (mEq/L)	1	4.27 (0.4)	4.29 (0.4)	0.377
	2	4.21 (0.4)	4.23 (0.4)	
Protein 6–8 (g/dL)	1	7.15 (0.5)	7.10 (0.4)	0.774
	2	7.22 (0.5)	7.16 (0.5)	
Sodium 134–144 (mEq/L)	1	139.2 (2)	139.0 (2)	0.388
	2	139.8 (2)	139.4 (2)	
Uric acid (mg/dL) F 3.0–7.0 M 4.0–8.5	1	5.46 (1.4)	5.33 (1.3)	**0.020**
	2	5.70 (1.4)	5.44 (1.4)	

Bold text was used for emphasis for *P* values < 0.05.
ALT/SGPT, alanine aminotransferase/serum glutamic-pyruvic transaminase; ANOVA, analysis of variance; AST/SGOT, aspartate aminotransferase/serum glutamic-oxaloacetic transaminase; BUN, blood urea nitrogen; GFR, glomerular filtration rate; GGT, gamma-glutamyl transferase; OST, oral sulfate tablets; PEG-EA, polyethylene glycol and ascorbate.
[a]*P* value from ANOVA with term for treatment.

experience. As shown below in Table 8, despite the higher rates of nausea and vomiting in solicited symptoms, the OST preparation was rated more favorably than PEG-EA for numerous measures. More subjects in the OST group found the preparation "easy" or "very easy" to complete compared with PEG-EA. Ratings of overall preparation experience also

favored OST, with significantly more subjects rating the preparation "good" or "excellent." Of the group of subjects with a previous colonoscopy, 65% felt the OST experience was better than their previous prep, compared with 46% with PEG-EA ($P < 0.001$). Significantly, more OST subjects indicated that they would request their current preparation again if they were to need a colonoscopy in the future (OST—78%, PEG-EA—67%, $P = 0.005$).

Laboratory results are shown below in Table 9 for the study population for visit 1 (baseline) and visit 2 (day of colonoscopy). Although some statistically significant differences between the treatment groups were detected for some analytes, changes tended to be small and none were deemed clinically important. Although not considered clinically important, serum magnesium increased above normal range for about 25% of OST subjects. This was not unexpected because of the presence of magnesium in the OST formulation. Comparisons of laboratory results between elderly and nonelderly populations taking OST revealed no interactions unique to the elderly population, except for anion gap where elderly OST subjects experienced a mean increase in anion gap of 2.6 mEq/L compared with an increase of 1.8 mEq/L in the PEG-EA group.

Vital sign and electrocardiogram measures were similar between the 2 preparations with no statistically significant changes between visits 1 and 2. Within-group changes were also not statistically significant.

DISCUSSION

This prospective, randomized, single-blind, multicenter, non-inferiority study found that the new 24-tablet sulfate bowel preparation (OST) provided equivalent colon cleansing to a traditional US FDA–approved polyethylene glycol and ascorbate (PEG-EA) preparation. Both preparations were given according to a split-dose regimen. These rates of successful preparation are similar to other US FDA–approved bowel cleansing agents with analogous formulations (5,6). OST was associated with significantly more preparations scored as Excellent. On average, segmental cleansing scores were equivalent except for the proximal (ascending) colon where the tablet preparation had significantly more Excellent scores. ADRs for the 2 preparations were also comparable.

Spontaneous reports of treatment-emergent adverse event rates were similar between groups and comparable with other US FDA–approved preparations. Solicited symptom reports showed somewhat higher rates of nausea and vomiting associated with OST relative to PEG-EA, although few of these symptoms were considered to be severe. This difference is believed to be due to the tendency of subjects to rapidly ingest the required tasteless water, in contrast to other preparations where fatigue for a flavored solution may slow consumption. The OST preparation was rated more favorably by subjects for many subjective experience measures such as ease of completion, overall experience, comparison with previous prep, and willingness to take again. This is likely due to the tasteless nature of the tablet formulation.

The study does have limitations which include the lack of generalizability of the ADR data because of the heterogenous colonoscopy population (including nonscreening patients). In addition, although the grading scale used is appropriate to evaluate the cleansing efficacy of OST and PEG-EA, it does not allow for comparisons to published studies which used other scales (e.g. BBPS, Aronchick). Finally, although similar patient preference questions have been asked in bowel preparation studies (13), this instrument has not undergone formal validation. This study indicates that OST is a safe and effective tablet preparation option that may be well-received by patients undergoing colonoscopy.

Study Highlights

WHAT IS KNOWN

✔ Bowel preparation in essential for safe and effective diagnostic and therapeutic procedures.
✔ Available methods do not strike the base balance of efficacy, safety, and tolerance.

WHAT IS NEW HERE

✔ A new oral sulfate tablet is safe, effective, and well-tolerated.

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