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A Randomized Clinical Study Evaluating the Safety and Efficacy of a New, Reduced-Volume, Oral Sulfate Colon-Cleansing Preparation for Colonoscopy

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OBJECTIVES: **We sought to evaluate a new, low-volume, oral sulfate solution as a bowel preparation for colonoscopy in adult patients.**

METHODS: **The investigations were designed as two multicenter, single-blind, randomized, non-inferiority studies to show that the sulfate regimen would effect cleansing that is acceptable and equivalent to polyethylene glycol electrolyte solution with ascorbic acid (PEG-EA), and would be suitable for colonoscopy. One study evaluated same-day administration; the other compared the two study preparations given by split-dose administration in which the first portion was taken the evening before colonoscopy and the second portion on the morning of the procedure. The primary efficacy variable was based on bowel cleansing graded by an investigator who was unaware of the preparation method received.**

RESULTS: **Study 1 randomized 408 outpatients scheduled for colonoscopy for routine indications, with 387 subjects taking the preparation. In all, 364 subjects were randomized and took the preparation in study 2. The demographics of the enrolled subjects were similar across both treatment groups in the two studies, including gender, race, and ethnic characteristics. The primary efficacy analysis supports the conclusion that the oral sulfate solution produces the same degree of cleansing as PEG-EA. Successful preparations were seen in 82.4% and 80.3% in study 1 and 97.2% and 95.6% in study 2 for the oral sulfate solution and the PEG-EA regimen, respectively. Although no difference in excellent preparations was seen in the 1-day preparation, split-dose administration resulted in more excellent preparations in the sulfate group than in the PEG-EA group (63.3 vs. 52.5%, *P*=0.043). Preparation-related symptoms of cramping, bloating, nausea, and vomiting were generally mild and infrequent. Sulfate subjects reported slightly increased gastrointestinal events and higher vomiting scores (*P*=0.009) in the 1-day preparation but not in the split-dose regimen. There were no other differences for adverse events or clinically significant laboratory findings, including no increased creatinine.**

CONCLUSIONS: **The new 960-ml oral sulfate solution is effective for colonoscopy cleansing and has an acceptable safety profile.**

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INTRODUCTION

Gut lavage using large volume orally administered solutions has been developed as colon-cleansing preparations for diagnostic and surgical procedures (1–5). Because these solutions are isotonic and electrolyte balanced, there is little change in patient hydration and electrolytes in spite of the large volumes required (1,2). Up to four liters are required for effective purging resulting in patient complaints related to the volume of solution that must be ingested (6). Concentrated sodium phosphate salts are available and given as low-volume aqueous

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solutions or as tablet or capsule formulations with supplemental water (4). These products are effective and well-tolerated, but concern had been raised about safety because of fluid and electrolyte shifts due to sodium and phosphate absorption and occasional renal failure from calcium phosphate deposition in the distal renal tubules (7,8). A greatly improved product would be of low volume and not produce fluid or electrolyte shifts, or nephrocalcinosis.

Sulfate is a poorly absorbed anion historically used as an osmotic agent both for laxatives and as a component in some large volume bowel preparations (1). A new formulation of oral sulfate salts that omits phosphates has been developed and shown to produce stool volumes in normal volunteers equivalent to the sodium phosphate preparations without significant fluid and electrolyte shifts (Patel V, unpublished communication).

These investigations compared the new oral sulfate solution to a polyethylene glycol electrolyte lavage solution with ascorbic acid (PEG-EA, MoviPrep, Salix Pharmaceuticals, Morrisville, NC). Because PEG-EA labeling allows for same-day or a split-dose preparation, two studies of colonoscopy cleansing were performed. One compared the oral sulfate solution and PEG-EA given on the same day (the night before colonoscopy). The second study utilized a split-dose method of administration for both products.

METHODS

Study design

These were single-blind, active control, parallel studies of adult outpatients undergoing routine elective colonoscopy. The trials were registered at http://www.clinicaltrials.gov/ study 1 (same day): NCT00503607; study 2 (split dose): NCT00503815.

Study population

The study subjects were adult outpatients undergoing colonoscopy for routine clinical indications. Patients with ileus or suspected bowel obstruction, bowel perforation, previous alimentary tract surgery, significant gastroparesis or gastric outlet obstruction, toxic colitis or megacolon, severe ulcerative colitis or those pregnant or lactating were excluded. These exclusion criteria are consistent with contraindications of currently approved bowel preparations; therefore, the results of these studies may be generalized to the target population of patients undergoing colonoscopy, including the elderly. Subjects were excluded with clinically significant electrolyte abnormalities, renal or hepatic insufficiency, congestive heart failure or those with impaired consciousness that predisposes to aspiration. Baseline evaluations included medical history, physical examinations, and collection of demographic data. Laboratory testing performed at baseline, after the preparation before colonoscopy and 30 days post colonoscopy included hematology and blood chemistry including amylase, GGT, ALT, AST, magnesium, serum osmolality, calcium, phosphorus, electrolytes, BUN, creatinine, total protein, and uric acid. Urine pregnancy tests were performed on female subjects of child-bearing potential.

Study centers

Data were collected at 21 US study sites, all of which used the same investigational protocols. Enrollment was competitive and subjects were recruited from both hospital-based and stand alone gastroenterology practices. The experimental protocol and informed consent materials were approved by an Institutional Review Board before initiation of the study. Written informed consent was obtained for all participating subjects. Enrollment began on 16 July 2007, with the last subject completing on 1 November 2007.

Study medications

Oral sulfate solution (SUPREP, Braintree Laboratories) consists of sodium sulfate (35.0 g), magnesium sulfate (3.2 g), potassium sulfate (6.3 g) and flavoring agents in aqueous liquid form supplied in two 6-ounce (oz) plastic bottles. The contents of each bottle are diluted with water to 16 oz and ingested. Bowel cleansing requires ingestion of both bottles of sulfate solution. The total preparation volume is 960 ml. PEG-EA (MoviPrep, Salix Pharmaceuticals) is FDA-approved for colonoscopy cleansing and was supplied to study subjects in market packaging. The total preparation volume is 2,000 ml. Both preparations were packaged in identical outer containers to maintain the integrity of the treatment blind.

Study colon-cleansing methods

Sulfate preparation study subjects were advised to have a light breakfast and clear liquids for lunch and dinner. PEG-EA subjects were permitted to have a normal breakfast, light lunch, and clear soup or yogurt for dinner as recommended by the manufacturer. A study coordinator interviewed each subject and provided written instructions for the preparation methods.

In study 1 (same day) at 1800 hours, sulfate subjects were instructed to pour one 6-oz bottle of study medication into a provided 16-oz mixing cup. They would fill the cup with water and drink the entire volume. They were then instructed to drink two additional 16-oz cups of water over the next hour. At approximately 1900 hours, study subjects were instructed to pour the second 6 oz bottle of study medication into the 16 oz mixing cup, fill with water and drink. Over the next hour, they were instructed to drink an additional two 16 oz cups of water.

In Study 1, subjects randomized to PEG-EA were instructed to drink the first 1 liter PEG-EA dose over one hour, drinking 8 oz every 15 min until complete. The second 1 l study dose of PEG-EA was taken 1½ hour later. In addition, 1 l (approximately 32 oz) of additional clear liquid was taken that evening.

In study 2 (split dose), sulfate subjects had the first bottle of the oral sulfate solution the evening before colonoscopy. The second bottle was given at approximately 0600 hours on the day of colonoscopy. In this second study, PEG-EA subjects took

their evening dose followed by 16 oz of clear liquid. The second 1 l dose of PEG-EA would be taken at 0600 hours followed by 16 oz of clear liquids. They were asked to return unused bowel preparation components.

Randomization

Study medications were provided by Braintree Laboratories. Subjects were randomly assigned to study treatment based on a randomization schedule implemented by Braintree Laboratories before kit distribution to the site. The randomization schedule for each site was constructed using random blocks of two balanced treatment assignments to ensure a 1:1 treatment ratio. Following receipt of a sequential series of drug kits, unblinded site personnel dispensed the lowest-numbered kit available to maintain the randomization schedule. Patients who met eligibility requirements were sequentially assigned a kit number from the randomization schedule. To ensure treatment blinding was maintained, the colonoscopist was not allowed to perform any drug-related activities, such as randomization, dispensing, return, or accountability. Subjects were instructed not to discuss their study preparation with any staff member.

Adequacy of cleansing

Bowel cleansing was scored by colonoscopists who were unaware of the preparation method. Cleansing was scored with a 4-point scale where 1 = "poor" (large amounts of fecal residue requiring additional cleansing); 2 = "fair" (enough feces or fluid to prevent a completely reliable exam); 3 = "good" (small amounts of feces or fluid not interfering with the exam); 4 = "excellent" (no more than small bits of adherent feces/fluid). This scale has been used in previous bowel-cleansing studies (9–12). For the primary efficacy variable, scores of 3 and 4 were considered "successful" and scores of 1 or 2 were considered a "failure." Subjects unable to tolerate their preparation or those who were not examined due to lack of bowel cleansing were also considered a "failure." Physicians were also asked to rate the cleansing as to clinical "adequacy" for diagnostic purposes.

Preparation tolerance

A treatment questionnaire was completed by study subjects over the course of their bowel preparation, which recorded the times at which the subject started taking the preparation, times of their first and last bowel movement, and a description of what they ate and drank on the day of the preparation. In addition, subjects filled out an overall symptom questionnaire at their final visit before colonoscopy where they rated symptoms associated with the entire preparation experience. Symptoms of bloating, cramping, nausea, vomiting, and overall discomfort were scored on a 5-point scale where 1 = "none," 2 = "mild," 3 = "bothersome," 4 = "distressing," and 5 = "severely distressing." This scale has been used in previous bowel-cleansing studies (9–12). Symptoms reported as "severely distressing" on the scale were documented as adverse events. In addition, investigators recorded any observed or subject-reported adverse experiences. Safety assessments also included adverse event monitoring as well as baseline and post preparation physical examination and laboratory testing.

Data analysis

The sample size calculation for a non-inferiority study was based upon the normal approximation to the binomial distribution. Using the results from a phase II pilot study (unpublished), the overall treatment success for the oral sulfate group was expected to be approximately 85%. The PEG-EA efficacy has been reported as 73% (13). Assuming an 85% sulfate response rate for overall treatment success, based on a one-sided χ^2-test, a sample size of 180 subjects per group will have 80% power to detect a treatment difference of 12% at the two-sided significance level of 0.05.

The primary efficacy analysis was based upon an intent-to-treat analysis and included subjects who were randomized and received any treatment. Subjects in these groups had a determination of preparation success or failure based on the colonoscopist's score of cleansing. Subjects who did not undergo colonoscopy because of inadequate preparation or preparation-related adverse events were considered to be failures. Success rate was analyzed using Cochran–Mantel–Haenszel (CMH) χ^2 adjusting for the effect on the investigator site.

Secondary end points were analyzed in a manner similar to the primary analysis using CMH χ^2 adjusting for any site effects for counts (percentage) responses and two-way analysis of variance (ANOVA) with terms for treatment, site, and their interaction for mean responses. Results were presented for the effect results (P values) and 95% confidence intervals for the treatment difference.

Treatment-emergent adverse event rates were descriptively presented by body system, preferred term, severity, and relationship to treatment group. Differences in adverse event rates between groups were assessed using Fisher's exact test.

The analysis was performed according to a statistical analysis plan approved before breaking of the study blind. Statistical consultation was provided by G Burton Seibert, PhD, StatNet Statistical Services Network, Plaistow, NH.

The study was monitored by Premier Research, Quincy, MA, and Braintree Laboratories.

RESULTS

Demographics

Study subject allocation and disposition for both studies are recorded in **Tables 1** and **2**. Study demographics (**Table 3**) were similar across both treatment groups in the two studies including gender, age, race, and ethnic characteristics. There were 787 randomized study subjects in the two studies. Seven hundred fifty-one received study medication and were included in the intent-to-treat analysis, including 180 subjects aged 65 years or older. **Tables 1** and **2** list reasons for discontinuation. Seven hundred forty-five fully completed the protocol.

Study compliance was excellent in both studies. Nearly all sulfate subjects (99%) completed the preparation in study 1,

Table 1. Subject disposition study 1, same day

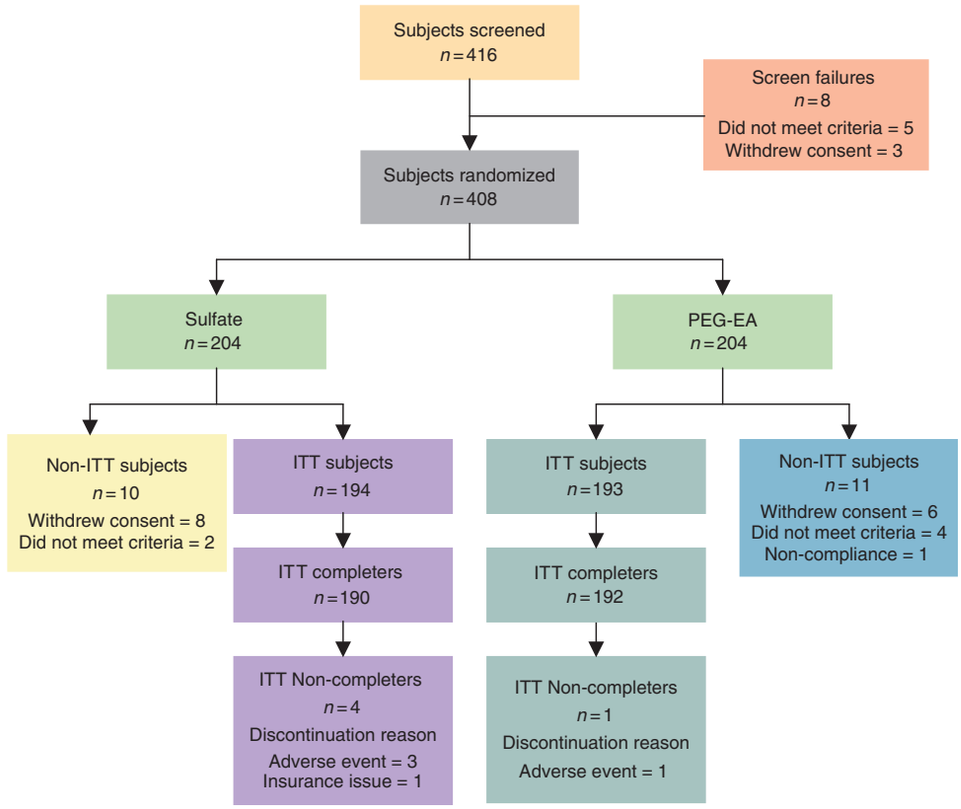

Table 2. Subject disposition study 2, split dose

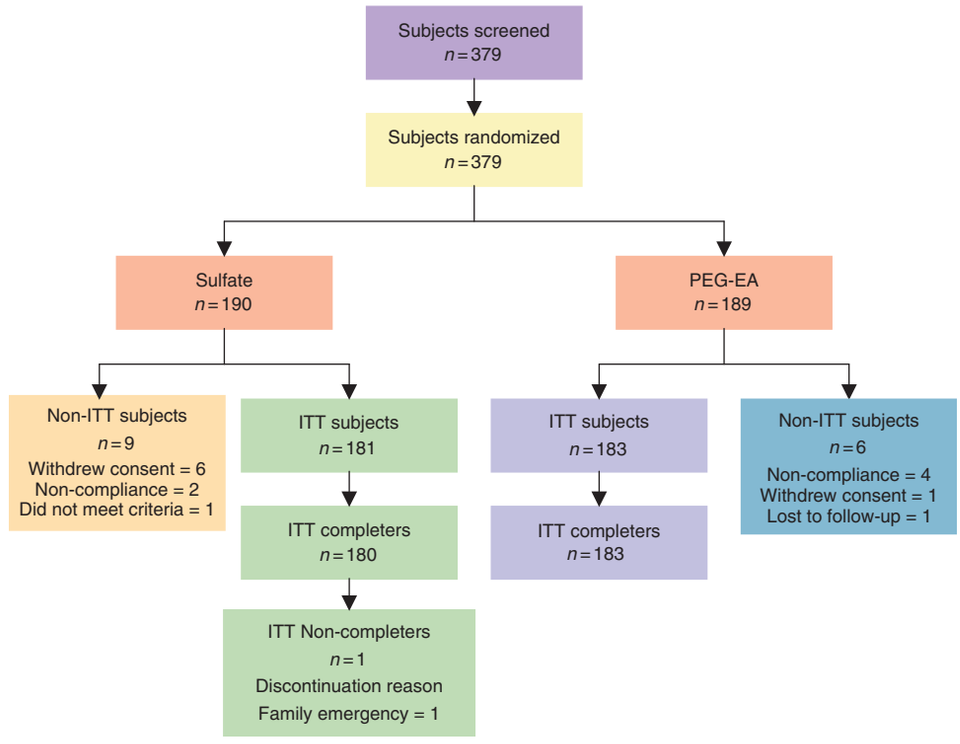

Table 3. Demographics—ITT population

	Study 1			Study 2		
	Same day			Split dose		
	Sulfate	PEG-EA	*P* value	Sulfate	PEG-EA	*P* value
n	194	193		181	183	
Age[a]	57.8 (10.7)	56.7 (11.6)	0.338	55.8 (12.4)	55.8 (10.8)	0.998
Gender						
Female	56%	54%	0.683	54%	54%	0.917
Race						
Caucasian	169 (87%)	169 (88%)	0.873	154 (85%)	160 (87%)	0.080
Black	21 (11%)	23 (12%)		16 (9%)	16 (9%)	
Other[b]	2 (1%)	0 (0%)		11 (6%)	3 (2%)	
Hispanic	14 (7%)	11 (6%)	0.680	6 (3%)	13 (7%)	0.156
Weight (lbs)[a]	184 (40)	186 (42)	0.613	84 (44)	184 (42)	0.968

[a]Mean (s.d.). [b]Some did not report data.

Table 4. Investigator grading of preparations—ITT population[a]

	Study 1		Study 2	
	Same day		Split dose	
	Sulfate	PEG-EA	Sulfate	PEG-EA
n	194	193	181	183
Primary efficacy success	159 (82.4%)	155 (80.3%)	175 (97.2%)	175 (95.6%)
Confidence interval	−5.7, 9.8		−2.2, 5.4	
P value[b]	<0.001		<0.001	
Scoring by grade				
Excellent	86 (44.6%)	72 (37.3%)	114 (63.3%)	96 (52.5%)
Good	73 (37.8%)	83 (43.0%)	61 (33.9%)	79 (43.2%)
Fair	22 (11.4%)	31 (16.1%)	3 (1.7%)	6 (3.3%)
Poor	9 (4.7%)	6 (3.1%)	2 (1.1%)	2 (1.1%)
			P value[c]	0.043
Mean rating	3.24	3.15	3.59	3.47
P value	0.278		0.050	
Consider adequate—"yes"	178 (94%)	182 (95%)	178 (99%)	181 (99%)

[a]Two sulfate patients were excluded from efficacy analyses because they withdrew before colonoscopy for a reason unrelated to safety or efficacy. [b]*P* value for non-inferiority hypothesis using an equivalence margin of 15%. [c]*P* value for comparison of excellent preparations—study 2.

compared with 95% of PEG-EA patients. In study 2 (split dose), compliance was approximately 98% for both treatment groups.

Efficacy

Non-inferiority testing of the primary efficacy end point confirmed that oral sulfate solution produces the same degree of cleansing as PEG-EA. This conclusion is consistent with the results seen in the individual studies for same-day and split-dose methods as seen in **Table 4**. Successful preparations were seen in 82.4 and 80.3% in study 1 and 97.2 and 95.6% in study 2 for the oral sulfate solution and the PEG-EA regimen, respectively. The table also illustrates that the split-dose regimen used in study 2 produced markedly superior cleansing results over the same-day method of study 1 for both preparations. Cleansing

Table 5. Symptom ratings[a]—ITT population

	Study 1			Study 2		
	Same day			Split dose		
	Sulfate	PEG-EA	*P* value	Sulfate	PEG-EA	*P* value
n	194	193		180	183	
Cramping[b]	1.51 (0.81)	1.45 (0.70)	0.191	1.53 (0.83)	1.57 (0.75)	0.687
Stomach bloating	1.86 (0.93)	1.83 (0.91)	0.627	1.57 (0.78)	1.74 (0.85)	0.063
Nausea	1.70 (0.93)	1.60 (0.93)	0.549	1.57 (0.88)	1.45 (0.75)	0.242
Vomiting	1.23 (0.71)	1.07 (0.41)	0.009	1.13 (0.51)	1.06 (0.40)	0.069
Overall	1.92 (0.88)	1.91 (0.93)	0.676	1.75 (0.80)	1.86 (0.71)	0.317

[a]Rating: 1—none to 5—severely distressing. [b]Mean (s.d.).

scores in **Table 4** show that in each study, and overall, sulfate achieved about 10% greater number of excellent preparations than PEG-EA ($P=0.043$ for study 2, study 1-not significant). In addition to grading the preparation, colonoscopist investigators were asked if the preparation was adequate to complete the colonoscopy. Nearly all ratings (>95%) for either treatment were considered adequate (**Table 1**).

As a population of interest, subjects aged 65 years or older were analyzed as a separate subgroup. In both studies, there were 180 elderly subjects. No difference in efficacy was seen in study 2 (split dose) with "successful" preps achieved in 95% of sulfate subjects and 89% of PEG-EA subjects, $P=0.403$. However, in study 1 (same day), sulfate preparation tended to result in more successful preparations than PEG-EA (86.0 vs. 72.9%; $P=0.073$). No significant differences in preparation efficacy were observed for gender or racial subgroups.

Primary efficacy results at each of the centers were consistent with the overall population in each study indicating no center effect. No multiplicity adjustments were made for analysis of demographic subgroups or analysis by study center, as these were pre-defined secondary end points.

Preparation tolerance

Table 5 lists subject-reported symptom ratings associated with their preparations. Overall the scores were low on the 1 (none) to 5 (severely distressing) scale. Sulfate subjects in study 1 (same day) reported slightly higher vomiting scores ($P=0.009$), but the difference was small (equal to a difference of 0.16 in the 5-point symptom scale) and not likely clinically significant. In study 2 (split dose) there was no statistically significant difference, although sulfate subjects also reported slightly higher vomiting scores (a 0.13 scale difference). Analysis of symptom ratings by severity (**Table 6**) confirms these results, and also shows that subjects taking PEG-EA reported greater overall discomfort in study 2 (split dose), although the difference is not likely to be clinically significant.

Treatment-emergent adverse events were infrequent overall with no differences detected between the two preparations as shown in **Table 7**.

Three sulfate subjects withdrew from the study. These included an 83-year-old with third degree atrioventricular block the day of colonoscopy (considered to be unrelated to study treatment and probably due to a pre-existing medical condition), and one each for nausea and vomiting. One PEG-EA subject (bloating and nausea) withdrew.

There were no deaths in the sulfate group and one death in the PEG-EA group attributed to a subsequent surgery unrelated to study medication. There were no additional serious adverse events in the sulfate group and two in the PEG-EA group (atypical chest pain—1, ischemic colitis—1).

A small difference in gastrointestinal treatment-emergent adverse events between study groups in the 180 subjects aged 65 years or older was observed ($P=0.035$). This was primarily due to study 1 (same-day preparation) elderly sulfate subjects who had more gastrointestinal-related adverse events (3 vs. 7 events in study 1). This is reflected in the slightly higher vomiting symptom scores reported by elderly subjects taking sulfate (1.28 vs. 1.00 on a scale of 1–5; $P<0.001$). Older subject scores of vomiting symptoms were not significantly different in Study 2 (split-dose). Overall discomfort was not rated differently in either study. Three hundred fifty-six subjects with a history of heart disease, renal failure, hypertension, and diabetes were enrolled in the two studies. Comparison of these "higher risk" subjects revealed no differences between the treatment groups with respect to adverse event frequency.

There were no clinically significant changes in physical examination, weight, temperature, pulse, or blood pressure. Both studies collected blood samples for chemistry and hematology testing at baseline (visit 1), immediately before colonoscopy (visit 2) and approximately 30 days post colonoscopy (visit 3). These are shown in **Table 8** for electrolytes and other selected measures.

Although statistically significant differences for a number of analytes were detected between the preparations at visit 2 (after ingesting the preparation), all of the differences were small and clinically insignificant. For example, although statistically

Table 6. Symptom ratings by severity—ITT population

	Study 1		Study 2	
	Same day		Split dose	
Symptom (score)	Sulfate (*n*=194)	PEG-EA (*n*=193)	Sulfate (*n*=181)	PEG-EA (*n*=183)
Cramping				
None (1)	123 (63%)	124 (64%)	111 (61%)	102 (56%)
Mild (2)	48 (25%)	56 (29%)	54 (30%)	62 (34%)
Bothersome (3)	14 (7%)	8 (4%)	6 (3%)	14 (8%)
Distressing (4)	6 (3%)	5 (3%)	7 (4%)	5 (3%)
Severely distressing (5)	1 (1%)	0	2 (1%)	0
P[a]	0.525		0.154	
Stomach bloating				
None (1)	81 (42%)	85 (44%)	103 (57%)	85 (46%)
Mild (2)	70 (36%)	66 (34%)	56 (31%)	70 (38%)
Bothersome (3)	30 (16%)	32 (17%)	17 (9%)	18 (10%)
Distressing (4)	8 (4%)	7 (4%)	3 (2%)	10 (6%)
Severely distressing (5)	3 (2%)	2 (1%)	1 (1%)	0
P[a]	0.972		0.070	
Nausea				
None (1)	104 (54%)	118 (61%)	111 (61%)	122 (67%)
Mild (2)	54 (28%)	48 (25%)	47 (26%)	45 (25%)
Bothersome (3)	23 (12%)	18 (9%)	11 (6%)	11 (6%)
Distressing (4)	9 (5%)	4 (2%)	10 (6%)	4 (2%)
Severely distressing (5)	2 (1%)	5 (3%)	1 (1%)	1 (1%)
P[a]	0.285		0.584	
Vomiting				
None (1)	168 (87%)	186 (96%)	165 (91%)	177 (97%)
Mild (2)	11 (6%)	4 (2%)	11 (6%)	4 (2%)
Bothersome (3)	7 (4%)	1 (1%)	1 (1%)	0
Distressing (4)	4 (2%)	1 (1%)	2 (1%)	1 (1%)
Severely distressing (5)	2 (1%)	1 (1%)	1 (1%)	1 (1%)
P[a]	0.017		0.262	
Overall discomfort				
None (1)	70 (36%)	76 (39%)	78 (43%)	57 (31%)
Mild (2)	78 (40%)	73 (38%)	76 (42%)	98 (54%)
Bothersome (3)	36 (19%)	32 (17%)	19 (11%)	26 (14%)
Distressing (4)	6 (3%)	10 (5%)	7 (4%)	1 (1%)
Severely distressing (5)	2 (1%)	2 (1%)	0	1 (1%)
P[a]	0.809		0.007	

[a]*P* value for difference between treatments by χ^2 test.

significant, the changes observed for creatinine were on the order of 0.01 or 0.02 mg/dl for either preparation. At the 1-month follow-up visit (visit 3) no change in serum creatinine relative to baseline for sulfate subjects was observed.

DISCUSSION

Large volume orally administered solutions such as polyethylene glycol electrolyte lavage solution (PEG-ELS, GoLYTELY, Braintree Laboratories; CoLyte, Schwartz Pharma, Milwaukee,

Table 7. Treatment-emergent adverse events—ITT population

	Sulfate 375	PEG-EA 376	95% CI	*P* value
Number of subjects with any event	35 (9.3)	27 (7.2)	(−1.8, 6.1)	0.292
Number of events	43	33		
Cardiac AV block	1 (0.3)	0	(0.3, 0.8)	0.499
Gastrointestinal	21 (5.6)	17 (4.5)	(−2.1, 4.2)	0.511
Abdominal distension	5 (1.3)	3 (0.8)	(−0.9, 2.0)	0.505
Abdominal pain	5 (1.3)	3 (0.8)	(−0.9, 2.0)	0.505
Anal discomfort	1 (0.3)	2 (0.5)	(−1.2, 0.6)	1.000
Ischemic colitis	0	1 (0.3)	(−0.8, 0.3)	1.000
Diarrhea	1 (0.3)	0	(−0.3, 0.8)	0.499
Dry mouth	1 (0.3)	0	(−0.3, 0.8)	0.499
Mouth ulceration	1 (0.3)	0	(−0.3, 0.8)	0.499
Nausea	6 (1.6)	8 (2.1)	(−2.5, 1.4)	0.789
Vomiting	6 (1.6)	3 (0.8)	(−0.8, 2.4)	0.340
General disorders	2 (0.5)	5 (1.3)	(−2.2, 0.6)	0.451
Infections and infestations	1 (0.3)	0	(−0.3, 0.8)	0.499
Nasopharyngitis	1 (0.3)	0	(−0.3, 0.8)	0.499
Investigations (laboratory)	3 (0.8)	0	(−0.1, 1.7)	0.124
Nervous system (headache)	6 (1.6)	5 (1.3)	(−1.4, 2.0)	0.773
Renal and urinary (dysurua)	1 (0.3)	0	(−0.3, 0.8)	0.499
Respiratory	0	1 (0.3)	(−0.8, 0.3)	1.000
Skin and tissue (pruritis)	1 (0.3)	0	(−0.3, 0.8)	0.499

WI) and sulfate-free electrolyte lavage solution (SF-ELS, NuLYTELY, Braintree Laboratories; Trilyte, Schwartz Pharma) have been developed as gastrointestinal washes for diagnostic purposes or as laxatives (1–6). Because the solutions are isotonic, patients are required to ingest upwards of a gallon of fluid to achieve adequate purging.

Sodium phosphate salts, when diluted in small volumes are concentrated solutions taken as laxatives in tablespoon sized (15 ml) daily doses or as colon-cleansing agents in larger volumes. These agents are available as liquid (Fleet's Phosphosoda, Fleet Pharmaceuticals, Lynchburg, VA) or non-aqueous tablet or capsule formulations (OsmoPrep, Salix Pharmaceuticals, Morrisville, NC) using similar doses of sodium phosphate (4). Phosphate solutions and tablets cause clinically significant electrolyte and fluid shifts (US Food and Drug Administration, Center for Drug Evaluation and Research, 17 September 2001) and hyperphosphatemia (5). Reacting to reports of acute phosphate nephropathy, the FDA has reclassified sodium phosphate solution as a prescription drug and has required that all sodium phosphate-based bowel preparations include a black box warning (US Food and Drug Administration, Center for Drug Evaluation and Research, FDA Alert December 2008). Thus, a greatly improved product would be of low volume and not produce clinically significant fluid or electrolyte shifts.

The safety of sulfate salts has been well established. The oral LD50 for sodium sulfate in rats is 3–4 g/kg (14). Sulfate salts have been used as laxatives when taken in small doses (sodium sulfate decahydrate, Glauber's Salts or sal mirabilis). In larger volumes, 22.74 g of sodium sulfate (about 15.4 g sulfate anion) has been included as an active osmotic agent in PEG-ELS solutions (GoLYTELY). In large quantities, sodium sulfate alone would be expected to cause significant electrolyte gains or losses. However, a combination of sulfate salts composed of different alkali metal counterions was developed that would not disrupt electrolytes.

The oral sodium salt solution (SUPREP) is composed of an aqueous combination of sodium, potassium and, magnesium salts of sulfate with appropriate flavoring yielding a preparation that delivers 29.67 g of sulfate anion (about twice the dose of sulfate used in the sulfate containing PEG-ELS solutions). The total dose is 960 ml. Because sulfates and magnesium are poorly absorbed, they remain in the lumen of the gastrointestinal tract where they exert an osmotic effect. The osmotic action of the poorly absorbed sulfate anion increases the water content of stool and, thereby, causes a watery diarrhea.

Table 8. Laboratory—ITT population

Measure (units)	Normal range	Drug	Baseline	Visit 2	Visit 3	Δ To visit 2
Bicarbonate (mEq/l)	22–29	Sulfate	25.2 (2.3)	24.3 (2.5)	25.3 (2.2)	−0.86 (2.8)
		PEG-EA	25.3 (2.2)	23.6 (2.4)	25.4 (2.2)	−1.68 (2.8)
BUN (mg/dl)	6–19	Sulfate	16.7 (5.0)	13.4 (3.9)	16.6 (5.0)	−3.45 (4.1)
		PEG-EA	16.7 (5.1)	13.9 (4.6)	17.0 (5.3)	−2.86 (3.8)
Calcium (mg/dl)	8.4–10.2	Sulfate	9.74 (0.36)	9.68 (0.46)	9.67 (0.39)	−0.06 (0.43)
		PEG-EA	9.74 (0.38)	9.59 (0.39)	9.66 (0.39)	−0.14 (0.39)
Chloride (mEq/l)	96–108	Sulfate	104.3 (2.5)	103.7 (2.9)	104.6 (2.8)	−0.73 (2.8)
		PEG-EA	104.1 (2.6)	105.3 (2.9)	104.4 (2.6)	1.26 (2.7)
Creatinine (mg/dl)	F 0.4–1.1	Sulfate	0.95 (0.20)	0.97 (0.20)	0.95 (0.20)	0.02 (0.13)
	M 0.5–1.2	PEG-EA	0.98 (0.25)	0.97 (0.23)	0.99 (0.24)	−0.01 (0.13)
Hematocrit (%)	F 37–47	Sulfate	43.0 (3.8)	44.0 (4.0)	42.6 (3.7)	0.97 (2.4)
	M 42–52	PEG-EA	42.8 (3.8)	43.6 (4.2)	42.5 (3.9)	0.85 (2.7)
Magnesium (mEq/l)	1.3–2.1	Sulfate	1.68 (0.14)	1.71 (0.15)	1.65 (0.14)	0.04 (0.13)
		PEG-EA	1.67 (0.14)	1.64 (0.14)	1.65 (0.14)	−0.03 (0.12)
Osmolality mOsm/kg	275–301	Sulfate	291.7 (5.9)	289.5 (5.3)	ND	−2.27 (5.9)
		PEG-EA	291.0 (6.0)	290.4 (5.6)		−0.68 (5.7)
Potassium (mEq/l)	3.5–5.1	Sulfate	4.38 (0.43)	4.30 (0.42)	4.40 (0.42)	−0.08 (0.46)
		PEG-EA	4.36 (0.44)	4.29 (0.43)	4.38 (0.41)	−0.07 (0.50)
Sodium (mEq/l)	136–145	Sulfate	140.1 (2.5)	140.3 (2.6)	140.3 (2.3)	0.13 (2.6)
		PEG-EA	139.8 (2.3)	140.5 (2.5)	140.2 (2.4)	0.65 (2.6)
T. Bilirubin (mg/dl)	0.1–1.2	Sulfate	0.59 (0.34)	0.89 (0.51)	0.66 (1.50)	0.30 (0.26)
		PEG-EA	0.59 (0.28)	0.86 (0.46)	0.59 (0.28)	0.27 (0.28)
T. Protein (g/dl)	6.4–8.3	Sulfate	7.31 (0.43)	7.46 (0.53)	7.17 (0.44)	0.15 (0.46)
		PEG-EA	7.27 (0.40)	7.31 (0.44)	7.18 (0.42)	0.03 (0.41)
Uric acid (mg/dl)	F 2.4–5.7	Sulfate	5.74 (1.6)	6.24 (1.5)	5.90 (1.4)	0.52 (0.83)
	M 3.4–7.0	PEG-EA	5.73 (1.7)	5.74 (1.6)	5.95 (1.7)	−0.02 (0.81)

Mean (s.d.) chemistry and hematology values by visit (studies 1 and 2).

In this report, two studies are presented. Both studies were designed as single-blind studies due to the differences in the preparation regimens. Although this represents a potential source of bias, precautions were taken to insure that the examining physicians remained blinded to the study preparation. PEG-EA (MoviPrep) was selected as the control agent because it is a reduced volume preparation (requiring ingestion of 2 l of solution) and its labeling allows for both same-day and split-dose administration. In addition, the contraindications for PEG-EA are similar to those for the sulfate preparation, unlike the sodium phosphate preparations. This similarity allowed for selection of a wider study population including higher risk patients.

In the first of the two studies presented in this report (same-day administration), cleansing with the oral sodium sulfate solution (success = 82.4%) produced the same degree of cleansing as PEG-EA (success = 80.3%). Treatment-emergent adverse experiences were equivalent although sulfate subjects reported slightly higher vomiting symptom scores (mean = 1.23 on a 5-point scale). These scores were much less than has been reported for 4 l lavage preparations (mean = 1.70) and the difference seems to be related to the close (1 h) proximity of the two sulfate doses given the evening before colonoscopy (9).

In the second trial (split dose), the degree of cleansing was again the same between the two preparations (success rates equal to 97.2 and 95.6% for oral sulfate solution and PEG-EA, respectively). However, much better cleansing results were obtained for both products with about a 15% improvement in successful preparations over the same-day administration. Split-dose administration has been reported to improve cleansing quality (15). The split-dose protocol also resulted in a statistically significant and marked increase in the number

of excellent sulfate preparations relative to PEG-EA. This result may be attributable to the more liberal diet allowed by the PEG-EA labeling.

There were no treatment-emergent serious adverse experiences in the sulfate group and there were no significant differences reported for abdominal cramping, nausea, bloating, or vomiting. Neither preparation induced clinically significant changes in blood chemistry or hematology, including creatinine.

These studies demonstrate that sulfate solution administered as a same-day or split-dose preparation is a safe and effective regimen for colon cleansing.

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Study 1—same day:

Charles Barish, MD, Wake Research Associates, Raleigh NC; Raj Bhandari, MD, Delta Research Partners, Monroe, LA; Richard Chasen, MD, Maryland Digestive Disease Research, LLC, Laurel, MD; Daniel Connell, MD, Regional Gastroenterology Associates of Lancaster, Lancaster, PA; Michael Goldstein, MD, Long Island GI Research Group, Great Neck, NY; Pramod Malik, MD, Gastroenterology Associates of Tidewater, Chesapeake, VA; Mark Nagrani, MD, United Medical Research, New Smyrna Beach, FL; Julio Salcedo, MD, Washington Gastroenterology, Washington DC; Howard Schwartz, MD, Miami Research Associates, Miami, FL; Michael Schwartz, MD, Jupiter Research Inc., Jupiter, FL; Reynaldo Rodriguez, DO, University of South Alabama, Mobile, AL.

Study 2—split dose:

William Burch, MD, Franklin Gastroenterology, PLLC, Franklin, TN; Roland Bennetts, MD, Northwest Gastroenterology Clinic, Portland, OR; Steven Duckor, MD, Advanced Clinical Research Institute, Orange, CA; Ronald Kotfila, MD, Gastroenterology Associates, Jackson, MS; Dennis Riff, MD, Advanced Clinical Research Institute, Anaheim, CA; Robert Souder, MD, Regional Research Institute, Jackson, TN; Ira Stein, MD, Gastrointestinal Institute, PLLC, Nashville, TN; Barry Winston, MD, Houston Medical Research Associates, Houston, TX; Robert Wohlman, MD, Northwest Gastroenterology Associates, Bellevue, WA; Lawrence Wruble, MD, Memphis Gastroenterology Group, Germantown, TN.

CONFLICT OF INTEREST

Guarantor of the article: Jack A. Di Palma, MD.

Specific author contributions: Concept, design of the protocol, data analysis, and writing of the paper: Di Palma; data acquisition, data analysis, and writing of the paper: Rodriguez; concept, protocol design, conduct of the study protocol, data acquisition, analysis of the data, and writing of the paper: Cleveland and McGowan.

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Study Highlights

WHAT IS CURRENT KNOWLEDGE

✓ Bowel preparation is essential for safe and effective diagnostic and therapeutic procedures.

✓ Available methods do not strike the best balance of efficacy, safety, and tolerance.

WHAT IS NEW HERE

✓ A new oral sulfate solution is of reduced volume—enhancing tolerability—and it is safe and effective.

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