Reprinted fromJOURNAL OF CLINICAL GASTROENTEROLOGY
Vol. 57 No. 9 October 2023
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Published by Lippincott Williams & Wilkins Printed in U.S.A.

ORIGINAL ARTICLE

Comparison of a Novel, Flavor-optimized, Polyethylene Glycol and Sulfate Bowel Preparation With Oral Sulfate Solution in Adults Undergoing Colonoscopy

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Introduction: A new bowel preparation for colonoscopy has been developed containing poorly absorbed sulfate salts and polyethylene glycol 3350, which retain water within the intestinal lumen resulting in copious diarrhea, thereby cleansing the bowel. The product was formulated to be safe and effective with a sports drink-like flavor. This study evaluated the new flavored polyethylene glycol and sulfate solution (FPSS) compared with a Food and Drug Administration-approved bowel preparation containing sulfate salts only [oral sulfate solution (OSS)].

Methods: Five hundred adults were enrolled in this multicenter, noninferiority study. Subjects were assigned FPSS or OSS administered in split-dose regimens (PM/AM). FPSS subjects took 2 L of the flavored osmotic solution (1 L at night and 1 L in the morning). OSS was taken according to its approved labeling. Colonoscopies were graded globally and segmentally by blinded local investigators using a 4-point scale (excellent, good, fair, and poor), with "good" and "excellent" considered successful. Safety was assessed by adverse events (AEs) and laboratory testing.

Results: A high rate of cleansing success was seen with FPSS (94%), which was noninferior to OSS (94%). This conclusion was confirmed by blinded central readers. Segmental success rates were >90% for both preparations, including the right colon. Questionnaire ratings indicated the FPSS experience was preferred over OSS with 87% of FPSS subjects noting their preparation was "tolerable" to "very easy" to consume versus 74% for OSS. The majority of FPSS subjects agreed their preparation tasted like a sports drink. Gastrointestinal symptoms were the most common AEs. There was no difference between preparations for any AE and no clinically significant differences in laboratory parameters.

Conclusions: The new sports drink-like flavored preparation achieved a high level of cleansing in the study, demonstrating noninferiority to OSS. FPSS was well-tolerated with low rates of expected gastrointestinal symptoms. The optimized flavor of FPSS resulted in significantly better acceptance ratings.

Key Words: bowel preparation, colonoscopy, colon cleansing

(*J Clin Gastroenterol* 2023;57:920–927)

INTRODUCTION

The success of colonoscopy, the pre-eminent method for colorectal cancer screening and detection, is dependent upon adequate cleansing of the colon.[1] Adequate cleansing requires ingestion of a large volume of fluid to wash out as much fecal matter as possible to allow for clear visualization of the intestinal mucosa. Thus, early US Food and Drug Administration (FDA) approved preparations required ingestion of about one gallon of an isotonic solution of polyethylene glycol (PEG) and electrolytes.[2,3] More recent studies have established that about 3 L of solution is typically required.[4] These solutions rely upon the osmotic activity of poorly absorbed ingredients, such as PEG or sulfate, which cause water to be retained within the lumen of the intestine rather than absorbed, thereby inducing copious diarrhea. The osmotically active agent is combined with added electrolytes in sufficient quantities to prevent electrolyte gains or losses resulting from diarrhea.[2–4] However, due to the large volumes of poor-tasting solution to be ingested, patients are often resistant to completion of their bowel preparation. In an attempt to improve patient compliance, hypertonic reduced volume solutions have been introduced that rely either upon the sulfate anion or a combination of PEG and ascorbate as the osmotic agents.[5,6] As a result of the hypertonicity of these solutions, additional water must be supplied to compensate for diarrheal water losses. Despite the many FDA-approved preparation options available, an unapproved bowel preparation composed of a debulking dose of stimulant laxative (eg, bisacodyl), followed by PEG3350 (available as an over the counter laxative), mixed with a commercially available sports drink (typically Gatorade, Pepsico), is recommended by some endoscopists.[7,8] This preparation has been associated with reports of poor efficacy and electrolyte imbalance and may require additional cleansing measures by the endoscopist.[7,9,10] It has seen increased use presumably due to its relatively low volume and well-tolerated flavor.

Recent work has resulted in the development of a low-volume, sports drink-like flavored preparation based on

Received for publication May 11, 2022; accepted June 18, 2023.
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This study was supported by Braintree Laboratories, part of Sebela Pharmaceuticals, Inc.
The trial was registered at Clinicaltrials.gov (identifier NCT04446312).
R.B., M.G., and D.S.M.: study participants, collecting data, and reviewing the manuscript. J.M. and M.V.C.: planning, collection of data analysis writing, and review of the manuscript. J.A.D.P.: planning conducting, monitoring, analysis, and writing of the report.
J.A.D.P. is a consultant medical director of Braintree Laboratories. M.V.C. is a scientific consultant for Braintree Laboratories. J.M. is an employee of Braintree Laboratories, Inc. The remaining authors declare that they have nothing to disclose.
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DOI: 10.1097/MCG.0000000000001894

TABLE 1. Preparation Cleansing Score

Score	Description
Poor	Large amounts of fecal residue, additional bowel preparation required
Fair	Enough feces even after washing and suctioning to prevent clear visualization of the entire colonic mucosa
Good	Feces and fluid require washing and suctioning but still achieves clear visualization of the entire colonic mucosa
Excellent	No more than small bits of feces/fluid, which can be suctioned easily; achieves clear visualization of the entire colonic mucosa

a rational formulation of sulfate salts, electrolytes, and PEG3350 (SUFLAVE, Braintree Laboratories, Inc.). This flavored PEG and sulfate solution (FPSS) preparation was formulated to induce about 3 L of cleansing diarrhea and to prevent losses or gains of electrolytes.[11] Furthermore, FPSS was formulated to avoid the use of a debulking dose of stimulant laxative, such as bisacodyl. Stimulant laxatives have been associated with side effects, such as ischemic colitis. Appropriately, prescription bowel preparations warn of the increased risk of ischemic colitis if stimulant laxatives are added to a bowel preparation regimen. As for all hypertonic preparations, additional water is required to prevent dehydration. This report describes a randomized, investigator-blinded comparison of the new sports drink-like flavored preparation to a well-established, FDA-approved, sulfate-based liquid formulation [oral sulfate solution (OSS), SUPREP, Braintree Laboratories, Inc.] for colonoscopy preparation.

METHODS

Study Design

This investigator-blinded, randomized, controlled, non-inferiority study was sponsored and conducted by Braintree Laboratories, Inc. The study compared FPSS (SUFLAVE) with OSS (SUPREP) in outpatients undergoing colonoscopy for routine indications. The trial was registered at Clinicaltrials.gov (identifier NCT04446312) and approved by respective facility Institutional Review Boards. Written informed consent was obtained for all participating study subjects. Enrollment began on July 13, 2020, and the last subject was completed on February 5, 2021.

Study Population

Male and female outpatients at least 18 years of age who required a colonoscopy for routine clinical indications were enrolled. These indications included screening, polyp or neoplasm surveillance, rectal or gastrointestinal bleeding, abdominal pain, changes in bowel habits, and inflammatory bowel diseases. Females of childbearing potential were required to be taking an acceptable form of birth control and to have had a negative serum 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 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. Patients were excluded based on the following medication use: laxatives (more than 2 to 3 times per week), diuretics, and antihypertensive medications, including angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers. In addition, patients with uncontrolled hypertension or a history of severe renal, liver, or cardiac insufficiency; patients withdrawing from alcohol or benzodiazepines, were also excluded. As part of the screening procedures, subjects underwent a physical examination, had vital signs taken, electrocardiogram, and provided blood and urine samples for laboratory testing.

Bowel preparations were assigned using an automated interactive web response system. The interactive web response system randomly assigned subjects to the two preparation groups in a 1:1 ratio.[12] Diaries were provided to allow the subject to record any food and liquid consumption and preparation dosing times. After completing their preparation, study subjects returned to the clinic for visit 2 and underwent a physical examination, vital signs, and laboratory sample collection. Study subjects were instructed to not discuss their study preparation with any staff member and blinded endoscopists were not allowed to perform any activities involving the study preparation (eg, dispensing and accountability). 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 to 48 hours after colonoscopy (visit 3). Subjects with ongoing adverse events (AEs) or abnormal laboratory values at this visit were asked to return for an additional follow-up 7 and 30 days after colonoscopy.

TABLE 2. Subject Disposition and Demographics

	FPSS n (%)	OSS n (%)	All n (%)
Subjects screened			517
Subjects randomized	250	250	500
Safety population	227 (90.8)	226 (90.4)	453 (90.6)
Efficacy population	226 (90.4)	224 (89.6)	450 (90.0)
Completing subjects (% ITT)	212 (84.8)	206 (82.4)	418 (83.6)
Subjects discontinued (% ITT)	38 (15.2)	44 (17.6)	82 (16.4)
Reasons for discontinuation*:			
Adverse event	2 (5.3)	0 (0)	2 (2.4)
Lost to follow-up	13 (34.2)	14 (31.8)	27 (32.9)
Screen fail (post random)	4 (10.5)	12 (27.3)	16 (19.5)
Subject withdrew consent	17 (44.7)	14 (31.8)	31 (37.8)
Other	2 (5.3)	4 (9.1)	6 (7.3)
Mean age (SD)	56.4 (11.8)	56.1 (11.7)	56.2 (11.7)
Age >65 yrs	68 (27.2)	65 (26.0)	133 (26.6)
Male	108 (43.2)	98 (39.2)	206 (41.2)
Female	142 (56.8)	152 (60.8)	294 (58.8)
African American	26 (10.4)	29 (11.6)	55 (11.0)
Caucasian	209 (83.6)	213 (85.2)	422 (84.4)
Other race	15 (6.0)	8 (3.2)	23 (4.6)

*Percentages based on the number of subjects who discontinued in each treatment group.

FPSS indicates flavored polyethylene glycol and sulfate solution; ITT, intention to treat; OSS, oral sulfate solution.

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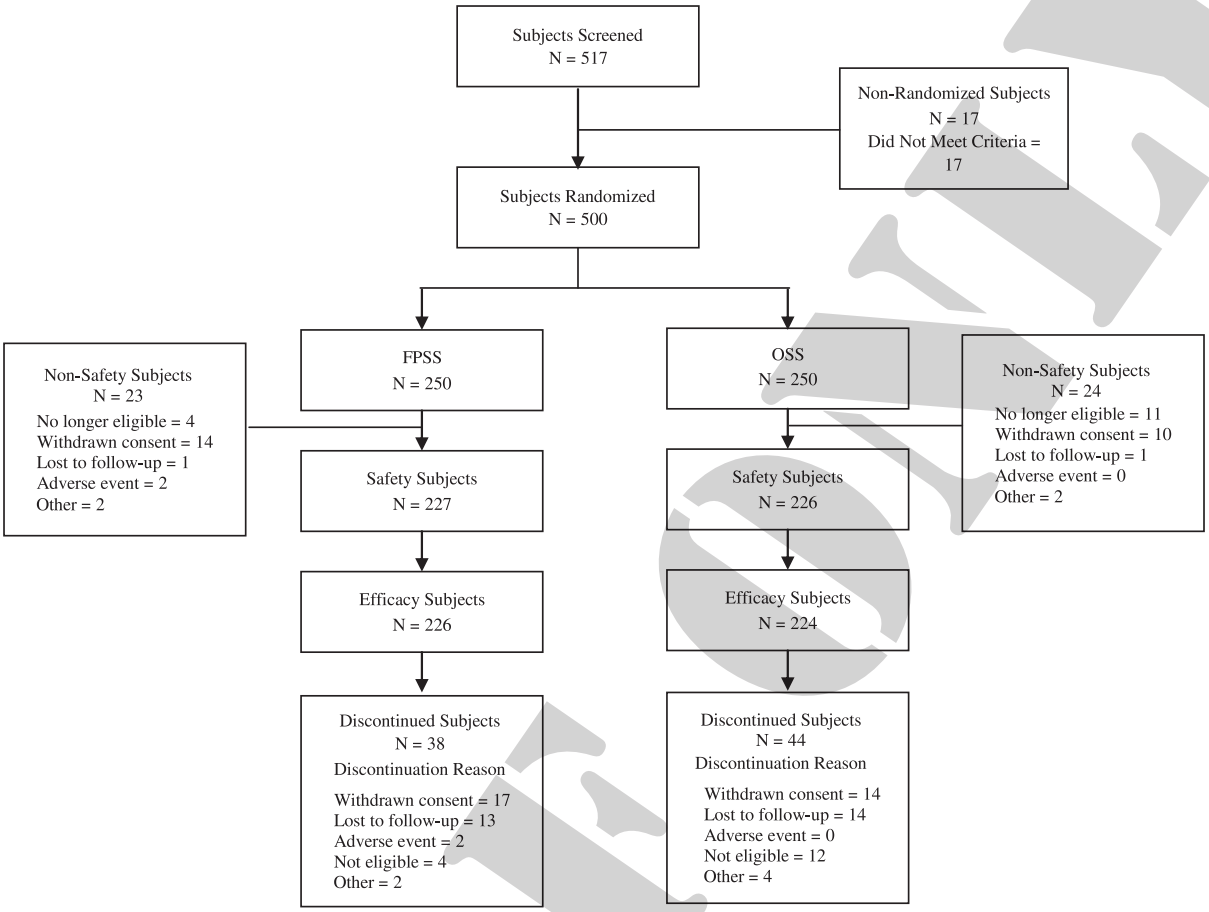


FIGURE 1. CONSORT diagram. FPSS indicates flavored polyethylene glycol and sulfate solution; OSS, oral sulfate solution.

TABLE 3. Local Endoscopist Cleansing Ratings (Primary Endpoint)

	FPSS (n = 226); n (%)	OSS (n = 224); n (%)	95% CI†	P‡	P§
Success*	212 (93.8)	211 (94.2)	−3.97, 4.27	0.944	< 0.001
Failure	14 (6.2)	13 (5.8)	—	—	—
Grade					
Excellent	106 (46.9)	139 (62.1)	—	—	—
Good	106 (46.9)	72 (32.1)	—	—	—
Fair	10 (4.4)	8 (3.6)	—	—	—
Poor	2 (0.9)	3 (1.3)	—	—	—
Missing	2 (0.9)	2 (0.9)	—	—	—

*Preparation success is defined as cleansing graded either "excellent" or "good."

†CI for the common risk difference.

‡*P* value based on a Cochran-Mantel-Haenszel test accounting for the effect of the investigator site.

§*P* value from the noninferiority test comparing the common risk difference of the proportions for the two treatment groups, using a margin of 10%.

FPSS indicates flavored polyethylene glycol and sulfate solution; OSS, oral sulfate solution.

TABLE 4. Central Reader Cleansing Success Ratings

	FPSS (n = 217); n (%)	OSS (n = 206); n (%)	95% CI†	P‡	P§
Global success					
Success*	212 (97.7)	194 (94.2)	0.36, 7.66	0.034	< 0.001
Failure	5 (2.3)	12 (5.8)	—	—	—
Insertion					
Success*	176 (81.1)	172 (83.5)	−8.62, 5.77	0.699	0.01
Failure	41 (18.9)	34 (16.5)	—	—	—
Withdrawal					
Success*	205 (94.5)	196 (95.1)	−5.01, 3.50	0.725	< 0.001
Failure	12 (5.5)	10 (4.9)	—	—	—

*Preparation success is defined as cleansing graded either "excellent" or "good."

†CI for the common risk difference.

‡*P* value based on a Cochran-Mantel-Haenszel test accounting for the effect of the investigator site.

§*P* value from the noninferiority test comparing the common risk difference of the proportions for the two treatment groups, using a margin of 10%.

FPSS indicates flavored polyethylene glycol and sulfate solution; OSS, oral sulfate solution.

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TABLE 5. Segmental Cleansing Assessment*

Segment grade	FPSS (n = 226)	OSS (n = 224)	P†
Proximal colon success (n %)	206 (91.2)	203 (90.6)	0.731
Excellent	92 (40.7)	135 (60.3)	
Good	114 (50.4)	68 (30.4)	
Fair	16 (7.1)	14 (6.3)	
Poor	2 (0.9)	5 (2.2)	
Missing	2 (0.9)	2 (0.9)	
Mid colon success (n %)	211 (93.4)	211 (94.2)	0.893
Excellent	122 (54.0)	148 (66.1)	
Good	89 (39.4)	63 (28.1)	
Fair	11 (4.9)	8 (3.6)	
Poor	2 (0.9)	3 (1.3)	
Missing	2 (0.9)	2 (0.9)	
Distal colon success (n %)	210 (92.9)	214 (95.5)	0.340
Excellent	122 (54.0)	144 (64.3)	
Good	88 (38.9)	70 (31.3)	
Fair	12 (5.3)	5 (2.2)	
Poor	2 (0.9)	3 (1.3)	
Missing	2 (0.9)	2 (0.9)	

*Percents for each treatment group are based on the total number of responses. Missing values were not included.

†*P*-value based on a Cochran-Mantel-Haenszel test accounting for the effect of Investigator site.

FPSS indicates flavored polyethylene glycol and sulfate solution; OSS, oral sulfate solution.

Study Centers

Data were collected at 32 US study sites using the same investigational protocol. Enrollment was competitive and subjects were recruited primarily from gastroenterology practices.

Administration of Study Preparations

Subjects assigned to the FPSS preparation were permitted a low-residue breakfast on the day before the colonoscopy, followed by clear liquids until 2 hours before the colonoscopy examination. FPSS was administered a "split dose" with 1 L of the formulation to be consumed on the night before the colonoscopy and 1 L again in the morning, 5 to 8 hours before their examination. Additional hydration consisted of 16 ounces of water required with each dose.

Subjects assigned to OSS were instructed to take the preparation according to the manufacturer's labeling for split-dose administration. This included a light breakfast the day before the colonoscopy, then clear liquids only. Subjects were instructed to ingest only clear liquids while they took OSS, a minimum of about 2.8 L, 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.

TABLE 6. Additional Secondary Endpoints

Endpoint	FPSS; n (%)	OSS; n (%)	P*
Preparation adequacy	224 (99.1)	217 (96.9)	0.097
Cecal intubation rate	224 (99.1)	220 (98.2)	0.366
ADR	78 (34.7)	87 (39.2)	0.261
Procedure duration (min); mean (SD)	15.5 (7.0)	15.2 (6.9)	0.552
Intraprocedural water (mL); mean (SD)	121.7 (173.9)	122.8 (216.1)	0.771

**P* value based on a Cochran-Mantel-Haenszel test accounting for the effect of Investigator site for categorical variables and based on an Analysis of Variance model with fixed effects of treatment and site for continuous variables.

ADR indicates adenoma detection rate; FPSS, flavored polyethylene glycol and sulfate solution; OSS, oral sulfate solution.

Efficacy and Safety Variables

A "US FDA Bowel Preparation Scoring Scale" (Table 1) for the quality of bowel cleansing was utilized, which also accounted for the work of endoscopist cleansing during the examination.[13] 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, additional bowel preparation required). Each colon segment (proximal, mid, and distal) was graded for cleansing efficacy during the 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 4-point scale was determined after the 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 success, adequacy of cleansing and need for re-preparation, 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 recorded using GI Hawkeye software and all videos underwent independent blinded central reading by GI reviewers, limited liability corporation. Central readers underwent a calibration session to review the scoring system and then graded each colon segment using the same 4-point scale first on insertion and then on withdrawal of the endoscope. At visit 2, subjects were queried for the occurrence of AEs and changes in concomitant medications. Blood samples were collected at each study visit for analysis at a central laboratory.

Subject Acceptance

To evaluate the subjects' perception of their 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 compare with your prior experiences ("worse" to "better")?; Would you ask your doctor for this preparation again if you need another colonoscopy in the future?; Would you refuse the same preparation again if it were to be prescribed to you

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TABLE 7. Number (%) of Subjects With Unsolicited Treatment-emergent AEs ≥1% by SOC and Preferred Term

SOC/preferred term*	FPSS (n = 227); n (%)	OSS (n = 226); n (%)	95% CI	P†
No. subjects with any event	61 (26.9)	55 (24.3)	−5.5,10.6	0.591
Total no. events	100	86	—	—
Gastrointestinal disorders	31 (13.7)	31 (13.7)	(−6.4, 6.3)	1.000
Abdominal distension	3 (1.3)	3 (1.3)	(−2.1, 2.1)	1.000
Abdominal pain	3 (1.3)	1 (0.4)	(−0.8, 2.6)	0.623
Nausea	15 (6.6)	14 (6.2)	(−4.1, 4.9)	1.000
Retching	3 (1.3)	1 (0.4)	(−0.8, 2.6)	0.623
Vomiting	8 (3.5)	16 (7.1)	(−7.7, 0.6)	0.098
Infections and infestations	7 (3.1)	8 (3.5)	(−3.8, 2.8)	0.800
COVID-19	3 (1.3)	3 (1.3)	(−2.1, 2.1)	1.000
Urinary tract infection	1 (0.4)	3 (1.3)	(−2.6, 0.8)	0.372
Investigations	20 (8.8)	16 (7.1)	(−3.2, 6.7)	0.603
Blood pressure decreased	4 (1.8)	3 (1.3)	(−1.8, 2.7)	1.000
Blood pressure increased	7 (3.1)	2 (0.9)	(−0.4, 4.8)	0.175
Blood pressure systolic increased	5 (2.2)	4 (1.8)	(−2.1, 3.0)	1.000
Nervous system disorders	5 (2.2)	4 (1.8)	(−2.1, 3.0)	1.000
Headache	4 (1.8)	4 (1.8)	(−2.4, 2.4)	1.000

*Subjects were counted once within each SOC and preferred term.

†Difference between treatment groups was tested using Fisher exact test together with a 95% CI for the difference in proportion of the treatment effect estimate.

AE indicates adverse event; COVID-19, coronavirus disease 2019; FPSS, flavored polyethylene glycol and sulfate solution; OSS, oral sulfate solution; SOC, system organ class.

in the future?; Please rate your feelings about the after-taste of the preparation ("very pleasant" to "very unpleasant"); To what degree do you believe the product tastes similar to a sports drink ("agree extremely" to "disagree extremely").

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" (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 due to the investigator's determination of insufficient fecal output, unclear fecal discharge, preparation-related AEs preventing preparation, as well as any subject, for whom cleaning was not adequate for evaluation by colonoscopy. The cleansing success rate was analyzed using the common risk difference of the proportions for the two treatment groups using a margin of 10%. This noninferiority margin has been utilized in recent studies supporting FDA approval of bowel preparations.[5,6,13]

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

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

The safety population included all subjects that took any portion of the 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 (eg, insurance coverage issue and lack of transportation to the clinic).

The protocol planned study size was ~520 subjects. Based on prior studies using a similar grading system, the success rate for OSS was expected to be >94%.[5] Assuming a similar success rate for FPSS, a 2-sided asymptotic 95% CI for the difference in success rates between groups (FPSS and OSS) will result in a lower CI bound > −10%, with a probability of 80%. This result would establish the noninferiority of FPSS to OSS for a noninferiority margin of 10%.

RESULTS

Demographics

Thirty-two sites in the United States contributed 517 subjects, and 500 were randomized and dispensed study preparation, 450 subjects took their preparation and were included in the analysis (226 received FPSS and 224 received OSS). The disposition of all study subjects is shown in Table 2 along with the reasons for discontinuation. The proportion of subjects discontinued was similar between the two preparation groups. Figure 1 presents the CONSORT diagram.

Demographic characteristics, such as age, weight, and racial distribution of the two treatment groups, were similar with no statistically significant differences detected. The average age of the study population was 56.2 years and included 120 elderly subjects. Slightly more females (58.8%) than males (41.2%) were enrolled. Of the subjects, 84% identified as white, 11% identified as African American, and 21% identified as being of Hispanic or Latino ethnicity.

Compliance with assigned bowel preparation was based on the review of used drug materials and completed subject questionnaires. Preparation compliance was excellent across groups, with 97% of subjects in the study completing at least 75% of preparation solution (FPSS = 96.5%, OSS = 97.8%).

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Efficacy

Global cleansing scores for the two preparations as rated by the local endoscopists are shown in Table 3. High rates of cleansing success (defined as scores of "excellent" and "good") were seen with both preparations (94% for FPSS and 94% for OSS), comparable to other FDA-approved split-dose preparations. OSS tended to have more "excellent" preparations (62% vs 47%, respectively). Analysis of noninferiority (using the standard 10% margin) confirmed that FPSS was noninferior to OSS (<0.001). No differences between the preparations in overall cleansing success were identified with respect to subject age, gender, or race.

Sensitivity analyses provide further evidence of FPSS noninferiority to OSS. Independent central readers reviewed all colonoscopy videos and provided a global cleansing grade, as well as segmental grades, on insertion and withdrawal using the same 4-point scale as shown in Table 4. The global cleansing success of FPSS based on central reader ratings was superior to OSS (97.7% vs 94.2%, respectively, $P = 0.034$). In the segmental analyses, each segment was required to be rated as "good" or "excellent" for the preparation to be considered a success. Insertional success ratings by central reading demonstrated FPSS to be noninferior to OSS (81.1% vs 83.5%, respectively, $P = 0.01$). Segmental cleansing on withdrawal using the same definition similarly demonstrated a

TABLE 8. Mean (SD) Chemistry Values by Visit

Analytic normal range	Visit	FPSS (n = 227); n (%)	OSS (n = 226); n (%)	P*
ALT/SGPT; 5-30 (U/L)	1	22.4 (17.8)	21.9 (11.2)	0.134
	2	24.9 (18.8)	23.6 (13.2)	—
Anion gap; 8-16 (mEq/L)	1	7.7 (2.2)	7.7 (2.1)	0.175
	2	8.9 (2.2)	9.3 (2.6)	—
AST/SGOT; 9-34 (U/L)	1	19.4 (10.2)	19.6 (7.2)	0.200
	2	22.0 (10.6)	21.6 (8.5)	—
Bicarbonate; 21-33 (mEq/L)	1	27.2 (2.5)	27.6 (2.8)	0.016
	2	26.3 (2.7)	26.9 (2.9)	—
Bilirubin; 0.1-1.1 (mg/dL)	1	0.560 (0.22)	0.578 (0.24)	0.791
	2	0.795 (0.32)	0.809 (0.33)	—
BUN; 5-22 (mg/dL)	1	15.2 (4.4)	15.6 (4.7)	0.481
	2	12.9 (3.9)	12.6 (3.6)	—
Calcium; 8.5-10.5 (mg/dL)	1	9.33 (0.40)	9.36 (0.43)	0.169
	2	9.41 (0.45)	9.38 (0.46)	—
Chloride; 95-110 (mEq/L)	1	103.7 (2.5)	103.8 (2.6)	0.042
	2	103.4 (2.6)	102.9 (3.0)	—
Creatine phosphokinase; 25-210 (U/L)	1	172.1 (583)	145.7 (259)	0.887
	2	127.9 (107)	121.2 (94)	—
Creatinine (mg/dL)				0.679
F; 0.49-1.12	1	0.806 (0.18)	0.816 (0.23)	—
M; 0.62-1.44	2	0.837 (0.19)	0.829 (0.20)	—
GFR (mL/min/1.73 m^2)				0.537
18-49 y; >60	1	92.0 (16)	92.0 (16)	—
≥50 y; ≥49	2	89.9 (17)	89.9 (16)	—
GGT (U/L)				0.437
F; 7-38	1	28.3 (27.8)	30.9 (33.3)	—
M; 11-52	2	29.5 (28.9)	32.4 (36.3)	—
Glucose (mg/dL); 60-155 mg/dL	1	102.9 (23.7)	103.9 (26.2)	0.257
	2	98.6 (17.5)	101.4 (23.4)	—
Magnesium; 1.8-2.4 (mEq/Lmg/dL)	1	2.19 (0.18)	2.18 (0.16)	0.616
	2	2.24 (0.20)	2.24 (0.19)	—
Osmolality; 276-295 (mOsm/kg)	1	295.5 (6)	296.5 (6)	0.786
	2	295.1 (7)	295.1 (5)	—
Phosphorus; 2.5-4.8 (mg/dL)	1	3.53 (0.53)	3.58 (0.55)	0.100
	2	3.46 (0.52)	3.42 (0.64)	—
Potassium; 3.5-5.1 (mEq/L)	1	4.27 (0,33)	4.23 (0.31)	0.935
	2	4.25 (0.35)	4.22 (0.35)	—
Protein; 6-8(g/dL)	1	7.08 (0.42)	7.05 (0.45)	0.498
	2	7.27 (0.46)	7.24 (0.50)	—
Sodium; 134-144 (mEq/L)	1	138.7 (2.2)	139.0 (2.2)	0.022
	2	138.5 (2.4)	139.2 (2.2)	—
Uric acid (mg/dL)				
F; 3.0-7.0	1	5.32 (1.44)	5.26 (1.34)	0.305
M; 4.0-8.5	2	5.70 (1.43)	5.64 (1.25)	—

*Treatment group differences for the change from baseline were tested using an Analysis of Covariance model with a fixed effect of the treatment group and the baseline value of the corresponding laboratory parameter as a covariate.

FPSS indicates flavored polyethylene glycol and sulfate solution; OSS, oral sulfate solution.

TABLE 9. Preference Questionnaire*

	FPSS (n = 227)	OSS (n = 226)	P†
Experience consuming prep	(n %)	(n %)	**0.017**
Very easy	41 (18.1)	31 (13.7)	
Easy	53 (23.3)	36 (15.9)	
Tolerable	103 (45.4)	101 (44.7)	
Difficult	23 (10.1)	40 (17.7)	
Very difficult	6 (2.6)	14 (6.2)	
Very easy + easy + tolerable	197 (86.8)	168 (74.3)	**0.009**
Overall experience			**0.016**
Excellent	48 (21.1)	41 (18.1)	
Good	120 (52.9)	91 (40.3)	
Fair	44 (19.4)	70 (31.0)	
Poor	9 (4.0)	9 (4.0)	
Bad	5 (2.2)	11 (4.9)	
Excellent + good	168 (74.0)	132 (58.4)	**<0.001**
Comparison to prior prep			**0.228**
Better	82 (57.3)	68 (46.6)	
Same	39 (27.3)	55 (37.7)	
Worse	22 (15.4)	23 (15.8)	
Not applicable	83	76	
Would you request again?			**0.015**
Yes	182 (80.2)	158 (69.9)	
No	43 (18.9)	64 (28.3)	
Would you refuse?			**0.042**
Yes	25 (11.0)	40 (17.7)	
No	200 (88.1)	182 (80.5)	
After-taste of preparation			**<0.001**
Very pleasant	24 (10.6)	12 (5.3)	
Quite pleasant	49 (21.6)	37 (16.4)	
Neither pleasant nor unpleasant	106 (46.7)	70 (31.0)	
Quite unpleasant	40 (17.6)	63 (27.9)	
Very unpleasant	7 (3.1)	40 (17.7)	
Pleasant after-taste of preparation			**<0.001**
Very or Quite Unpleasant	47 (20.7)	103 (45.6)	
Tastes like a sports-drink‡			**< 0.001**
Agree	130 (57.3)	80 (35.4)	
Neither agree nor disagree	24 (10.6)	20 (8.8)	
Disagree	72 (31.7)	121 (53.5)	

*Safety Population.

†*P*-value for difference between treatments is from a Cochran-Mantel-Haenszel Chi-Square, controlling for site.

‡Agree/Disagree categories include responses for slightly, moderately, very much and extremely.

FPSS indicates flavored polyethylene glycol and sulfate solution; OSS, oral sulfate solution.

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high rate of success and non-inferiority (95% success for both preparations).

The results of the segmental cleansing ratings were similar to the overall assessment discussed and are shown in Table 5. Similar to OSS, FPSS resulted in >90% successful preparation in each colon segment, including the right colon. As with the global evaluation, OSS tended to achieve more "excellent" preparations in each colon segment.

Analysis of secondary intraprocedural efficacy endpoints revealed no statistically significant differences between the two preparations. Cecal intubation rates were >98% for each preparation group, in compliance with the recommended target of 90% to 95%.[14] The proportion of preparations that were considered clinically adequate by the investigators in both groups was ~97%. Secondary indicators of endoscopist effort were similar between groups and are shown in Table 6. These include the volume of irrigation water needed during the procedure (about 122 mL) and the average procedure duration (~15 minutes). ADRs were also similar between the two preparations (FPSS, 35%; OSS, 39%).

Safety and Tolerance

Both preparations were safe and well-tolerated in the overall study population, including the elderly. No difference between the treatment groups was detected for treatment-emergent AEs, shown in Table 7. There were no serious AEs reported in the FPSS group and 3 in the OSS group, which were considered unrelated to preparation (concussion, rectal bleeding, and coronavirus disease 2019). The most common AEs for each treatment group were gastrointestinal. As shown in Table 7, subjects in the FPSS group reported about 50% less vomiting compared with subjects in the OSS group.

Laboratory results are shown below in Table 8 for the study population for visit 1 (baseline) and visit 2 (day of colonoscopy). While some statistically significant differences between the treatment groups were detected for some analytes, changes from baseline tended to be small and none were deemed clinically important.

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

Subject Satisfaction

Subjects completed a preference questionnaire at visit 2 to capture the subject's perceptions of the preparation experience. As shown below in Table 9, the FPSS preparation was rated more favorably than OSS for numerous measures. Of the subjects, 87% in the FPSS group found the preparation "tolerable" to "very easy" to consume, compared with 74% for OSS. Ratings of overall preparation experience also favored FPSS, with 74% of subjects rating the preparation "good" or "excellent" compared with 58% for OSS ($P < 0.001$). Of FPSS subjects, 80% indicated that they would request their current preparation again if they were to need a colonoscopy in the future, compared with 70% for OSS ($P = 0.015$), and fewer subjects would refuse it compared with OSS (11% vs 18%, $P = 0.042$). With respect to taste, fewer FPSS subjects found the preparation taste unpleasant compared with OSS (21% vs 46%, respectively, $P < 0.001$), with the majority of FPSS subjects agreeing that the preparation tastes like a sports drink.

DISCUSSION

A new bowel cleansing formulation (FPSS) designed to imitate the popular but unapproved PEG and sports drink preparation [8,9] has been shown in a prospective, randomized, single-blind, multicenter, noninferiority study to provide equivalent colon cleansing to a well-established, FDA-approved sulfate preparation (OSS). Both preparations were given according to a split dose regimen. Scored on withdrawal, the rates of successful preparation for FPSS were similar to other FDA-approved bowel cleansing agents. On average, segmental cleansing scores were equivalent, although OSS tended to produce more "excellent" cleansing scores. Similar results were obtained for successful cleansing scores based on scope insertion, although the overall scores tended to be 10% less for both FPSS and OSS. This difference from withdrawal scoring is believed to be attributable to the investigator's cleansing effort. ADRs for the two preparations were also comparable.

Spontaneous reports of treatment-emergent AE rates were similar between groups, and comparable to other FDA-approved preparations. A somewhat higher rate of vomiting was associated with OSS relative to FPSS, although few of these symptoms were considered to be severe. This difference is thought to be due to taste fatigue associated with the OSS preparation. The FPSS preparation was rated more favorably by subjects for many subjective experience measures, such as ease of completion, overall experience, comparison to prior preparation, and willingness to take it again. This is likely due to the pleasant sports drink-like flavor of the formulation.

The study does have limitations, which include the lack of generalizability of the ADR data since the study enrolled patients undergoing screening, surveillance, and diagnostic colonoscopies. In addition, although the grading scale used is appropriate to evaluate the cleansing efficacy of FPSS and OSS in a clinical trial setting, it does not allow for comparisons to published studies in real-world settings, which used other scales (eg, boston bowel preperation scale, Aronchick). Future studies should include a comparison of the unapproved PEG and sports drink preparation.[8,9] This study indicates that FPSS is a safe and effective preparation option that may be well-received by patients undergoing colonoscopy.

ACKNOWLEDGMENTS

The authors thank the following investigators for their involvement in conducting the study: Fadi Deeb, MD, Tucson, AZ; Paul Hellstern, MD, Inverness, FL; Bezawit Tekola, MD, Fairfax, VA; Charles Berkelhammer, MD, Oak Lawn, IL; Daniel Pambianco, MD, Charlottesville, VA; Robert Wohlman, MD, Bellevue, WA; William Harlan, MD, Asheville, NC; Gregory Wiener, MD, Chula Vista, CA; John Baber, MD, Little Rock, AR; Robert Murphy, MD, North Little Rock, AR; David Carney, MD, Wilmington, NC; Nydia Sanchez, MD, Jacksonville, FL; Chintamaneni Choudari, MD, Hagerstown, MD; Michael Herman, DO, Fleming Island, FL; Michael Kreines, MD, Cincinnati, OH; Joseph Pouzar Jr, MD, Houston, TX; Salam Zakko, MD, Bristol, CT; Robert Souder, MD, Jackson, TN; Thomas Jarrett, MD, High Point, NC; Lemuel Jenkins, MD, Covington, LA; Nikhil Inamdar, MD, Webster, TX; Javier Sobrado, MD, Miami, FL; Orestes Pablos, MD, Miami, FL; Ariel Malamud, MD, Los Angeles, CA; Junaid Siddiqui, MD, Cedar Park, TX, Dallas Shone, MD, Kingsport, TN; Jonathon Chapman, MD, Baton Rouge, LA; Charles Owen Jr, MD, Southlake, TX; Raj

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REFERENCES

1. 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. *Gastroenterology*. 2017;153:307–323.
2. Davis GR, Santa Ana CA, Morawski SG, et al. Development of a lavage solution associated with minimal water and electrolyte absorption or secretion. *Gastroenterology*. 1980;78(5 pt 1):991–995.
3. Fordtran JS, Santa Ana CA, Cleveland MVB. A sulfate-free gastrointestinal lavage. *Gastroenterology*. 1990;98:11–16.
4. Patel V, Nicar M, Emmett M, et al. Intestinal and renal effects of low-volume phosphate and sulfate cathartic solutions designed for cleansing the colon: pathophysiological studies in five normal subjects. *Am J Gastroenterol*. 2009;104:953–965.
5. Di Palma JA, Rodriguez R, McGowan J, et al. A randomized clinical study evaluating the safety and efficacy of a new, reduced-volume, oral sulfate colon-cleansing preparation for colonoscopy. *Am J Gastroenterol*. 2009;104:2275–2284.
6. DeMicco MP, Clayton LB, Pilot J, et al. NOCT Study Group. Novel 1 L polyethylene glycol-based bowel preparation NER1006 for overall and right-sided colon cleansing: a randomized controlled phase 3 trial versus trisulfate. *Gastrointest Endosc*. 2018;87:677–687.
7. Matro R, Daskalakis C, Negoianu D, et al. Randomised clinical trial: polyethylene glycol 3350 with sports drink vs. polyethylene glycol with electrolyte solution as purgatives for colonoscopy—the incidence of hyponatraemia. *Aliment Pharmacol Ther*. 2014;40:610–619.
8. Gu P, Lew D, Oh SJ, et al. Comparing the real-world effectiveness of competing colonoscopy preparations: results of a prospective trial. *Am J Gastroenterol*. 2019;114:305–314.
9. Schoenfeld P. Safety of MiraLAX/Gatorade bowel preparation has not been established in appropriately-designed studies. *Clin Gastroenterol Hepatol*. 2013;11:582.
10. Lewis J, Schoenfeld P. Severe hyponatremia and Miralax-Gatorade bowel preparation. *Am J Gastro*. 2011;106:5582–5583.
11. Walker ML, Cleveland MV, Hague KM, et al. A formulation development study of BLI4900, a novel flavor enhanced bowel preparation for colonoscopy. *Gastrointest Endosc*. 2022;95:AB67.
12. Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. *Biometrics*. 1975;31:103–115.
13. Di Palma JA, Bhandari R, Cleveland MV, et al. A safety and efficacy comparison of a new sulfate-based tablet bowel preparation versus a PEG and ascorbate comparator in adult subjects undergoing colonoscopy. *Am J Gastroenterol*. 2021;116:319–328.
14. Rex DK, Schoenfeld PS, Cohen J, et al. Quality indicators for colonoscopy. *Gastrointest Endosc*. 2015;81:31–53.

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