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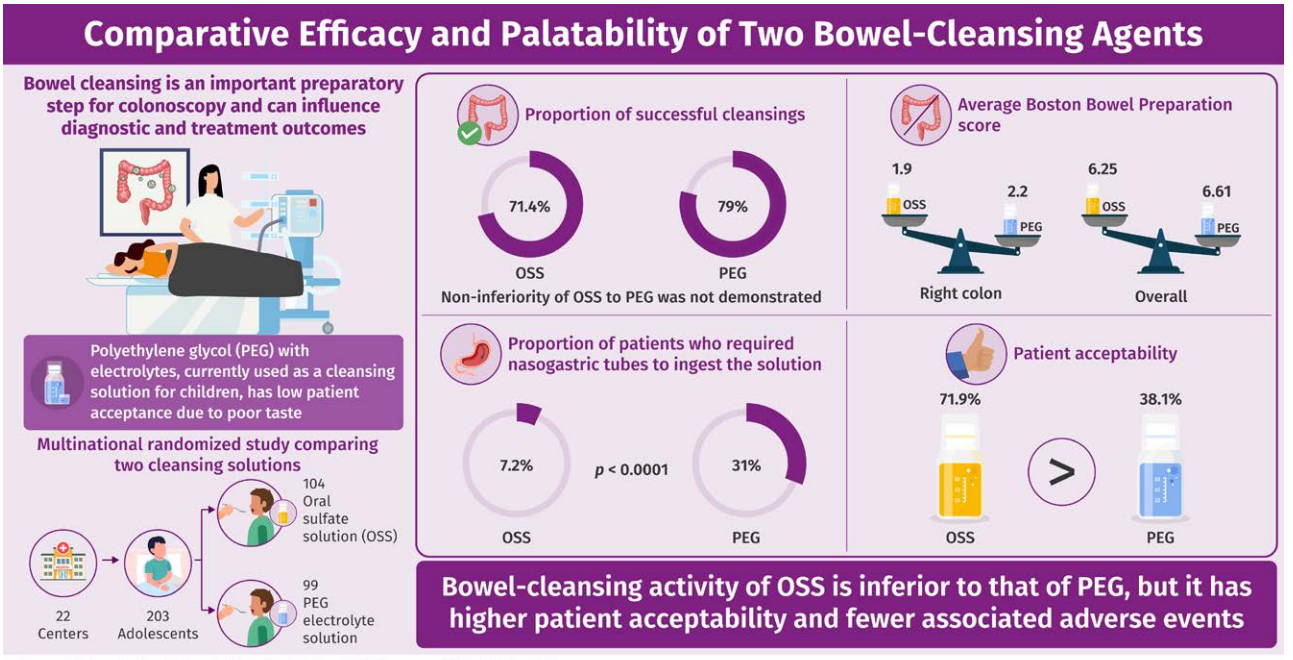
*Piotr Socha, MD, PhD, †‡Carsten Posovszky, MD, *Monika Szychta, MD, PhD, §Federica Viscogliosi, MD, §Luigi Martemucci, MD, ‖¶Urszula Grzybowska-Chlebowczyk, MD, #Valerie Perrot, MD, **Anne Kornowski, MD, and ††Marc A. Benninga, MD, PhD on behalf of the EASYKID Study Group



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From *Children's Memorial Health Institute, Warsaw, Poland, †University-Children's Hospital, Zurich, Switzerland, the ‡Department for Pediatrics and Adolescent Medicine, University Medical Center Ulm, Ulm, Germany, §AORN Santobono Pausilibon, Naples, Italy, ‖John Paul II Upper Silesian Child Health Centre, Katowice, Poland, the ¶Department of Paediatrics I, Faculty of Medical Science, Medical University of Silesia, Katowice, Poland, #Ipsen Pharma, Boulogne-Billancourt, France, **Ipsen Consumer HealthCare, Boulogne-Billancourt, France, and ††Emma Children's Hospital, Amsterdam University Medical Centre, Amsterdam, The Netherlands.

Address correspondence and reprint requests to Piotr Socha, Department of Gastroenterology, Hepatology, Nutritional Disorders and Pediatrics, Children's Memorial Health Institute, ul. Aleja Dzieci Polskich 20, 04-730 Warsaw, Poland (e-mail: P.Socha@IPCZD.PL).

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ABSTRACT

Objectives: Many protocols and preparations are used for bowel cleansing before pediatric colonoscopy but few are based on scientific evidence. We evaluated efficacy, safety, tolerability, and patient preference of oral sulfate solution (OSS) at 75% of the adult dose versus polyethylene glycol (PEG)-electrolyte solution in adolescents presenting for diagnostic colonoscopy.

Methods: Phase III, randomized, evaluator-blinded, non-inferiority study of OSS and PEG in adolescents aged 12–17 years. OSS and PEG were administered in 2 doses on the day before colonoscopy. Primary endpoint included proportion of patients with successful overall preparation (4-point scale). Secondary endpoints included overall and segmental bowel cleansing (Boston Bowel Preparation Scale; BBPS), completed colonoscopies, duration of examination, time to cecal intubation, proportion of nasogastric tubes (NGTs), adverse events (AEs) and acceptability.

Results: Successful cleansing was achieved in 71.4% and 79.0% of patients receiving OSS and PEG, respectively [adjusted difference −7.61 (95% confidence interval, CI, −18.45 to 3.24); $P = 0.0907$]. Segmental BBPS score for the left and transverse colon were similar between treatment groups, but better for the right colon with PEG than OSS [2.2 (95% CI, 2.0–2.4) and 1.9 (95% CI, 1.7–2.1), respectively; $P = 0.0015$]. Significantly fewer OSS patients needed NGT placement to ingest the whole solution [9/125 (7.2%)] than PEG patients [36/116 (31.0%); $P < 0.0001$]. Treatment acceptability was significantly higher with OSS than PEG ($P < 0.0001$). Duration of examination, completed colonoscopies, and time to cecal intubation were similar between preparations. Gastrointestinal AEs including nausea, vomiting, abdominal pain, and distension were similar in both groups but more patients receiving PEG had AEs assessed as incapacitating.

Conclusions: Non-inferiority of OSS to PEG was not demonstrated, but OSS was associated with a lower requirement for NGT, better acceptability, and less frequent severe AEs than with PEG.

Key Words: bowel cleansing, OSS, pediatrics, PEG

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Effective bowel cleansing before colonoscopy is crucial to allow complete visualization of the colonic mucosa (1). Several protocols and cleansing preparations are used as there are few randomized trials to guide recommendations in children (2–7). In addition, bowel cleansing solutions in children are limited by acceptance and safety issues. With the available solutions, compliance is poor due to bad taste, which leads to insufficient bowel cleansing. Indeed, inadequate preparation is reported in up to one-third of adolescent patients, leading to extended procedure time, incomplete examination, and in some cases, a need to repeat the procedure (2,3,8,9).

Dosing the day before colonoscopy (4,5) is used more often than split dosing in children because of fasting before anesthesia, even though this is generally less effective (10,11). Oral sulfate solution (OSS; Eziclen/Izinova, Ipsen Consumer Healthcare, France), a low-volume, osmotic bowel preparation composed of sodium sulfate anhydrous, potassium sulfate, and magnesium sulfate heptahydrate, is approved as a bowel cleansing preparation in adults undergoing colonoscopy (12). In adults, OSS has demonstrated non-inferiority to macrogol 3350 (Moviprep, Norgine, UK) in split-dose or day-before dosing regimens (13–16), non-inferiority to 4 L polyethylene glycol (PEG) in split-dose (14), and superiority to sodium picosulfate plus magnesium citrate (Prepopik, Ferring Pharmaceuticals, Parsippany, NJ) in split-dose (17).

What Is Known

- Suboptimal bowel cleansing is frequent in children and can affect diagnostic and therapeutic outcomes.
- Polyethylene glycol (PEG)-electrolyte solution for bowel cleansing is not well tolerated by many children.

What Is New

- In adolescents, we failed to show that oral sulfate solution (OSS) was non-inferior to PEG-electrolyte solution in terms of successful colonoscopy preparation, but OSS was superior to PEG-electrolyte solution in terms of tolerability and preference.

In an unpublished US phase III study (NCT02819323) administration of OSS at 75% of the adult dose as a split-dose resulted in excellent or good cleansing of the proximal colon in 89.3% of adolescent patients. Gastrointestinal (GI) adverse events (AEs) including abdominal distension, abdominal pain, nausea, and vomiting occurred in approximately 90% of patients, and were mostly mild to moderate in intensity. Following these studies, OSS was approved for use in adolescents at 75% of the adult dose in the United States (18).

The aim of this phase III randomized trial was to evaluate the efficacy, safety, tolerability, and patient preference of OSS administered at 75% of the adult dose versus PEG-electrolyte solution (70 mL/kg; Klean-Prep, Norgine, UK) (19) in adolescents presenting for diagnostic colonoscopy.

METHODS

Study Design

This was a European, multicenter (22 centers in the Czech Republic, France, Germany, Italy, the Netherlands, and Poland), phase III randomized, investigator-blinded, non-inferiority study conducted in adolescents aged 12–17 years, weighing >40 kg and scheduled to undergo diagnostic colonoscopy (NCT03008460 first posted on ClinicalTrials.gov on January 2, 2017, first patient enrolled October 15, 2017, and study completed June 29, 2020). The study consisted of a 1-day enrolment and investigator-blind label dosing period (baseline/Visit 1/Day 1), a colonoscopy (Visit 2/Day 2), a phone contact (Visit 3/Day 3), and a final visit approximately 30 days after colonoscopy (Visit 4/Day 32). During the baseline visit, participants were hospitalized and randomized (1:1 ratio) using an Electronic Case Report Form to receive OSS at 75% of the adult dose (ie, 750 mL of OSS + 1500 mL of water) or PEG-electrolyte solution 70 mL/kg. For randomization, 2 lists were generated by an independent statistician: (1) a list of randomization numbers produced in blocks on a balanced ratio of the 2 treatments stratified by country; and (2) a list of treatment numbers produced in blocks on a balanced ratio. After eligibility was confirmed, patients were assigned to a randomization number and to the associated treatment arm in sequential order within each center. To maintain investigator blinding, randomization and dispensation of assigned treatment was done by unblinded pharmacists or nurses, and questionnaires were dispensed and collected by the study nurse. Unblinding of the pharmacists and nurses also allowed optimal and tailored guidance for patients. Compliance was ensured by administration of treatment in the hospital setting.

Both solutions (vanilla flavored; no additives to improve taste were allowed) were administered as a 1-day regimen on the day before colonoscopy. For OSS, 2 bottles (2 × 180 mL concentrate sulfate salt solution) were diluted up to 1000 mL with water; 375 mL of the preparation were drunk slowly over 30–60 minutes followed by 750 mL of water over the next hour. Approximately 2 hours after starting the first half of the preparation, the second dose of 375 mL was drunk slowly over 30–60 minutes followed by 750 mL of water over the next hour. The total volume of preparation consumed was 750 mL, with an additional 1500 mL of water, for a total of 2250 mL.

PEG is a powder for oral solution packaged in 4 sachets. PEG was to be given orally on the evening of the day before colonoscopy. The dosage was 70 mL/kg (19). The volume to be taken was calculated based on the patient's weight. The maximum volume administered was 4000 mL. The whole solution was administered in 2 half doses (1000 mL per hour), with a 1-hour pause between the 2 half doses.

For both treatments, a nasogastric tube (NGT) was placed to administer the complete preparation if a patient experienced difficulty in drinking the bowel cleansing preparation. Patients, with the assistance of their nurse, reported the reason the preparation could not be completed in the questionnaire (inability to complete preparation due to taste, volume, or an AE). Rescue treatment (normal saline enema) could be administered if clear discharge was not obtained 1 hour before the colonoscopy. One blinded investigator (gastro-pediatrician) per center undertook the colonoscopy procedure, and they were selected based on their experience in colonoscopy in adolescents. Patients were questioned about AEs on the day of the colonoscopy, and if no AEs had occurred, they were discharged. Patients were contacted by phone, 1–2 days after the colonoscopy, for evaluation of potential AEs, and visited the hospital approximately 30 days after the colonoscopy for a physical examination (to evaluate vital signs), further evaluation of potential AEs, and laboratory tests. Serum and urine sulfate levels were measured at baseline before colonoscopy and study end.

Study Population

Patients were aged ≥12 to ≤17 years, >40 kg in weight, and scheduled to undergo colonoscopy for a routine indication. Detailed information regarding the study inclusion and exclusion criteria are summarized in Table 1 (Supplemental Digital Content, *http://links.lww.com/MPG/D85*).

Study Endpoints

The primary endpoint was the proportion of participants with excellent or good overall preparation assessed by a treatment-blinded endoscopist using a 4-point scale (Table 2; Supplemental Digital Content, *http://links.lww.com/MPG/D85*). The 4-point scale has been used in the OSS registration studies and the US adolescent study (13,17,20–22).

Secondary endpoints were: successful global colon cleansing defined as Boston Bowel Preparation Score (BBPS) ≥6; segmental bowel cleansing using the BBPS; proportion of complete colonoscopies; time to cecal intubation and to clear effluent; duration of examination; waking up during the night; time to first bowel movement; proportion of NGT needed in each group; time between last intake of fluids and start of the colonoscopy procedure; compliance; treatment acceptability using a questionnaire graded from 0 (very badly accepted/unacceptable) to 5 (very well accepted); treatment acceptability (assessed with the question: "If it was necessary, would you agree to undergo preparation with this product again?"); nature, frequency, and intensity of AEs (mild: symptoms did not alter the patient's normal functioning; moderate: symptoms produced some degree of impairment to function, but were not hazardous, uncomfortable, or embarrassing to patients; severe: symptoms definitely hazardous to well-being, significant impairment of function or incapacitation); and standard biochemistry, blood, and urine sulfates (assessed centrally).

AEs were monitored from informed consent signature and were elicited by spontaneous reports and by direct, non-leading questioning after both dose administrations. Thus, if an AE occurred after both doses of the product with recovery/resolution between doses, both instances were counted as separate AEs.

Ethics

The study was conducted under the provisions of the Declaration of Helsinki, in accordance with the International Council on Harmonization Consolidated Guideline on Good Clinical Practice, in compliance with Independent Ethics Committees and informed consent regulations and adhered to all local regulatory requirements. Written informed consent was obtained from the parents or legal representative and assent was obtained from the patient (where applicable) before the patient entered the study.

Statistics

A non-inferiority margin of 15% was selected for consistency with other OSS studies (13). Assuming a success rate of 85% in both groups, a 1-sided alpha of 0.025 and 90% power, 120 participants were required per treatment group. Assuming a drop-out/non-compliance to protocol of 4%, 125 participants was the target for randomization into each treatment group. The primary analysis was performed on the modified intent-to-treat (mITT) population which included all randomized patients who received ≥1 partial dose of study treatment and produced a primary efficacy assessment. The per-protocol (PP) population was defined as patients in the mITT who underwent colonoscopy and had no major protocol deviations. Non-inferiority based on the difference of proportion of patients with successful preparation was demonstrated if the lower limit of the 95% confidence interval (CI) of this difference was above −15%. Analyses of secondary endpoints were performed using the ITT population, which included all randomized patients who received ≥1 partial dose of study treatment. For qualitative parameters, adjusted treatment difference was estimated using Cochran-Mantel-Haenszel chi-square stratified by country. For quantitative parameters, the adjusted treatment difference was estimated using a 2-way analysis of variance with treatment and country as covariates, and median time to event was estimated using Kaplan-Meier product limit method. Patient baseline characteristics and incidence of AEs were compared using chi-square test or Fisher exact test for qualitative parameters and Student *t* test for quantitative parameters.

RESULTS

Patient Disposition and Baseline Characteristics

Of the 26 study centers initiated in 6 countries, 22 study centers were able to actively recruit patients. Countries that included the most patients were Poland (n = 139), the Netherlands (n = 40), and Germany (n = 26). The full study duration was 28 months. Of the 250 patients randomized, 125 of 126 randomized to OSS received OSS and 116 of 124 randomized to PEG received PEG, and underwent colonoscopy (mITT population; Fig. 1). The PP population consisted of 203 patients (104 OSS recipients and 99 PEG recipients).

Baseline characteristics were generally well-balanced (Table 1). Overall, the most frequently reported colonoscopy indications in the ITT population were abdominal pain (24.9%), surveillance of IBD (Crohn's disease/ulcerative colitis/other) (24.9%), and exploration of GI bleeding (12.4%; Table 1). Overall, IBD

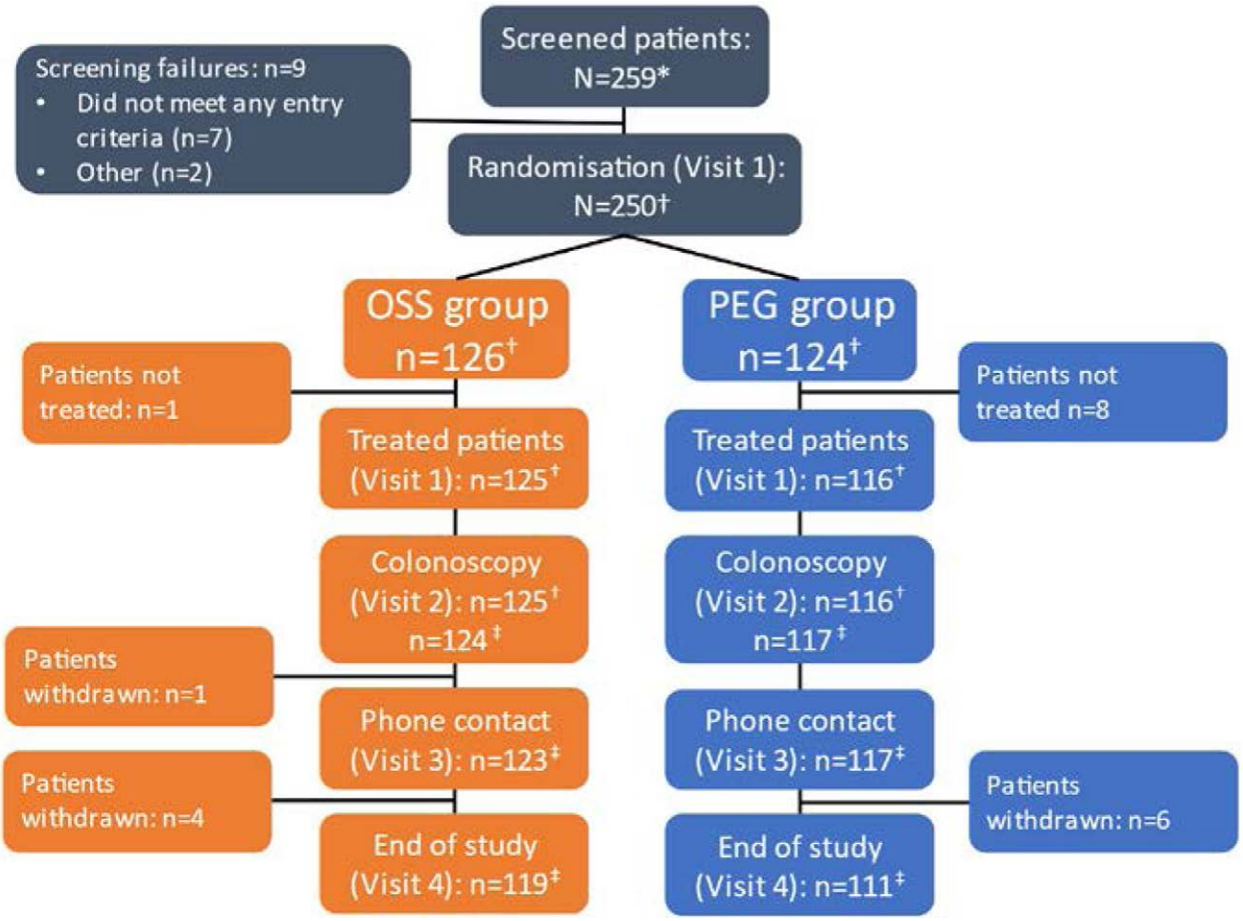

FIGURE 1. Patient disposition. *Number of patients in the screened population. †Number of patients in the randomized population. ‡Number of patients in the safety population: one patient randomized in the OSS group was mistakenly administered PEG and was therefore included in the PEG group in the safety population. OSS = oral sulfate solution; PEG = polyethylene glycol.

exploration (for either surveillance or confirmation of mucosal healing) was the most frequent indication (32.8%).

Efficacy

Successful cleansing evaluated on the 4-point scale (primary endpoint) was achieved in 71.4% (95% CI, 56.3–82.9) in the OSS group and 79.0% (95% CI, 65.3–88.3) in the PEG group, and the adjusted treatment difference was −7.6 (95% CI, −18.5 to 3.2; Fig. 2). The non-inferiority of OSS versus PEG was not demonstrated since the lower limit of the 95% CI of the difference was not higher than −15% (P = 0.0907). These results were confirmed in the PP population [adjusted treatment difference −9.8 (95% CI, −21.6 to 2.0); P= 0.1947].

Successful overall preparation evaluated by BBPS ≥6 was similar for OSS [71.5% (63.6–79.5)] and PEG [71.3% (63.0–79.6); adjusted treatment difference was 1.0 (95% CI, 0.9–1.2; P = 0.9450)]. Segmental scores (BBPS) for the left colon and the transverse colon were similar and were ≥2 for both treatment groups; the segmental score for the right colon was better in the PEG group compared to the OSS group [2.2 (2.0–2.4) vs 1.9 (1.7–2.1); P = 0.0015; Figure 1, Supplemental Digital Content, *http://links.lww.com/MPG/D85*].

Complete colonoscopy, assessed by cecal intubation was completed in a similar proportion of patients in the OSS and PEG groups [96.8% (93.7–99.9) and 96.6% (93.2–99.9), respectively]. Median (95% CI) time to cecal intubation was similar between groups; –13.0 (10.0–15.0) minutes in the OSS group and 15.0 (12.0–15.0) minutes in the PEG group (P = 0.6074). Similarly, adjusted mean (95% CI) duration of examination was similar in both groups: 14.8 (12.6–16.9) minutes in the OSS group and 15.7 (13.5–17.9) minutes in the PEG group (P = 0.4459).

A numerically but not significantly higher proportion of patients in the OSS group than the PEG group needed rescue treatment before colonoscopy: 20.2% (13.1–27.2) and 14.7% (8.2–21.1), respectively. Median (95% CI) time to first bowel movement was similar between treatment groups: 1.3 (1.2–1.5) hours in the OSS group and 1.5 (1.3–1.9) hours in PEG group. Likewise, median (95% CI) time to clear effluent was similar between treatment groups: 4.3 (3.5–5.3) hours in the OSS group and 4.8 (3.8–5.8) hours in the PEG group. A similar proportion of patients in the OSS and PEG groups woke up during the night to have a bowel movement (39.5% vs 39.1%; P = 0.9844).

Mean length of time between last administration of preparation and colonoscopy was >12 hours in both groups, but significantly longer in the OSS group (15.3 hours) than in the PEG group [14.2 hours; adjusted treatment difference: 1.1 hours (0.4–1.7 hours), P = 0.0015].

Compliance and Preference

Significantly more patients in the PEG group (36/116, 31.0%) needed NGT placement to achieve administration of the

TABLE 1. Patient baseline characteristics (ITT population)

	Treatment group			
	OSS	PEG	All	*P* value
Characteristic	n = 125	n = 116	N = 241	
Age, y				
Mean (SD)	15.1 (1.6)	15.3 (1.6)	15.2 (1.6)	0.3332*
Age class, n (%)				0.3021†
12–13 y	23 (18.4)	23 (19.8)	46 (19.1)	
14–15 y	46 (36.8)	32 (27.6)	78 (32.4)	
16–17 y	56 (44.8)	61 (52.6)	117 (48.5)	
Pubertal stage, n (%)				0.9415†
I–II	18 (14.4)	18 (15.5)	36 (14.9)	
IV	39 (31.2)	32 (27.6)	71 (29.5)	
V	52 (41.6)	50 (43.1)	102 (42.3)	
Missing	16 (12.8)	16 (13.8)	32 (13.3)	
Sex, male				
n (%)	65 (52.0)	69 (59.5)	134 (55.6)	0.2427†
Weight				
Mean (SD)	61.3 (14.3)	62.1 (11.2)	61.7 (12.9)	0.6285*
Weight class, n (%)				0.6171†
40–<50 kg	22 (17.6)	15 (12.9)	37 (15.4)	
≥50–60 kg	43 (34.4)	41 (35.3)	84 (34.9)	
>60 kg	60 (48.0)	59 (50.9)	119 (49.4)	
Missing	0	1 (0.9)	1 (0.4)	
BMI, kg/m^2				
Mean (SD)	21.4 (4.3)	21.6 (4.1)	21.5 (4.2)	0.7126*
Indication for colonoscopy, n (%)				0.0523†‡
Abdominal pain	36 (28.8)	24 (20.7)	60 (24.9)	
Surveillance of IBD (CD/UC/other)	33 (26.4)	27 (23.3)	60 (24.9)	
Unexplained diarrhea or constipation	13 (10.4)	8 (6.9)	21 (8.7)	
Confirmation of mucosal healing (CD/UC/other)§	8 (6.4)	11 (9.5)	19 (7.9)	
Exploration of GI bleeding	8 (6.4)	22 (19.0)	30 (12.4)	
Polyposis coli surveillance	7 (5.6)	10 (8.6)	17 (7.1)	
Weight loss	4 (3.2)	1 (0.9)	5 (2.1)	
Polyposis coli diagnosis	3 (2.4)	1 (0.9)	4 (1.7)	
Anemia of unknown etiology	2 (1.6)	1 (0.9)	3 (1.2)	
Other§	11 (8.8)	11 (9.5)	22 (9.1)	

BMI = body mass index; CD = Crohn's disease; GI = gastrointestinal; IBD = inflammatory bowel disease; ITT = intent-to-treat; OSS = oral sulfate solution; PEG = polyethylene glycol; SD = standard deviation; UC = ulcerative colitis. *Student *t* test. †Chi-square test. ‡Weight loss, polyposis coli diagnosis, and anemia of unknown etiology were analyzed with other. §Most frequent "other" indications were rectal blood loss (n = 8), suspected IBD (n = 8), and polyposis syndromes (n = 3).

complete preparation than in the OSS group (9/125, 7.2%; $P < 0.0001$). Failure to complete administration of the preparation was most frequently due to its taste, in 77.8% (7/9) of patients in the OSS group and 80.6% (29/36) of patients in the PEG group. Inability to drink the full volume [OSS: 0, PEG: 20/36 (55.6%)] and occurrence of an AE (mostly nausea; OSS: 2/9 (22.2%); PEG: 7/36 (19.4%)] were other reasons for NGT placement.

Despite the lower frequency of NGT placement, overall compliance was higher in the OSS group than the PEG group (96.8% and 89.3%, respectively; $P = 0.0036$). Treatment acceptability was significantly higher in the OSS group for both doses administered. A higher proportion of patients in the OSS group than the PEG group stated that they would take the preparation again (71.9% vs 38.1%; $P < 0.0001$).

Safety

Overall, 90.3% of patients in the OSS group and 93.2% of patients in the PEG group reported a treatment-emergent AE (TEAE; Table 2). Most of these (OSS: 86.3%; PEG: 89.7%) were considered related to treatment administration. In both treatment groups, the most frequently reported TEAEs were GI complaints

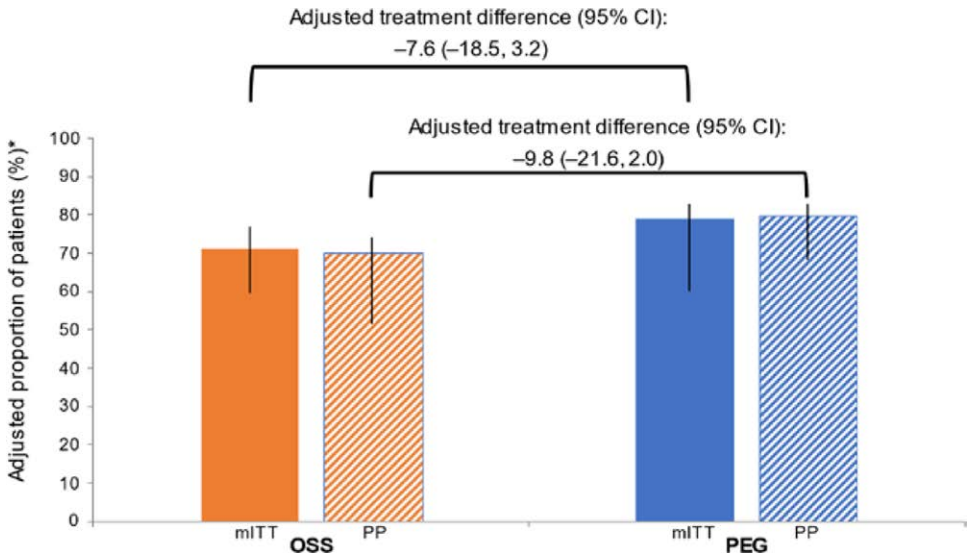

FIGURE 2. Primary endpoint: proportion of patients with successful overall preparation, mITT, and PP populations. The adjusted proportions are estimated using a logistic regression model including treatment and country as covariates. Error bars represent 95% confidence interval. mITT = modified intent-to-treat; PP = per-protocol.

(nausea, abdominal distension, epigastric pain, and vomiting; Table 2). There were more related TEAEs in females than males for both preparations [OSS group 91.7% (81.6–97.2) vs 81.3% (69.5–89.9), respectively; PEG group 95.7% (85.5–99.5) vs 85.7% (75.3–92.9), respectively].

Most treatment-related TEAEs were mild or moderate in intensity (Table 2). Fewer patients in the OSS group had treatment-related TEAEs of severe intensity (15.3%) than in the PEG group (25.6%). The most frequently reported TEAEs of severe intensity were nausea (OSS: 11.3%; PEG: 21.4%), abdominal distension (OSS: 4.0%; PEG: 7.7%), epigastric pain (OSS: 3.2%; PEG: 8.5%), and vomiting (OSS: 0%; PEG: 1.7%). No lesions with a suspected cause of colonic lavage were reported. A post-hoc analysis was conducted and showed a numerical trend to more severe TEAEs in the PEG group versus the OSS group [OR 0.52 (0.28–0.98), P= 0.0485], and severe related TEAEs [OR 0.49 (0.26–0.94), P = 0.0310].

A total of 4 (3.2%) patients in the OSS group (abdominal pain due to constipation, intestinal stenosis and Crohn's disease, intestinal polyposis, Crohn's disease) and 3 (2.6%) patients in the PEG group [Crohn's disease, drug hypersensitivity (to concomitant immunoglobulin infusion), increased blood creatinine phosphokinase] experienced at least 1 serious AE; none were considered to be related to treatment (Table 2). There were no deaths during the study.

DISCUSSION

In this European multicenter, investigator-blinded, randomized, phase III comparative study in adolescent patients, successful cleansing was achieved in 71% of patients who received OSS and 79% patients who received PEG. The primary endpoint of non-inferiority of OSS to PEG-electrolyte solution was not demonstrated. Secondary efficacy endpoints, including colon cleansing evaluated by BBPS, (OSS: 72% versus PEG: 71%), and complete colonoscopy as assessed by cecal intubation (97% of patients for both OSS and PEG), were similar with both preparations. Significantly more patients required NGT placement to complete administration with PEG (31.0%) than with OSS (7.2%). A significantly higher proportion of OSS than PEG patients stated that they would take the preparation again, and OSS had better treatment acceptability than PEG. The safety profiles showed similar overall frequencies of AEs, although more patients receiving PEG had AEs assessed as incapacitating or hazardous to well-being. While the primary endpoint failed to demonstrate non-inferiority of OSS for bowel cleansing in the adolescent population, results for secondary endpoints indicate that the benefits of both treatments overall may be similar.

Successful overall colonic bowel preparation, defined in this study as a BBPS ≥6, was below the 85% previously reported for adults administered evening before OSS and below that expected for high volume PEG plus electrolytes (13), but was at least as good as reported in many adolescent studies using evening before preparations (2,5,8,23).

Although the efficacy results obtained by the primary and secondary endpoints are not in agreement in this trial, they were assessed using different scoring systems: the primary endpoint was measured with the 4-point scale; while the secondary endpoint was assessed with the BBPS. Other studies have demonstrated that different cleansing scores can produce quite different results (2,24), so our findings are not unusual. It should also be stressed that while the 4-point scale used in this study was chosen for consistency with previous OSS studies, the BBPS is generally accepted as a validated, standardized tool.

In this study, the dosing regimen used was the administration of the bowel cleansing preparation the evening before colonoscopy. In practice, administration was done >12 hours before colonoscopy in both groups, leading to a long interval between the ingestion of the last dose of preparation and colonoscopy. It has been shown that each hour of waiting after preparation leads to an almost 10% decrease in the probability of having a good or excellent quality rating (25). The interval of >12 hours in the current study is longer than the upper limit of 5 hours recommended for optimal quality in adult endoscopy (11) and is likely the main reason for insufficient bowel cleansing observed in both arms. In many of the participating centers in this study, the timing of colonoscopies was largely determined by administrative needs rather than related to clinical indicators of preparation

TABLE 2. Summary of adverse events, safety population*

	OSS	PEG	*P* value
n (%)	n = 124	n = 117	
Any TEAE	112 (90.3)	109 (93.2)	0.4245‖
Treatment-related	107 (86.3)	105 (89.7)	0.4102‖
Intensity of treatment-related TEAE†,‡			
Severe	21 (16.9)	33 (28.2)	0.0360‖
Moderate	58 (46.8)	61 (52.1)	0.4053‖
Mild	87 (70.2)	75 (64.1)	0.3166‖
Most common (≥2% of patients)			
Nausea	90 (72.6)	84 (71.8)	0.8918‖
Abdominal distension	67 (54.0)	77 (65.8)	0.0624‖
Epigastric pain	64 (51.6)	64 (54.7)	0.6312‖
Vomiting	11 (8.9)	10 (8.5)	0.9291‖
Crohn's disease§	10 (8.1)	3 (2.6)	0.0589‖
Abdominal pain	6 (4.8)	3 (2.6)	0.5012¶
Ulcerative colitis§	1 (0.8)	6 (5.1)	0.0598¶
Gastritis§	4 (3.2)	3 (2.6)	1.0000‖
Headache	9 (7.3)	2 (1.7)	0.0532‖
Any SAE	4 (3.2)	3 (2.6)	1.0000¶
Treatment-related	0	0	

SAE = serious adverse event; OSS = oral sulfate solution; PEG = polyethylene glycol; TEAE = treatment-emergent adverse event. *All randomized patients who received ≥1 partial dose of study medication. †In the event of multiple AEs being reported by the same patient, all AEs were reported for that patient, meaning that the total number of AEs may be greater than 100% of patients. In the event of multiple occurrence of the same AE being reported by the same patient, the maximum intensity (severe > missing > moderate > mild) and the most serious causality (related > not related) for each patient was chosen. ‡One patient in the PEG group was missing an intensity rating. §Endoscopy diagnostic finding reported as AE. ‖Chi-square test. ¶Fisher exact test.

adequacy, which also means the difference between the 2 groups is difficult to explain. In our opinion, a split-dose regimen would help to solve this problem and improve tolerability. Two studies conducted in Asia have demonstrated that split-dose regimens (half the dose given the day before colonoscopy between 18:00 and 20:00, and half the dose given the day of colonoscopy between 06:00 and 08:00) for bowel cleansing are both effective and well tolerated (5,6); however, in most European centers, adherence to fasting times for deep sedation or general anesthesia in pediatrics does not allow colonoscopy on the same day as oral bowel cleansing.

Reasons for the apparent preference for OSS, as demonstrated by the higher number of patients reporting that they would use OSS again versus PEG, were not explored. However, the reasons for this could be the lower proportion of patients who required a NGT with OSS, which in turn was a consequence of the taste and quantity of the preparations. While the frequency of AEs occurring with both solutions was high, the higher frequency of AEs of severe intensity associated with PEG versus OSS (including nausea, abdominal distension, epigastric pain, and vomiting) may also have contributed to the overall reluctance to take the PEG preparation again if required. The frequency of epigastric pain is likely a consequence of the hypertonicity of the concentrated sulfate solution and the large volume of PEG solution.

Safety, acceptability, and tolerability are also important when considering bowel preparation in adolescents preparing for colonoscopy. No new safety findings were identified with OSS treatment in this study and the safety profile was similar to the overall safety profile of OSS previously demonstrated in adults (12). The observation that there were more related TEAEs in females than males has also been observed with adults receiving OSS (14,15).

A strength of our study was that it used methodology that included randomization of patients and blinding of the clinician evaluating cleansing efficacy. Moreover, the required number of participants were recruited based on previous experience.

One limitation of our study was related to the daily practice of bowel cleansing in adolescent patients; intake of the bowel cleansing dosing regimen the day before colonoscopy made the waiting time before investigation very long, which possibly had a negative impact on the cleansing result. Another limitation was the lack of central re-evaluation of the results, which was not included in the protocol as it was anticipated that the use of a simple scale (4 points) and standard BBPS by experienced endoscopists would not produce large inter-observer differences. In hindsight, central review would have been of value for our study. Another potential limitation may be that the dose of OSS chosen was based on an unpublished study; however, OSS was subsequently approved at this dose by the FDA for use in adolescents (18).

CONCLUSIONS

In summary, non-inferiority of OSS versus PEG-electrolyte solution with regard to successful colonoscopy preparation was not demonstrated in this study, but OSS had tolerability and acceptability advantages over PEG. Shorter fasting intervals, including the split-doses approach, need to be considered in future studies to improve bowel cleansing in adolescent patients.

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