Novel 1-L polyethylene glycol + ascorbate versus high-volume polyethylene glycol regimen for colonoscopy cleansing: a multicenter, randomized, phase IV study

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Background and Aims: Adequate bowel cleansing is critical to ensure quality and safety of a colonoscopy. A novel 1-L polyethylene glycol plus ascorbate (1L-PEG+ASC) regimen was previously validated against low-volume regimens but was never compared with high-volume regimens.

Methods: In a phase IV study, patients undergoing colonoscopy were randomized 1:1 to receive split-dose 1L PEG+ASC or a split-dose 4-L PEG-based regimen (4L-PEG) in 5 Italian centers. Preparation was assessed with the Boston Bowel Preparation Scale (BBPS) by local endoscopists and centralized reading, both blinded to the randomization arm. The primary endpoint was noninferiority of 1L-PEG+ASC in colon cleansing. Secondary endpoints were superiority of 1L-PEG+ASC, patient compliance, segmental colon cleansing, adenoma detection rate, tolerability, and safety.

Results: Three hundred eighty-eight patients (median age, 59.8 years) were randomized between January 2019 and October 2019: 195 to 1L-PEG+ASC and 193 to 4L-PEG. Noninferiority of 1L-PEG+ASC was demonstrated for cleansing in both the entire colon (BBPS $\geq$ 6: 97.9% vs 93%; relative risk [RR], 1.03; 95% confidence interval [CI], 1.001-1.04; *P* superiority = .027) and in the right-sided colon segment (98.4% vs 96.0%; RR, 1.02; 95% CI, .99-1.02; *P* noninferiority = .013). Compliance was higher with 1L-PEG+ASC than with 4L-PEG (178/192 [92.7%] vs 154/190 patients [81.1%]; RR, 1.10; 95% CI, 1.05-1.12), whereas no difference was found regarding safety (moderate/severe side effects: 20.8% vs 25.8%; *P* = .253). No difference in adenoma detection rate (38.8% vs 43.0%) was found.

Conclusions: One-liter PEG+ASC showed noninferiority compared with 4L-PEG in achieving adequate colon cleansing and provided a higher patient compliance. No differences in tolerability and safety were detected. (Clinical trial registration number: NCT03742232.) (Gastrointest Endosc 2021;94:823-31.)

Abbreviations: BBPS, Boston Bowel Preparation Scale; CI, confidence interval; FAS, full analysis set; OR, odds ratio; PEG, polyethylene glycol; PEG+ASC, polyethylene glycol plus ascorbate; RR, relative risk.

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Bowel preparation is critical for screening and surveillance colonoscopy because accuracy in detection of colorectal neoplasia depends on an adequate visualization of the colonic mucosa. Inadequate bowel preparation leads to a higher miss rate of precancerous and cancerous lesions, suboptimal cecal intubation rate, repetition of the procedure before planned surveillance, and increased hospitalization, with a negative impact on patient tolerability and healthcare costs.[1-5]

High-volume (3-4 L) iso-osmotic solutions of polyethylene glycol (PEG), administered in a split regimen,[6,7] have represented the standard of care because of their safety profile.[1] However, such regimens have been challenged by hyperosmolar low-volume regimens to improve patient compliance and tolerability.[8] Recently, a 1-L PEG-based formulation, PEG plus ascorbate (1L-PEG+ASC), was developed based on the possibility to further decrease the PEG component by increasing the ascorbate content. In 3 phase III randomized trials, 1L-PEG+ASC was found to be noninferior or superior to the 3 main low-volume regimens, namely 2L-PEG+ASC, sodium picosulfate + magnesium citrate, and trisulfate.[9-11] Thus, its use is now formally recommended for clinical practice. Unexpectedly, a high rate of transient hypernatremia, up to 40%, was observed in 1 trial,[9] but the clinical relevance was unclear.[12,13] However, no study has yet evaluated, in a real-life clinical setting, the efficacy and safety of 1L-PEG+ASC compared with a high-volume PEG solution. Therefore, the aim of this phase IV, randomized, endoscopist-blind, controlled trial was to evaluate the efficacy, safety, and tolerability of 1L-PEG+ASC (PLENVU; Norgine, Amsterdam, the Netherlands) versus a high-volume 4-L PEG-based preparation (4L-PEG; SELG-ESSE; Alpha-Sigma, Bologna, Italy) using a 2-day split-dosing regimen.

METHODS

Study design

This was an endoscopist-blinded, prospective, multicenter, randomized study involving adults aged ≥18 years undergoing colonoscopy in 5 Italian centers from January 2019 through October 2019. The study design was defined in compliance with internationally recognized guidelines for clinical studies and was registered at ClinicalTrials.gov (NCT03742232). Approval of the study was obtained by the local ethics review committees of all participating clinical sites. Written informed consent was obtained from all patients. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

Participants

Eligible participants included women and men, 18 to 85 years of age, undergoing colonoscopy for colorectal cancer screening, surveillance, or diagnostic purposes. Reasons for exclusion are provided in Appendix 1 (available online at www.giejournal.org). A complete medical history, physical examination with vital signs, previous and current medications, and routine blood tests were obtained at the time of enrollment. All of these medical activities were performed by a physician who was not involved in the subsequent colonoscopy. A serum pregnancy test was performed for women of childbearing age.

Treatments allocation and masking

At the time of enrollment, eligible patients were randomly assigned to either the 1L-PEG+ASC (PLENVU; Norgine) or 4L-PEG (SELG-ESSE) regimen in a 1:1 ratio using a computer-generated sequence, generated for each center by the coordinating center and available for 1 subject at a time. Randomization was stratified by center, sex, age, and personal history of adenomas. The study was observer-blind: Endoscopists were not allowed to perform any activities associated with randomization or bowel preparation before and after colonoscopy and had to avoid any discussion with the patients and the staff that could disclose the type of bowel preparation. Details on colon cleansing preparations and colonoscopy procedure are provided in Appendix 1.

Assessments

Efficacy. All study procedures were performed by expert endoscopists (>2000 screening colonoscopies) who were blinded to the bowel preparation agent. All operators had undergone training in the evaluation of the Boston Bowel Preparation Scale (BBPS). Bowel assessment was made by the operating endoscopist during both the insertion and withdrawal phases of colonoscopy. Furthermore, the full examination was video recorded and sent to a central reader who was blinded to the preparation agent used and to the operators' bowel cleansing assessment, and the video underwent a second bowel cleansing assessment.

Washing and suctioning to clean the bowel was allowed only during withdrawal. Cleansing quality for each segment of the colon (right-sided, transverse, and left-sided colon segments) was graded using the BBPS after the required washing and suctioning, as reported elsewhere[14] (0 = inadequate, 1 = fair, 2 = good, 3 = excellent). If the endoscopist was unable to reach the colon segment because of poor quality of bowel preparation, the segment was automatically rated as inadequate. Scores of all segments were added as the total BBPS score, ranging from 0 to 9. The preparation quality for the entire colon was also divided into 4 grades: excellent (total score, 8-9), good (total score, 6-7, and each colon segment score ≥2), fair (total score, 3-5 or total score, 6-7, but 1 or more colon segment score <2), and poor (0-2). For the primary efficacy endpoint, excellent and good cleansing (ie, total BBPS ≥6) according to the local

endoscopist was considered as "successful" and poor or fair as "failure."

Secondary efficacy endpoints were high-quality cleansing rate (total BBPS score, 8-9 vs 0-7), polyp detection rate, adenoma detection rate, indicators of quality such as cecal intubation (full colonic examination), time to reach the caecum (intubation time), and withdrawal time. Adenoma and polyp detection rates were calculated as the percentage of patients analyzed who had at least 1 adenoma or polyp for all patients included in the study. Randomized patients who did not undergo colonoscopy and those without a BBPS total score for reasons independent from bowel preparations (anatomic structures, poor tolerability) were excluded from the efficacy analysis.

Tolerability, acceptability, and compliance. A patient diary was used to collect data on tolerability, acceptability, and compliance. Details on diary questions and assessment methodology are provided in Appendix 1. Briefly, tolerability was assessed inquiring on the occurrence and the severity of side effects after bowel preparation. Acceptability was evaluated by the subjective assessment provided by patients concerning the difficulty of following the bowel preparation instructions, taking the solution, taste of the preparation, and interference with daily activity. Treatment compliance was scored according to a 3-grade scale and recording the amount of fluid/food consumption.

Safety. The safety of the preparations was based on serious adverse event occurrence and clinical laboratory test abnormalities. Adverse events were monitored throughout the study. The duration and intensity of each event were recorded by the investigators, as well as the causative relationship with study drugs, outcomes, and seriousness. Vital signs, complete physical examination, and blood tests (when possible according to the timing of the procedure) were performed at the time of patient enrollment and on the day of colonoscopy and included hematology and blood chemistry, including creatinine, potassium, sodium, chlorides, and calcium.

Statistical analysis

The primary endpoint of this trial was the demonstration of the noninferiority of 1L-PEG+ASC versus 4L-PEG in colon cleansing according to local endoscopists of BBPS during withdrawal. A sample size of 185 assessable patients per arm was required, based on expected overall cleansing success rates of 90% for both arms, noninferiority margin of 10%, power of 90%, and alpha level of 2.5% (1-sided). Noninferiority was met for the primary endpoint if the lower 2-sided 95% confidence interval (CI) excluded a 10% or greater difference in favor of 4L-PEG group. The 10% noninferiority margin reflects a typical maximum clinically acceptable difference for comparative bowel preparation studies of this type. If noninferiority was demonstrated for the primary endpoint, the endpoint was assessed for superiority (1-sided $P < .025$) using the Fisher exact test.

A full analysis set (FAS) for safety, demographics, and all baseline characteristics was defined for all randomized subjects, except those who did not receive any study drug. A modified FAS approach was used to analyze the data and included all FAS patients who produced at least 1 postbaseline study assessment. For efficacy outcomes, the primary analysis set was defined as a subset of the FAS for subjects who produced efficacy assessments for the BBPS (ie, excluding patients with missing colonoscopy data). The efficacy set reflects cleansing performance as seen by endoscopists by only including patients who actually underwent a colonoscopy with bowel cleansing assessment. Sensitivity analyses of efficacy variables using the FAS population with missing data imputed as failures were performed to assess the robustness of the study results. For acceptability, tolerability, and compliance outcomes, the analysis set consisted of all patients in the FAS population with patient diary responses (ie, excluding patients with missing data).

Baseline characteristics were summarized by descriptive statistics, such as mean and standard deviation for continuous variables and rates for categorical variables. A 2-sided t test was used to compare the means of continuous variables; a likelihood ratio χ^2 test was used to compare the rates of categorical measures. The categorical efficacy endpoint, the BBPS, was summarized by the percentage of patients successfully cleansed (ie, total BBPS $\geq$6 and all segment scores $\geq$2) according to the local endoscopist. Noninferiority was established for this outcome if the lower limit of the 2-sided 95.0% CI for the difference in adequate rates between the 2 treatment arms was less than –10%. If the noninferiority criteria were satisfied, superiority could be demonstrated if the lower bound of the CI for the treatment difference was greater than 0%.

At the segment level, multilevel logistic regression was used to evaluate the factors associated with segmental bowel cleansing levels (ie, BBPS segment scores) adjusting for the possible correlation between multiple observations (ie, segment scores) within each patient (cluster). Two alternative primary outcomes were evaluated: adequate BBPS segment scores (ie, adequate BBPS segmental scores 3-2 vs inadequate 0-1) and high BBPS segment scores (ie, high BBPS segment scores of 3 vs 0-2). For each outcome, we conducted univariate and multivariable analyses, both at the segmental level, taking the segmental cleansing levels as the dependent variable. The potential predictors tested for association were patient sex, age, body mass index, indication for colonoscopy, use of sedation, colonoscopy time, colonoscopy phase, compliance with bowel preparation, and colon segment.

Data are presented as odds ratios (ORs) of having adequate (high) segmental bowel cleansing and 95% confidence limits. Results from the patient acceptability and tolerability questionnaire were compared between

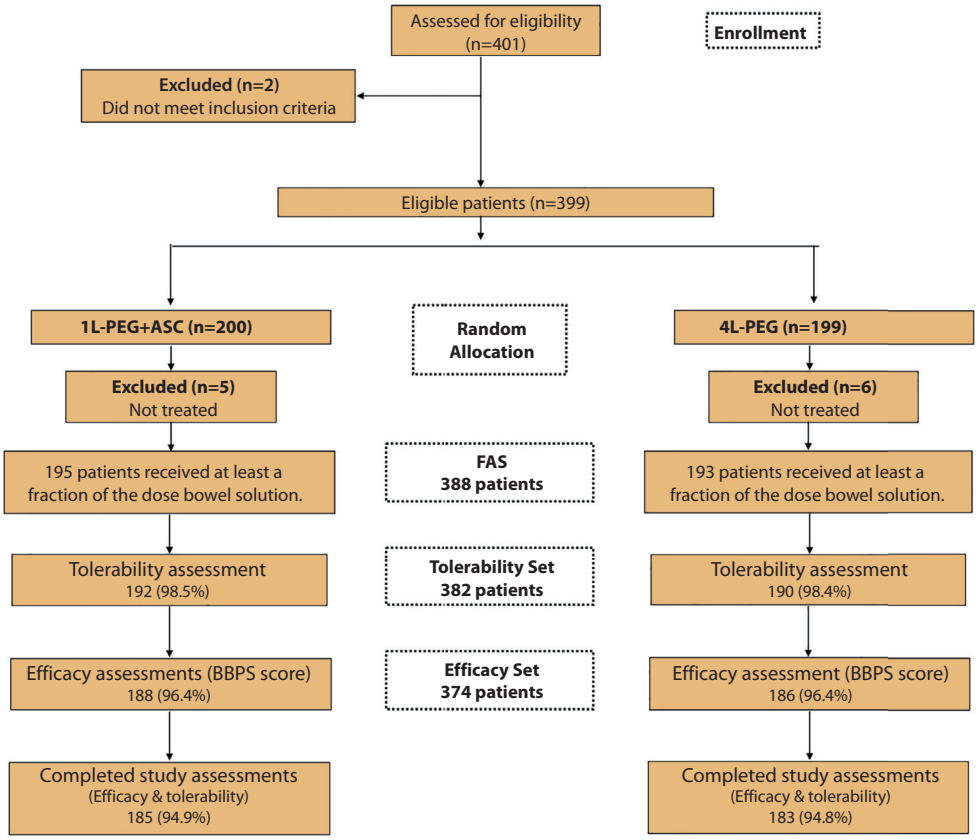


Figure 1. Patient flow. The full analysis set (FAS) included all randomized patients receiving treatment and having at least 1 study assessment after randomization (n = 388). The efficacy set was the primary set for analysis of efficacy variables and consisted of randomized patients who had received the study drug and produced efficacy assessment for the BBPS (n = 374). A secondary analysis set for acceptability/tolerability variables was defined as a subset of the FAS for subjects who responded to the questionnaire regarding their bowel preparation experience (n = 382). *BBPS*, Boston Bowel Preparation Scale; *PEG*, polyethylene glycol; *PEG+ASC*, polyethylene glycol plus ascorbate.

treatment arms using a χ^2 test for pooled responses. Descriptive analyses were performed for safety outcomes. A $P < .05$ was considered statistically significant. All statistical analyses were performed with statistical computing software R (version 3.5.1; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Demographics and baseline

Figure 1 shows the flow of patients throughout the study. Of the 399 randomized patients, 11 were excluded because they did not receive any treatment (confirmed from patient diary). The remaining 388 patients represented the FAS, with 195 patients randomized to the 1L-PEG+ASC group and 193 to the 4L-PEG group. Fourteen patients (3.6% of the FAS) were excluded from the analysis of efficacy (no BBPS scores, colonoscopy not performed) and 6 patients (1.5% of the FAS patients) were excluded from the analysis of acceptability/tolerability variables for incomplete data reporting. Accordingly, 374 patients were included in the efficacy analysis set and 382 in the acceptability/tolerability analysis set.

Baseline demographic and clinical characteristics of included patients were similar between groups (Table 1, Supplementary Table 1, available online at www.giejournal.org). Mean patient age was 59.8 years (range, 21-84), and 52.4% (204/388) were women. The most common reasons for colonoscopy were follow-up colonoscopy after a positive screening fecal immunochemical test (203/388, 52.3%).

Efficacy of bowel preparation

Characteristics of colonoscopy procedures for the 374 assessable patients are shown in Table 2. The 2 groups were comparable with respect to cecal intubation, procedure times, and sedation.

For overall bowel-cleansing success, 1L-PEG+ASC demonstrated noninferiority versus 4L-PEG, as assessed using the BBPS score in the efficacy set (Table 3). Overall cleansing success was achieved for 97.9% of patients (184/188) in the 1L-PEG+ASC group and 93.0% (173/186) in the 4L-PEG group (relative risk [RR], 1.03; 95% CI, 1.01-1.04; P for noninferiority < .001; P for superiority = .027) (Table 3; Supplementary Fig. 1, available online at www.giejournal.org). High-quality cleansing (total BBPS

TABLE 1. Patient characteristics in the full analysis set (n = 388)*

Variable	1L-PEG+ASC (n = 195)	4L-PEG (n = 193)	*P* value
Sex, male/female	85/110	99/94	.06
Mean age (SD), y	59.5 (11.3)	60.1 (12.0)	.7
Mean body mass index (SD), kg/m^2	25.6 (4.2)	25.3 (4.3)	.48
Setting			.78
Outpatient	187 (95.9)	182 (94.3)	
Inpatient	8 (4.1)	11 (5.7)	
Indication for colonoscopy			.35
Diagnostic colonoscopy	47 (24.1)	52 (26.9)	
Screening (fecal immunochemical test positive)	98 (50.3)	105 (54.4)	
Surveillance for colonic neoplasia	50 (25.6)	36 (18.7)	

Values are n (%) unless otherwise defined.
PEG, Polyethylene glycol; *PEG+ASC*, polyethylene glycol plus ascorbate; *SD*, standard deviation.
*For efficacy and tolerability sets, see Supplementary Table 1.

TABLE 2. Characteristics of the colonoscopy procedures

	1L-PEG+ASC (n = 188)	4L-PEG (n = 186)	*P* value
Patient compliance with bowel preparation dosage			
Poor compliance (<75% intake) dose 1 bowel preparation	0 (0.0)	5 (2.7)	.068
Poor compliance (<75% intake) dose 2 bowel preparation	2 (1.1)	11 (5.9)	<.001
Time between completion of bowel preparation and start of colonoscopy, mean (SD), h	3.9 (1.2)	4.4 (1.1)	<.001
Timing of colonoscopy			
Morning colonoscopies	105 (55.9)	112 (60.2)	.453
Afternoon colonoscopies	83 (44.1)	74 (39.8)	
Cecal intubation success	188 (100)	184 (98.9)	.243
Reason for incomplete colonoscopy			
Very poor preparation	0 (0.0)	2 (1.1)	.474
Stenosing lesion	0 (0.0)	1 (0.5)	.995
Cecal intubation time, mean (SD)	10.0 (19.7)	9.0 (6.7)	.423
Colonoscopy duration, mean (SD), min	22.1 (11.5)	21.4 (9.5)	.511
BBPS during withdrawal, mean (SD)	8.3 (1.2)	7.7 (1.6)	<.001
BBPS during insertion, mean (SD)	7.1 (1.6)	6.6 (1.9)	.012

Values are n (%) unless otherwise defined.
PEG, Polyethylene glycol; *PEG+ASC*, polyethylene glycol plus ascorbate; *SD*, standard deviation; *BBPS*, Boston Bowel Preparation Scale.

score, 8-9) was obtained for 78.7% of patients (148/188) in the 1L-PEG+ASC group and 64.5% (120/186) in the 4L-PEG group (RR, 1.17; 95% CI, 1.08-1.24) (Fig. 2). The BBPS scores assessed during the insertion phase were lower than those during the withdrawal phase in both study groups (Table 3), but differences between groups remained significant (overall colon cleansing: 91.5% vs 82.3%; RR, 1.08; 95% CI, 1.03-1.11) (Table 3, Supplementary Fig. 1). Agreement between the local and centralized reading (adequate vs inadequate) was obtained in 350 of 374 patients (93.6%).

The 1L-PEG+ASC regime was not inferior to 4L-PEG in all colonic segments and in the right-sided colon segment (98.4% vs 96.2%; RR, 1.02; 95% CI, .99-1.02), whereas it was superior in the transverse (99.5% vs 96.2%; $P = .036$) and left-sided colon (99.5% vs 94%; $P = .003$) (Table 3). Results did not change when assessing the level of cleansing during insertion (Table 4). Sensitivity analyses conducted in the FAS set (including all patients without BBPS scores as failures) supported the results of the primary analyses in the efficacy set (Supplementary Fig. 2, available online at www.giejournal.org).

Supplementary Table 2 (available online at www.giejournal.org) shows results from univariate and multivariable analyses of the factors associated with segmental cleansing levels. On multivariable logistic regression, independent predictors of

TABLE 3. Efficacy of bowel cleansing in patients undergoing colonoscopy

Bowel preparation quality	Patients BBPS ≥6 (each segment ≥2) n (%)		Treatment difference* % (95% confidence interval)	*P* value (noninferiority)†,‡	*P* value (superiority)
	1L-PEG+ASC (n = 188)	4L-PEG (n = 186)			
Entire colon	184 (97.9)	173 (93.0)	4.9 (.1-9.6)	<.001	.027
Right-sided colon segment	185 (98.4)	179 (96.2)	2.2 (−1.6 to 6.2)	.013	.164
Transverse colon segment	187 (99.5)	179 (96.2)	3.5 (.0-7.1)	.002	.036
Left-sided colon segment	187 (99.5)	175 (94.0)	5.5 (1.3-9.5)	<.001	.003

BBPS, Boston Bowel Preparation Scale; *PEG*, polyethylene glycol; *PEG+ASC*, polyethylene glycol plus ascorbate.
*Treatment difference was calculated by subtracting the percentage of patients successfully cleansed in the 4L-PEG treatment group from the percentage of patients successfully cleansed in the 1L-PEG+ASC treatment group.
†Noninferiority was demonstrated if the lower limit of the 2-sided 95.0% confidence interval for the treatment difference was greater than −10%; superiority was achieved if the lower limit of 2-sided 95% confidence interval for the treatment difference was greater than 0%.
‡*P*-value, 1-sided Fisher exact.

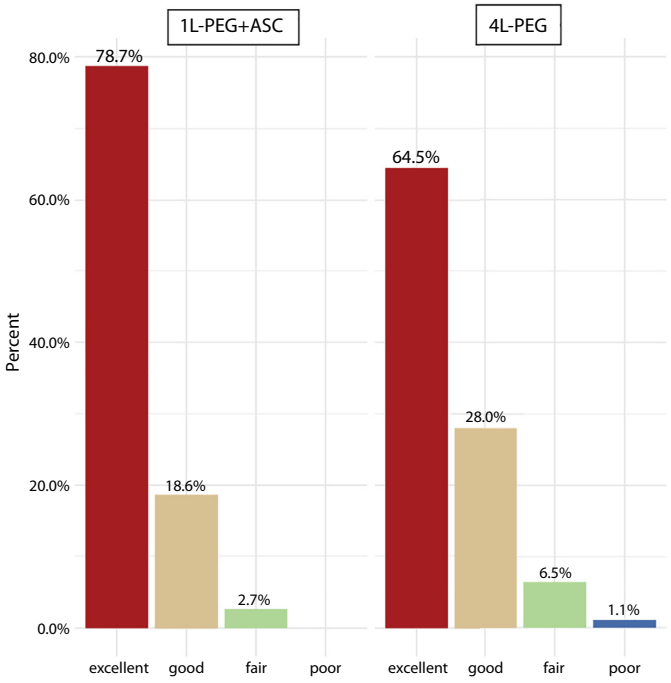


Figure 2. Results of bowel cleansing quality assessment based on the Boston Bowel Preparation Scale. Preparation quality of the entire colon was divided into 4 grades: excellent (total score 8-9), good (total score 6-7 and each colon segment score ≥2), fair (total score 3-5 or total score 6-7, but 1 or more colon segment score <2), and poor (0-2). *PEG*, Polyethylene glycol; *PEG+ASC*, polyethylene glycol plus ascorbate.

adequate BBPS scores (ie, adequate BBPS segment scores ≥2) were study arm (1L-PEG+ASC vs 4L-PEG: OR, 2.63; 95% CI, 1.38-5.00), colonoscopy phase (insertion vs withdrawal: OR, .25; 95% CI, .17-.37), and colon location (transverse vs right-sided colon: OR, 1.71; 95% CI, 1.23-2.38). Results for high BBPS segment scores are available in Supplementary Table 2.

Compliance and acceptability

The analyses of compliance, acceptability, and tolerability variables were based on 382 FAS patients who completed the patient diary (excluding patients with missing patient diary responses) (Fig. 1, Table 1). Patient diary responses (Supplementary Table 3, available online at www.giejournal.org) indicated better compliance in the 1L-PEG+ASC group than in the 4L-PEG group when defined as intake of 100% (178/192 [92.7%] vs 154/190 patients [81.1%]; RR, 1.10; 95% CI, 1.05-1.12; $P < .001$) and <75% solution intake (2/192 [1.0%] vs 14/190 [7.4%]; RR, .14; 95% CI, .02-.49) (Fig. 3). Compliance with adjunctive fluid intake (≥75%) and dietary restriction before colonoscopy was similar between study groups. The time to consume the bowel preparation was significantly shorter in the 1L-PEG+ASC group (Supplementary Table 3).

Briefly, compared with 4L-PEG, more 1L-PEG+ASC patients found it "very or quite easy" to consume the full volume of the preparation (145 [75.5%] vs 121 [63.7%], $P = .012$), and more patients found it "very easy" to drink the recommended volume of additional clear fluids (183 [95.3%] vs 121 [63.7%], $P < .001$). Self-reported moderate to severe embarrassment, solution taste, and disturbance in regular daily activities did not differ significantly between study arms (Supplementary Table 3). At least 1 stop during travel occurred in 10 patients in the 1L-PEG+ASC group and in 3 in the 4L-PEG group (5.2% vs 1.6%, $P = .086$). Willingness to repeat the same preparation for future endoscopies was reported by 77.1% of patients in the 1L-PEG+ASC group (148/192) and 66.8% of patients in the 4L-PEG group (127/190; RR, 1.13; 95% CI, 1.02-1.21; $P = .027$).

Tolerability

The 1L-PEG+ASC and 4L-PEG products did not differ significantly in terms of tolerability, as demonstrated by the similar rate of patients who reported (moderate to severe) side effects after bowel preparation (Supplementary Table 4, available online at www.giejournal.org). Side effects, if experienced, were reported as moderate for most patients in both study arms, with 89 patients

TABLE 4. Bowel preparation quality assessed during insertion

Bowel preparation quality assessed on colonoscopy insertion	Patients BBPS ≥6 (each segment ≥2) n (%)		Treatment difference % (95% confidence interval)	*P* value (noninferiority)	*P* value (superiority)
	1L-PEG+ASC (n = 188)	4L-PEG (n = 186)			
Entire colon	172 (91.5)	153 (82.3)	9.2 (2.0-16.6)	<.001	.009
Right-sided colon segment	172 (91.5)	160 (86.0)	5.5 (−1.5 to −12.4%)	.002	.103
Transverse colon segment	182 (96.8)	168 (90.3)	6.8 (1.0-12.0)	<.001	.011
Left-sided colon segment	176 (93.6)	156 (83.9)	9.7 (2.9-16.6)	<.001	.003

BBPS, Boston Bowel Preparation Scale; *PEG*, polyethylene glycol; *PEG+ASC*, polyethylene glycol plus ascorbate.

defining symptoms as severe (1L-PEG+ASC, 40/192 [20.8%], vs 4L-PEG, 49/190 [25.8%]; $P = .253$). Nausea/vomiting and bowel distension, either alone or in combination, were the most common GI complaints in both study groups, with no statistically significant differences (Supplementary Table 4). Compared with patients receiving 4L-PEG, fewer patients receiving 1L-PEG+ASC reported (moderate to severe) sleep disturbance (43/192 [22.4%] vs 65/190 [34.2%]; RR, .65; 95% CI, .47-.91; $P = .011$) and more patients reported excessive dryness of the mouth (3.6% vs .0%, $P = .014$). All reported symptoms were self-limited and did not require medical care.

Safety

There were no deaths in the study and no serious adverse events considered related to the preparation. The baseline vital sign measurements and blood tests were similar between study arms (Supplementary Table 5, available online at www.giejournal.org), and both arms exhibited statistically significant changes after bowel preparation. However, the changes all fell within normal ranges (Supplementary Table 6, available online at www.giejournal.org). In detail, mean Na+ values at baseline assessment were 141.5 mEq/L (range, 141.1-142.0) for 1L-PEG+ASC and 141.4 mEq/L (141.1-142.0) for 4L-PEG. An increase in Na+ was observed more frequently in the 1L-PEG+ASC group than the 4L-PEG group (12/114 [10.5%] vs 1/121 [.8%]; RR, 12.7; 95% CI, 1.7-96.4) and was ≤150 mEq/L in all the cases (Supplementary Table 7, available online at www.giejournal.org). When comparing patients with electrolyte shift with those without, no statistically significant differences in patient characteristics (ie, age, gender, comorbidities) were found as compared with the overall study population.

Lesion detection

There were no significant differences between the 1L-PEG+ASC and 4L-PEG arm in terms of polyp detection rate (1L-PEG+ASC vs 4L-PEG: 105/188 [55.9%] vs 111/186 [59.7%]; RR, .94; 95% CI, .79-1.11). Adenoma detection rate was also similar between the 2 groups (1L-PEG+ASC vs 4L-PEG: 73/188 [38.8%] vs 80/186 [43.0%]; RR, .90; 95% CI, .71-1.15). The mean number of detected polyps per patient was 1.30 (standard deviation, 2.10) and 1.24 (standard deviation,1.57; $P = .749$). Supplementary Tables 8 and 9 (available online at www.giejournal.org) summarize the characteristics of detected polyps. Polyp characteristics were similar between groups.

DISCUSSION

According to our findings, 1L PEG+ASC was noninferior and superior to 4L-PEG in achieving both an overall successful bowel cleansing, defined as BBPS ≥6 and all segment scores ≥2, and a high-quality overall bowel cleansing (BBPS of 8-9), whereas its low volume resulted in an improved patient experience, both in terms of acceptability and compliance. The noninferiority of 1L-PEG+ASC was confirmed in the right-sided colon segment, whereas it was superior in the left-sided and transverse colon segments. Despite its hyperosmolarity, no higher risk of adverse events was observed in the 1L-PEG+ASC group. In particular, the shifts of sodium were limited in terms of frequency and clinical relevance.

It may be argued that the small difference, 97.8% versus 93%, is clinically unrewarding, because both of them are over the 85% to 90% required by the U.S. Multi-Society Task Force on Colorectal Cancer[15] and the European Society of Gastrointestinal Endoscopy.[1] In addition, the number of patients needed to treat with 1L-PEG+ASC to achieve 1 more adequate cleansing than with 4L-PEG is 21, which by itself does not support a preferential choice for the formed regimen. However, when considering the difference in high-quality cleansing, the difference between 78.7% in the 1L-PEG+ASC group and 64.5% in the 4L-PEG group is likely to be clinically relevant[16] as supported by a number needed to treat of 7 for such an endpoint. Consistent with this observation, 1L-PEG+ASC has also separately demonstrated over 70% success in high-quality cleansing in 2 other independent randomized controlled trials, a level of cleansing success that both comparators, 2L-PEG+ASC and oral sulfate solution, failed to attain.[17]

We also assessed the safety of the 1L-PEG+ASC solution because of the previous reports of a clinically relevant

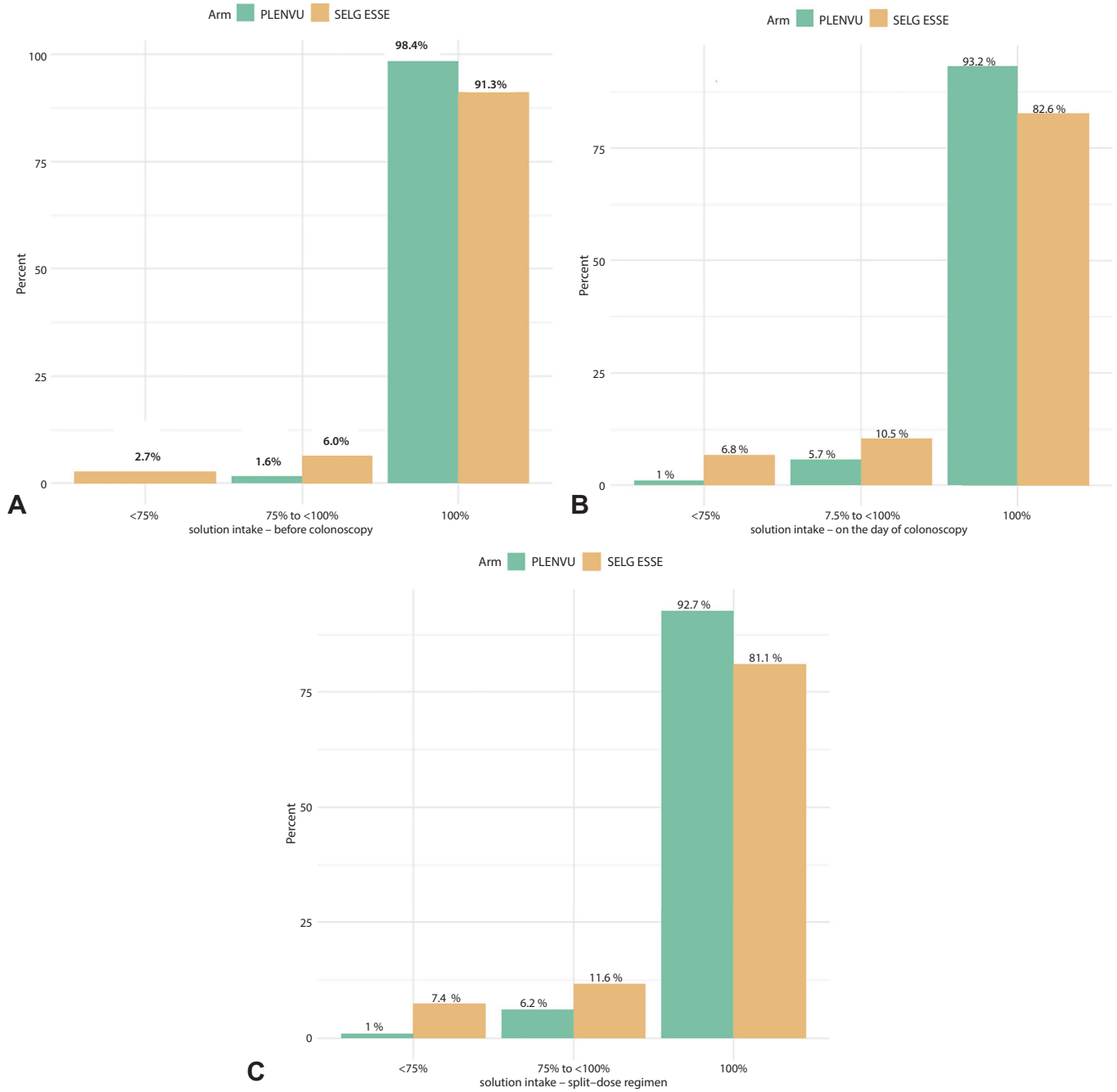


Figure 3. Compliance with the split-dose bowel preparation regimen by study arm. **A,** The first split dose of bowel preparation the day before colonoscopy. **B,** The second split dose of bowel preparation the day of the colonoscopy. **C,** The study split-dose bowel preparation regimen. *PLENVU*, 1-L polyethylene glycol plus ascorbate regime; *SELG-ESSE*, 4-L polyethylene glycol regime.

hypernatremia in 1 of 3 previous phase III studies. According to our data, only a modest increase in sodium level was observed in approximately 10% of patients; this was of modest entity (<150 mEq/L) in all cases. This may be related to the recommendation of drinking additional fluids.[9] Interestingly, 1L-PEG+ASC showed a statistically lower rate of sleep disturbance versus 4L-PEG. Although this impact on quality of life is likely attributable to the time saving of over 3 hours for a bowel preparation with 1L-PEG+ASC versus 4L-PEG, it is entirely plausible that such a large average time savings per patient could also be valuable for inpatients because this may require less staff support.

The overall result of our study should not be surprising. In a phase III trial, 1L-PEG+ASC was already shown to be superior to the 2L-PEG regimen in a per-protocol population[11] that in turn was shown to be equivalent to 4L-PEG in a recent meta-analysis[8] that included 17 randomized

controlled trials and 7528 patients. In addition, 1L-PEG+ASC was also shown to be superior to sodium picosulfate + magnesium citrate.

The degree of cleansing in both arms is on average much higher than that reported in previous phase III studies. This may be mainly because of a methodologic difference between this phase IV study and previous phase III trials. In detail, in our study the BBPS assessment for primary endpoint calculation was performed after washing and suctioning, whereas in previous trials this assessment was done before, often with another, less clinical preparation scale (Harefield Preparation Scale). Although we believe that scoring bowel preparation level after washing and suctioning is more compliant with real-life clinical practice, we nonetheless assessed and confirmed noninferiority and/or superiority of 1L-PEG+ASC also when focusing on the BBPS at insertion (see Table 4).

This study has several strengths. First, the blinding of the operating endoscopists ensured an unbiased evaluation of the preparation quality. Second, confirmation of the quality evaluation by a central reader has shown a concordance of >90% with the operating endoscopist. This is in line with previous studies on the 1L-PEG+ASC regimen. Third, between our FAS set and our efficacy set we lost a small number of patients, strengthening the intention-to-treat calculations results.

There are also limitations in our study. We excluded patients with severe constipation and with severe renal or hepatic insufficiency, so our results may not be fully generalizable to the entire patient population. Also, patients with major colorectal surgery and affected by inflammatory bowel diseases were excluded from this study.

In conclusion, this phase IV, randomized, endoscopist-blinded, controlled trial has shown noninferiority of 1L-PEG+ASC compared with 4L-PEG in achieving adequate colon cleansing as well as providing a higher patient compliance. No differences in tolerability and safety were detected.

REFERENCES

1. Hassan C, East J, Radaelli F, et al. Bowel preparation for colonoscopy: European Society of Gastrointestinal Endoscopy (ESGE) guideline—update 2019. Endoscopy 2019;51:775-94.
2. Sulz MC, Kröger A, Prakash M, et al. Meta-analysis of the effect of bowel preparation on adenoma detection: early adenomas affected stronger than advanced adenomas. PLoS One 2016;11:e0154149.
3. Clark BT, Rustagi T, Laine L. What level of bowel prep quality requires early repeat colonoscopy: systematic review and meta-analysis of the impact of preparation quality on adenoma detection rate. Am J Gastroenterol 2014;109:1714-23; quiz 1724.
4. Anderson JC, Baron JA, Ahnen DJ, et al. Factors associated with shorter colonoscopy surveillance intervals for patients with low-risk colorectal adenomas and effects on outcome. Gastroenterology 2017;152:1933-43.
5. Kingsley J, Karanth S, Revere FL, et al. Cost effectiveness of screening colonoscopy depends on adequate bowel preparation rates—a modeling study. PLoS One 2016;11:e0167452.
6. Bucci C, Rotondano G, Hassan C, et al. Optimal bowel cleansing for colonoscopy: split the dose! A series of meta-analyses of controlled studies Gastrointest Endosc 2014;80:566-76.
7. Vanella G, Hassan C, De Bellis M, et al. IMPlementing split Regimen OVEr Single dose using a Plan-Do-Study-Act approach (IMPROVES study). Endosc Int Open 2019;7:E1457-67.
8. Spadaccini M, Frazzoni L, Vanella G, et al. Efficacy and tolerability of high- vs low-volume split-dose bowel cleansing regimens for colonoscopy: a systematic review and meta-analysis. Clin Gastroenterol Hepatol 2020;18:1454-65.e14.
9. DeMicco MP, Clayton LB, Pilot J, et al. 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;87:677-87.
10. Schreiber S, Baumgart DC, Drenth JPH, et al. Colon cleansing efficacy and safety with 1 L NER1006 versus sodium picosulfate with magnesium citrate: a randomized phase 3 trial. Endoscopy 2019;51:73-84.
11. Bisschops R, Manning J, Clayton LB, et al. Colon cleansing efficacy and safety with 1 L NER1006 versus 2 L polyethylene glycol + ascorbate: a randomized phase 3 trial. Endoscopy 2019;51:60-72.
12. Rex DK. Hyperosmotic low-volume bowel preparations: Is NER1006 safe? Gastrointest Endosc 2019;89:656-8.
13. Repici A, Hassan C, Hoorn EJ, et al. NER1006 is clinically safe. Gastrointest Endosc 2019;89:908-9.
14. Lai EJ, Calderwood AH, Doros G, et al. The Boston Bowel Preparation Scale: a valid and reliable instrument for colonoscopy-oriented research. Gastrointest Endosc 2009;69(3 Pt 2):620-5.
15. Johnson DA, Barkun AN, Cohen LB, et al. US Multi-Society Task Force on Colorectal Cancer. Optimizing adequacy of bowel cleansing for colonoscopy: recommendations from the US multi-society task force on colorectal cancer. Gastroenterology 2014;147:903-24.
16. Clark BT, Laine L. High-quality bowel preparation is required for detection of sessile serrated polyps. Clin Gastroenterol Hepatol 2016;14:1155-62.
17. Repici A, Coron E, Sharma P, et al. Improved high-quality colon cleansing with 1L NER1006 versus 2L polyethylene glycol + ascorbate or oral sulfate solution. Dig Liver Dis 2019;51:1671-7.

APPENDIX 1

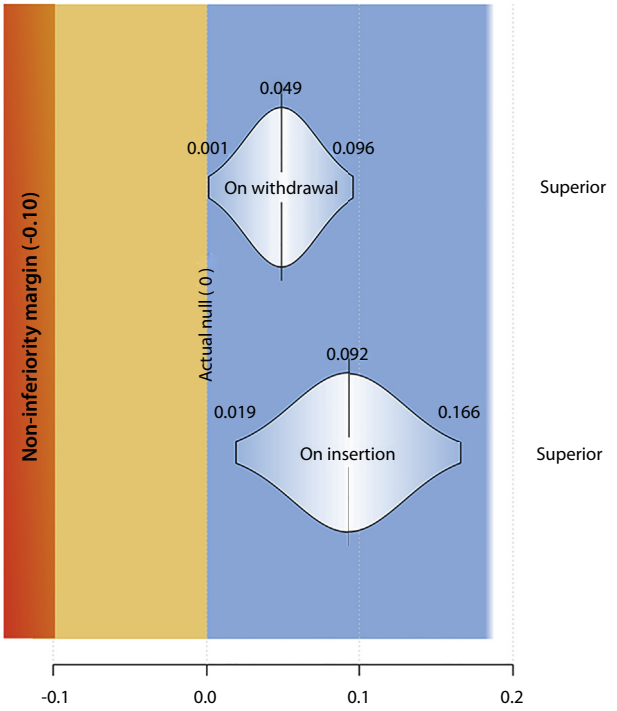
Additional Materials and Methods

Reasons for exclusion. Patients were considered ineligible for study participation in presence of any of the following: pregnant or lactating women, known or suspected hypersensitivity to the active principle and/or formulations ingredients, known or suspected GI obstruction or perforation, severe acute inflammatory bowel disease or diverticulitis, toxic megacolon, major colonic resection, heart failure (class III or IV), serious cardiovascular disease, severe liver failure and end-stage renal insufficiency, previous or current episodes of severe constipation (requiring repeated use of laxatives/enema or physical intervention before resolution), and those undergoing colonoscopy for foreign body removal or decompression. Concomitant use of lithium, laxatives, constipating drugs, antidiarrheal agents, or oral iron preparations was not permitted in the study.

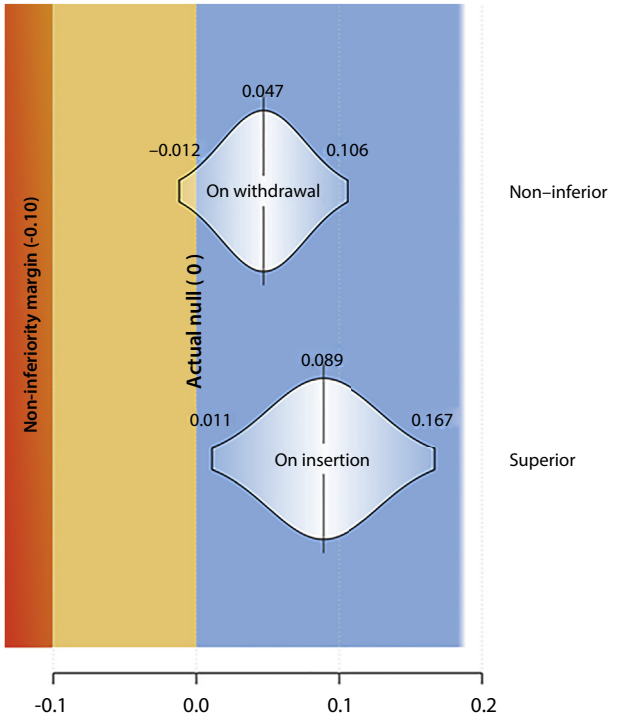
Colon cleansing preparations. The study preparation was 1 L polyethylene glycol plus ascorbate regime (PLENVU; Norgine). As active control, a 4 L polyethylene glycol (SELG-ESSE; Alpha-Sigma) was used. Each treatment was administered as an overnight 2-day split-dose regimen. The first dose was to be taken on the night before the endoscopic examination at 8 PM. The second dose was to be taken on the morning of the examination between 6 and 10 AM, within 5 hours from the initiation of the colonoscopy. The preparations were dispensed by a nurse who carefully explained how the products should be taken, emphasizing the importance of complete intake of the solution to ensure a safe and effective procedure. Moreover, each patient was provided with dietary instructions: low-residue diet for 3 days before colonoscopy. During and after bowel preparation, solid food was not allowed. Clear liquids could be taken until 2 hours before the procedure.

Colonoscopy procedure. Conscious sedation and analgesia were used according to the center's preference. Colonoscopy was performed using standard high-definition endoscopes. The exam was considered complete if the cecum was visualized. All detected lesions were measured with open biopsy forceps and annotated according to size, morphology, and localization. Advanced adenomas were defined as adenomas that were either $\geq$10 mm in diameter, included a villous component, harbored high-grade dysplasia, or were cancerous.

Analysis of tolerability, acceptance, and compliance. A patient diary was used to collect data on tolerability, acceptability, and compliance. Tolerability was assessed inquiring on the occurrence (yes or no) and severity (none/mild, moderate, or severe) of the side effects after bowel preparation, including GI symptoms (ie, nausea, bloating, abdominal pain/cramps and anal irritation), central nervous system symptoms (ie, headache, dizziness, sleep disturbance), and systemic symptoms (ie, fatigue, fever/sweats). Acceptability was evaluated by the subjective assessment provided by patients concerning the difficulty of following the bowel preparation instructions (very easy or easy, moderately difficult, difficult), difficulty of taking the solution (very easy or easy, moderately difficult, difficult), taste of the preparation (1 = very bad to 5 = very well), and interference with daily activity (none, mild, moderate, severe). Willingness to repeat the same bowel cleansing agent in the future was also collected and evaluated through a "yes or no" binary questionnaire. Treatment compliance was scored according to a 3-grade scale specifying the percentage of drunk solution: optimal, intake of the entire solution (grade = 0); good, intake of at least 75% of the solution (grade = 1); poor, intake of <75% of the solution (grade = 2). The amount of fluid/food consumed was also recorded to assess compliance.



Supplementary Figure 1. Evaluation of bowel preparation quality during the withdrawal phase. as measured by the Boston Bowel Preparation Scale (BBPS), 1L-PEG+ASC was superior to 4L-PEG in overall cleansing of the colon. A patient was considered successfully cleansed after administration of the preparation if colon cleansing was rated excellent or good (total BBPS ≥6). The lower bound of the 2-sided 95% confidence interval for the treatment difference between 1L-PEG+ASC and 4L-PEG in overall colon cleansing met the a priori criteria for noninferiority (more than –10.0%) and superiority (0%); thus, noninferiority and superiority of 1L-PEG+ASC were established. *PEG*, Polyethylene glycol; *PEG+ASC*, polyethylene glycol plus ascorbate.



Supplementary Figure 2. Analysis of efficacy variables on the 388 randomized patients (full analysis set [FAS]). A patient was considered successfully cleansed after administration of the preparation if colon cleansing was rated excellent or good (total Boston Bowel Preparation Scale [BBPS] ≥6). All patients (n = 14) without efficacy data were included in the FAS of efficacy as failures; the resulting estimates of efficacy were therefore conservative. One liter of polyethylene glycol plus ascorbate (1L-PEG+ASC) was noninferior to 4 L of polyethylene glycol (4L-PEG) in overall cleansing of the colon, as measured by the BBPS. For assessment during the withdrawal phase of the colonoscopy, the lower bound of the 2-sided 95% confidence interval (CI) for the treatment difference between 1L-PEG+ASC and 4L-PEG in overall colon cleansing met the a priori criteria for noninferiority (more than –10.0%): rate of adequate bowel cleansing, 184 of 195 (94.3%) in the 1L-PEG+ASC group versus 173 of 193 (89.6%) in the 4L-PEG treatment; 95% CI mean difference, –.012 to .106; *P* for superiority, .094; odds ratio, 1.93; 95% CI, .85-4.69. For assessment during the insertion phase of the colonoscopy, the lower bound of the 2-sided 95% CI for the treatment difference between 1L-PEG+ASC and 4L-PEG in overall colon cleansing met the a priori criteria for noninferiority (more than –10.0%) and superiority (0%); thus, noninferiority and superiority of 1L-PEG+ASC were established. Rate of adequate bowel cleansing was 172 of 195 (88.2%) in the 1L-PEG+ASC group versus 149 of 193 (77.2%) in the 4L-PEG treatment; 95% CI mean difference, 3.0%-19%; *P* value for superiority, .007.

SUPPLEMENTARY TABLE 1. Patient characteristics in the efficacy and compliance sets

Variable	Efficacy set (n = 374)		Compliance/acceptability/tolerability set (n = 382)		
	1L-PEG+ASC (n = 188)	4L-PEG (n = 186)	1L-PEG+ASC (n = 192)	4L-PEG (n = 190)	*P* value
Gender, male/female	85/110	99/94	82/110	97/93	.126
Mean age (standard deviation), y	59.5 (11.2)	60.0 (12.1)	59.4 (11.3)	60.1 (12.0)	.543
Mean body mass index (standard deviation), kg/m^2	25.6 (4.2)	25.3 (4.3)	25.6 (4.2)	25.3 (4.3)	.558
Setting					.792
Outpatient	181 (96.3)	177 (95.2)	184 (95.8)	180 (94.7)	
Inpatient	7 (3.7)	9 (4.8)	8 (4.2)	10 (5.3)	
Indication for colonoscopy					.296
Diagnostic colonoscopy	47 (25.0)	50 (26.9)	47 (24.5)	50 (26.3)	
Screening (fecal immunochemical test positive)	94 (50.0)	101 (54.3)	97 (50.5)	105 (55.3)	
Surveillance for colonic neoplasia	47 (25.0)	35 (18.8)	48 (25.0)	35 (18.4)	

Values are n (%) unless otherwise defined.
PEG, Polyethylene glycol; *PEG+ASC*, polyethylene glycol plus ascorbate.

SUPPLEMENTARY TABLE 2. Univariate and multivariable logistic regression analysis: risk factors for segmental cleansing levels

	Adequate BBPS segment scores*				High BBPS segment scores†			
	Univariate analysis		Multivariable analysis		Univariate analysis		Multivariable analysis	
	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
Treatment arm								
4L-PEG	1		1		1		1	
1L-PEG+ASC	2.72 (1.48-5.00)	.003	2.63 (1.38-5.00)	.005	1.57 (1.15-2.14)	.009	1.77 (1.23-2.53)	.001
Gender								
Female	1				1			
Male	.60 (.31-1.15)	.117	NE		.68 (.40-1.18)	.176	NE	
Patient age, y								
18-64	1		NE		1		1	
>64	.69 (.37-1.28)	.231			.69 (.50-0.96)	.031	.73 (.52-1.03)	.072
Body mass index, kg/m^2			NE				NE	
<30	1				1			
>29	.80 (.30-2.11)	.656			.97 (.41-2.29)	.943		
Indication for colonoscopy			NE					
Surveillance	1				1		1	
Screening, fecal immunochemical test positive	1.00 (.47-2.15)	.989			2.05 (1.45-2.91)	<.001	2.28 (1.55-3.37)	<.001
Diagnostic	.96 (.39-2.36)	.905			.97 (.65-1.45)	.895	1.00 (.63-1.62)	.986
Compliance with bowel preparation intake								
Poor (<75% drug intake)	1		1		1		NE	
Good (>75% drug intake)	2.98 (.86-10.29)	.084	2.32 (.32-16.6)	.245	1.63 (.63-4.19)	.316		
Time from preparation to colonoscopy			NE				NE	
<5 h	1				1			
≥5 h	.85 (.46-1.57)	.597			1.10 (.70-1.72)	.66		
Timing of colonoscopy			NE				NE	
Morning	1				1			
Afternoon	.85 (.46-1.57)	.608			.70 (.40-1.23)	.218		
Sedation			NE				NE	
Midazolam and fentanyl	1				1			
Propofol	.72 (.38-1.36)	.309			1.51 (.75-3.03)	.241		
Colonoscopy phase								
Withdrawal	1		1		1		1	
Insertion	.26 (.18-.38)	<.001	.25 (.17-.37)	<.001	.27 (.23-.32)	<.001	.24 (.20-.29)	<.001
Colonoscopy duration (as continuous variable)	1.01 (.98-1.03)	.499	NE		1.01 (.99-1.03)	.293	NE	
Colon location								
Right-sided colon	1		1		1		1	
Left-sided colon	.96 (.75-1.24)	.752	.96 (.72-1.27)	.751	1.20 (.92-1.55)	.176	1.12 (.97-1.30)	.142
Transverse colon	1.67 (1.21-2.30)	.002	1.71 (1.23-2.38)	.004	2.14 (1.64-2.80)	.002	1.62 (1.39-1.87)	<.001
Polyp detection			NE				NE	
No polyps	1				1			
At least 1 polyp	.96 (.51-1.85)	.909			.70 (.40-1.22)	.213		

BBPS, Boston Bowel Preparation Scale; *CI*, confidence interval; *PEG*, polyethylene glycol; *PEG+ASC*, polyethylene glycol plus ascorbate; *NE*, not entered.
*Adequate, BBPS segment scores of 2-3 versus 0-1.
†High, BBPS segment scores of 3 versus 0-2.

SUPPLEMENTARY TABLE 3. Compliance and acceptability (patient diary responses)

Patient diary response*	1L-PEG+ASC (n = 192)	4L-PEG (n = 190)	*P* value
Patient compliance (≥75% taken)			
Dose 1, bowel preparation	192 (100)	185 (97.4)	.030
Dose 2, bowel preparation	190 (99.0)	177 (93.2)	.006
Overall,† bowel preparation	190 (99.0)	176 (92.6)	.002
Mandatory fluids	183 (95.3)	177 (93.2)	.388
Adjusted fluid intake	127 (66.1)	113 (59.5)	.204
Compliant to dietary restrictions	191 (99.5)	186 (97.9)	.214
How long did it take to complete your bowel prep?			
Dose 1, mean time (interquartile range), min	65 (25-35)	196 (15-180)	<.001
Dose 2, mean time (interquartile range), min	45 (30-35)	118 (90-130)	<.001
Very or quite easy-to-follow instructions for preparation	174 (90.6)	161 (84.7)	.189
Very or quite easy-to-consume the bowel preparation	145 (75.5)	121 (63.7)	<.001
Very or quite easy-to-consume drink the recommended volume of additional clear fluids	183 (95.3)	123 (64.7)	<.001
None or little embarrassment during bowel preparation	106 (55.2)	96 (50.5)	.288
Taste pleasant or acceptable	102 (53.1)	106 (55.8)	.685
Did not interfere at all or interfered a little in normal daily activities	123 (64.1)	110 (57.9)	.443
At least 1 stop during the travel	10 (5.2)	3 (1.6)	.086
Willingness to repeat the same preparation for future endoscopies	148 (77.1)	127 (66.8)	.027

Values are n (%) unless otherwise defined.
FAS, Full analysis set; *PEG*, polyethylene glycol; *PEG+ASC*, polyethylene glycol plus ascorbate.
*Numeric results and percentage are based on those FAS patients who completed the patient diary (excluding FAS patients with missing data).
†Overall, patients taking ≥75% of both doses of the bowel preparation.

SUPPLEMENTARY TABLE 4. Self-reported side effects after bowel preparation

	Moderate or severe side effects				Severe side effects			
	1L-PEG+ASC (n = 192)	4L-PEG (n = 190)	Odds ratio (95% CI)	*P* value	1L-PEG+ASC (n = 192)	4L-PEG (n = 190)	Odds ratio (95% CI)	*P* value
Nausea or vomiting	63 (32.8)	48 (25.3)	1.45 (.93-2.26)	.104	28 (14.6)	19 (10.0)	1.53 (.83-2.90)	.175
Bowel distension	43 (22.4)	47 (24.7)	.88 (.55-1.39)	.581	9 (4.7)	8 (4.2)	1.12 (.54-2.31)	.761
Cramps/pain, n (%)	28 (14.6)	31 (16.3)	.88 (.50-1.52)	.640	7 (3.7)	3 (1.6)	2.36 (.86-8.16)	.179
Excessive dryness of the mouth (xerostomia)	7 (3.6)	0 (.0)	>1.45	.014	2 (1.1)	0 (.0)		.499
Anal irritation	4 (2.1)	6 (3.2)	.65 (.35-1.20)	.169	2 (1.0)	3 (1.6)	.66 (.09-4.35)	.662
Chills	4 (2.1)	9 (4.7)	.43 (.11-1.37)	.164	2 (1.0)	5 (2.6)	.39 (.06-1.83)	.263
Dizziness or headache	6 (3.1)	1 (.5)	.36 (.08-1.27)	.137	2 (1.0)	1 (.5)	2.00 (.10-125)	.999
Sleep disturbance	43 (22.4)	65 (34.2)	.55 (.35-0.87)	.011	16 (8.3)	32 (16.8)	.45 (.23-0.84)	.014
At least 1 symptom	107 (55.7)	98 (51.6)	1.18 (.80-1.74)	.399	40 (20.8)	49 (25.8)	.76 (.47-1.22)	.253
More than 1 symptom	54 (28.1)	61 (32.1)	.83 (.53-1.28)	.397	19 (9.9)	16 (8.4)	1.19 (.59-2.42)	.618

Values are n (%).
CI, Confidence interval; *PEG*, polyethylene glycol; *PEG+ASC*, polyethylene glycol plus ascorbate.

SUPPLEMENTARY TABLE 5. Vital signs and results from laboratory tests at the baseline visit (before bowel preparation intake)

	1L-PEG+ASC Mean (95% CI)	4L-PEG Mean (95% CI)	Difference (Δ) Mean (95% CI)	*P* value
Diastolic blood pressure, mm Hg	76.0 (74.0-77.0)	77.0 (76.0-79.0)	−1.4 (−3.5 to .7)	.183
Systolic blood pressure, mm Hg	125.0 (123.0-127.0)	123.0 (121.0-125.0)	1.3 (−1.5 to 4.2)	.363
Heart rate, bpm	70.0 (69.0-71.0)	70.0 (69.0-72.0)	.39 (−1.5 to 2.3)	.686
Body temperature, °C	36.0 (36.1-36.2)	36.0 (36.1-36.2)	.0 (.0-.1)	.935
Sodium, mEq/L	141.4 (141-142.0)	141.4 (140.9-142.0)	.0 (−.6 to .7)	.937
Potassium, mEq/L	4.4 (4.3-4.5)	4.3 (4.0-4.5)	.1 (−.1 to .2)	.286
Chlorine, mEq/L	104.1 (104.3-105.0)	104.4 (104.2-105.4)	−.7 (−1.6 to .18)	.118
Creatinine, mg/dL	.79 (.74-.83)	.79 (.74-.82)	.0 (−.1 to .1)	.894

CI, Confidence interval; *PEG*, polyethylene glycol; *PEG+ASC*, polyethylene glycol plus ascorbate.

SUPPLEMENTARY TABLE 6. Comparison of mean changes (Δ) of vital signs and of serum electrolyte levels in the 2 study groups before and after bowel preparation

	1L-PEG+ASC			4L-PEG			
	Mean change (Δ)*	95% CI	Range	Mean change (Δ)*	95% CI	Range	*P* value
Diastolic blood pressure, mm Hg	2.4†	(.34-4.4)	(−38.0 to 80.0)	.9	(−1.1 to 3.0)	(−50.0 to 58.0)	.022
Systolic blood pressure, mm Hg	8.5†	(5.1-11.9)	(−70.0 to 88.0)	9.5†	(6.0-11.9)	(−65.0 to 95.0)	.689
Heart rate, bpm	6.3	(2.3-6.8)	(−34.0 to 56.0)	4.6	(4.1-8.6)	(−27.0 to 97.0)	.276
Body temperature, °C	0.1	(.0-.1)	(−1.0-2.1)	.1	(.0-.1)	(−1.1 to 1.2)	.775
Sodium, mEq/L	1.3†	(.4-2.2)	(−29.0 to 11.0)	−1.7†	(−2.6 to −.8)	(−44.0 to 5.0)	<.001
Potassium, mEq/L	−1.5	(−3.1 to .1)	(−1.4 to 1.5)	−.5	(−2.1 to 1.0)	(−2.1 to .5)	.397
Chlorine, mEq/L	4.4†	(2.4-6.4)	(−2.0 to 48.0)	−1.0	(−2.9 to .8)	(−6.0 to 4.0)	<.001
Creatinine, mg/dL	0.0	(.1-.1)	(.5-.2)	.0	(.1-.1)	(.3-.2)	.680

CI, Confidence interval; *PEG*, polyethylene glycol; *PEG+ASC*, polyethylene glycol plus ascorbate.
*Δ = mean changes before and after bowel preparation.
†Significant changes of the values pre– and post–bowel preparation within study arm.

SUPPLEMENTARY TABLE 7. Sodium and chloride variations

Sodium (NA) 1L-PEG+ASC group (n = 114): The mean baseline sodium level was 141.5 (standard deviation [SD], 2.4; median, 141; interquartile range [IQR], 140-146). In detail, 112 of 114 participants (98.2%) had NA+ level within the normal range (normal, 135-146 mEq/L), whereas 1.8% (2/114) and .0% (0/114) had higher and lower NA+ levels, respectively. The NA+ level increased after intake of 1L-PEG+ASC (mean, 142.8; SD, 4.2; median, 143.0; IQR, 142-145). In detail, shifts occurred in 14 patients with normal baseline sodium level. Of these, 12 (87.5%) had higher sodium level (mean sodium level, 148.25; range, 147-150; median, 148; mean shift, 5.6; range, 3-6) and the remaining 2 (14.3%) had lower sodium levels (see Table below).
Sodium 4L-PEG group (n = 121) The mean baseline sodium level was 141.4 (SD, 2.6; median, 141; IQR, 140-143). In detail, a total of 118/121 (97.5%) participants had NA+ level above the normal range normal: 135-146 mEq/L), while 1.7% (2/121) and 0.9% (1/121) had higher and lower NA+ level, respectively. The NA+ level decreased after intake of 4L-PEG (mean, 140.0; SD, 5.6; median, 140.0; IQR, 138-142). In detail, shifts occurred in 7 patients with normal baseline sodium level. Of these, 6 (85.7%) had lower sodium level (mean sodium level, 122.3; range, 102-134; median, 131; mean shift, –18.5; range, –44 to –6; median shift, –8) and 1 patient (14.3%) had lower sodium levels (see Table 9A).
Chloride (CL) 1L-PEG+ASC group (n = 34): The mean baseline chloride level was 103.5 (SD, 3.1; median, 104; IQR, 102-105). In detail, 27 of 34 patients (79.4%) had CL level above the normal range (normal, 96-106 mEq/L), whereas 17.6% (6/34) and 2.9% (1/34) had higher and lower CL levels, respectively. The CL level increased after intake of 1L-PEG+ASC (mean, 107.9; SD, 8.3; median, 106.5; IQR, 104.3-110). In detail, shifts occurred in 12 of 27 (44.4%) patients with normal baseline chloride level. All of these patients had higher CL level (mean chloride level, 113; range, 107-150; median, 110; mean shift, 9.6; range, 3-48) (see Table 9B).
CL 4L-PEG group (n = 39): The CL level did not change significantly after bowel preparation.

TABLE 7A. Sodium level before and after bowel preparation

ID.Scheda	ID.Ente	NA before	NA after	Shift	Value NA after	Arm
75	144	138	149	11	Abnormal+	1L-PEG+ASC
18	220	141	148	7	Abnormal+	1L-PEG+ASC
2	220	143	150	7	Abnormal+	1L-PEG+ASC
127	144	142	148	6	Abnormal+	1L-PEG+ASC
13	220	144	150	6	Abnormal+	1L-PEG+ASC
52	48	141	147	6	Abnormal+	1L-PEG+ASC
97	144	141	147	6	Abnormal+	1L-PEG+ASC
49	220	145	150	5	Abnormal+	1L-PEG+ASC
74	144	144	148	4	Abnormal+	1L-PEG+ASC
107	144	144	147	3	Abnormal+	1L-PEG+ASC
27	304	144	147	3	Abnormal+	1L-PEG+ASC
6	220	145	148	3	Abnormal+	1L-PEG+ASC
141	144	141	133	–8	Abnormal–	1L-PEG+ASC
10	220	141	112	–29	Abnormal–	1L-PEG+ASC
50	220	144	147	3	Abnormal+	4L-PEG
113	144	137	131	–6	Abnormal–	4L-PEG
118	144	142	134	–8	Abnormal–	4L-PEG
14	220	142	104	–38	Abnormal–	4L-PEG
148	144	140	132	–8	Abnormal–	4L-PEG
16	220	146	102	–44	Abnormal–	4L-PEG
55	144	138	131	–7	Abnormal–	4L-PEG

TABLE 7B. CL level before and after bowel preparation

ID.Scheda	ID.Ente	Cloro baseline	Cloro after		CL.post	Arm
10	220	103	112	9	Abnormal+	1L-PEG+ASC
102	144	103	108	5	Abnormal+	1L-PEG+ASC
13	220	102	150	48	Abnormal+	1L-PEG+ASC
18	220	103	110	7	Abnormal+	1L-PEG+ASC
19	220	104	110	6	Abnormal+	1L-PEG+ASC
2	220	102	110	8	Abnormal+	1L-PEG+ASC
26	220	105	108	3	Abnormal+	1L-PEG+ASC
35	220	105	109	4	Abnormal+	1L-PEG+ASC
40	220	104	107	3	Abnormal+	1L-PEG+ASC
42	220	101	110	9	Abnormal+	1L-PEG+ASC
49	220	104	110	6	Abnormal+	1L-PEG+ASC
58	220	104	111	7	Abnormal+	1L-PEG+ASC

PEG, polyethylene glycol; *PEG+ASC*, polyethylene glycol plus ascorbate.

SUPPLEMENTARY TABLE 8. Histology and dysplasia of detected adenomas by treatment arm

	1L-PEG+ASC	4L-PEG	*P* value
Polyps >9 mm			.514
Adenocarcinoma	1 (2.9)	3 (8.0)	
Adenoma	24 (70.6)	23 (63.9)	
Serrated	2 (5.9)	1 (2.8)	
Hyperplastic	1 (2.9)	3 (8.0)	
Missing value/not removed	6 (17.6)	6 (16.7)	
Total	34	36	
Polyps 6-9 mm			.677
Adenocarcinoma	0 (2.9)	1 (3.7)	
Adenoma	16 (59.3)	18 (66.7)	
Serrated	3 (11.1)	2 (7.4)	
Hyperplastic	5 (18.5)	5 (18.5)	
Missing value/not removed	3 (11.1)	1 (3.7)	
Total	27	27	
Polyps <6 mm			.722
Adenoma	111 (60.7)	108 (64.3)	
Serrated	8 (4.4)	4 (2.4)	
Hyperplastic	58 (31.7)	50 (29.8)	
Missing value/not removed	6 (3.3)	6 (3.6)	
Total	183	168	
General			
Total no. of polyps	244	231	
Total no. of adenomas or adenocarcinomas	152 (62.3)	153 (66.2)	.389
Total no. of adenomas with high-grade dysplasia	14 (5.7)	24 (10.4)	.065

Values n (%) unless otherwise defined.
PEG, Polyethylene glycol; *PEG+ASC*, polyethylene glycol plus ascorbate.

SUPPLEMENTARY TABLE 9. Morphology of detected adenomas and location of detected polyps

	1L-PEG+ASC	4L-PEG	Odds ratio* (95% CI)
Morphology of detected polyps			
Adenoma	152	153	
Pedunculated	23 (15.1)	15 (9.8)	1
Sessile	105 (69.1)	100 (65.4)	.68 (.27-1.71)
Flat	24 (15.8)	38 (24.8)	.41 (.15-1.13)
Not adenomatous polyps	92	78	
Pedunculated	6 (6.5)	3 (3.8)	1
Sessile	62 (67.4)	51 (65.4)	.61 (.14-2.67)
Flat	24 (15.8)	22 (35.4)	.52 (.11-2.57)
Missing value	0 (.0)	1 (1.3)	
Colon location of detected polyps			
Adenoma	152	153	
Rectosigmoid	43 (28.3)	34 (22.2)	1
Proximal†	109 (71.7)	119 (77.8)	.72 (.42-1.25)
Not adenomatous polyps	92	78	
Rectosigmoid	34 (37.0)	34 (43.6)	1
Proximal†	58 (63.0)	44 (56.4)	1.31 (.70-2.47)
General			
Total no. of polyps	244	231	
Pedunculated	29 (11.9)	18 (7.8)	1
Sessile	167 (68.4)	151 (65.4)	.69 (.32-1.48)
Flat	48 (19.7)	61 (26.4)	.49 (.21-1.13)
Rectosigmoid	77 (31.6)	68 (29.4)	1
Proximal†	167 (68.4)	163 (70.6)	1.11 (.72-1.69)

Values are n (%) unless otherwise defined.

CI, Confidence interval; *PEG*, polyethylene glycol; *PEG+ASC*, polyethylene glycol plus ascorbate.

*The odds ratio compares the odds of the polyp characteristics among 1L-PEG+ASC patients with the odds of the polyp characteristics among 4L-PEG patients.

†Proximal is defined as descending colon, transverse colon, ascending colon, or cecum.