

## Alimentary Tract

## Mannitol for bowel preparation: Efficacy and safety results from the SATISFACTION randomised clinical trial



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## ARTICLE INFO

## Article history:

Received 9 May 2024

Accepted 27 September 2024

Available online 18 November 2024

## Keywords:

Bowel preparation

Colonoscopy

Oral mannitol

PEG-ASC

## ABSTRACT

**Background:** Bowel preparation represents a significant issue to high-quality colonoscopy. Oral mannitol requires a single dose, is of low volume, and has a pleasant taste and rapid action.

**Aims:** This SATISFACTION study compared single-dose (same day) oral mannitol 100 g/750 mL with standard split-dose PEG-ASC 2 L (MoviPrep®).

**Methods:** The primary endpoint was the proportion of patients with adequate bowel cleansing. Secondary endpoints included efficacy (adenoma detection rate, caecal intubation rate, time of evacuation), safety (intestinal gases concentration, haemato-chemical parameters, adverse events), and patient satisfaction.

**Results:** The study included 703 patients (352 treated with mannitol and 351 with PEG-ASC). Mannitol was not inferior to PEG-ASC for the primary endpoint (91.1 % and 95.5 %, respectively; p-value for the

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non-inferiority =0.0131). There was no significant difference for secondary efficacy endpoints. The acceptability profile was significantly better in the mannitol group for ease of use, taste, and willingness to reuse ( $p < 0.0001$  for all). The concentration of intestinal gases ( $H_2$ ,  $CH_4$ ) was similar between groups and well below those potentially critical.

**Conclusions:** The SATISFACTION study indicated that low-volume, single-dose mannitol may satisfy an unmet clinical need since it was more acceptable to the patient and not inferior to the split-dose PEG-ASC for bowel cleansing efficacy.

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## 1. Introduction

The ideal bowel cleansing agent should combine effectiveness, safety, easy administration, good patient acceptance, and low cost [1]. Most currently available preparations are reasonably effective and safe; however, patients' acceptance is still a significant issue, possibly representing a major obstacle to screening programmes and surveillance schedules [1,2]. In this respect, split-dose regimens and low-volume bowel cleansing agents, particularly those based on polyethylene glycol (PEG), have progressively replaced day-before preparations and high-volume formulations because of their higher efficacy and patients' preference. Nonetheless, bowel preparation remains a highly burdensome aspect of the procedure, as perceived by several patients [3–6].

Mannitol is a sugar alcohol that is partly absorbed following oral administration. It acts as an osmotic laxative and was widely used in the late 1970s and early 1980s as a bowel cleansing agent for colonoscopy [7,8]. The preparation with mannitol had extensive diffusion, and despite its use having to be considered off-label, it is still largely utilised in some Latin American countries, mainly in Brazil, where it is reported to be effective, to have high patient acceptance, and to lack significant adverse reactions [9].

In Europe and the U.S., mannitol has been discontinued in the past century following a few cases of intestinal gas explosion solely attributed to an increased intestinal concentration of methane ( $CH_4$ ) and/or hydrogen ( $H_2$ ) resulting from bacterial fermentation of non-absorbable sugar [10]. However, this hypothesis has never been confirmed, while several other intestinal gas explosions have also been reported using standard enema or polyethylene glycol (PEG) preparations [5,11]. Interestingly, intestinal gas explosion has almost disappeared in modern endoscopy despite the worldwide increase of procedures, even in countries where the use of mannitol is currently widespread [12–14]. Thus, should its good safety profile be confirmed, mannitol is a valuable alternative to current colonic preparations due to its excellent efficacy and potentially optimal patient acceptance. Therefore, we have conducted the SATISFACTION project, which included trials to assess whether a single dose of low-volume oral mannitol administered 4 h before colonoscopy might represent a valid alternative to traditional split-dose PEG-ASC colon preparation as regards efficacy, safety, and patients' satisfaction.

## 2. Materials and methods

### 2.1. Study design and aims

The study consisted of a Phase II/III, international, multicentre, randomized, parallel-group, endoscopist-blinded, dose-finding/non-inferiority study. In the Phase II part of the study, three single doses of oral mannitol (50 g, 100 g, and 150 g) were comparatively evaluated, and the 100 g/750 mL dose was identified as the optimal amount in terms of efficacy, safety, and tolerability [15]. As a further contribution to the choice of the optimal dose of

mannitol, a pharmacokinetic sub-study was carried out as part of the Phase II study, which showed dose-dependent kinetics with a bioavailability of around 20 % [16].

The Phase III part of the study was designed to demonstrate the non-inferiority of the low-volume, single dose of mannitol administered 4 h before colonoscopy when compared to the standard split-dose 2 L PEG-ASC preparation in terms of bowel cleansing efficacy and its superiority in terms of patient acceptance. In addition, all patients receiving oral mannitol or PEG-ASC underwent intestinal  $H_2$  and  $CH_4$  levels measurements at the different colonic segments to evaluate the relative risk between the two drugs of causing potentially critical gas concentrations. Results from the Phase III study are presented in this paper.

The study was conducted in 30 centres in Italy, Germany, France, and Russia between March 2021 and July 2021. The Ethics Committees of each center approved the study protocol. The trial protocol was registered in ClinicalTrials.gov (<https://clinicaltrials.gov/ct2/show/NCT04759885>) and in EudraCT (eudract\_number:2019–002,856–18). The design of the study is summarised in the Fig. 1. The bowel preparation procedure was performed according to ESGE guidelines [3].

### 2.2. Treatments

Enrolled patients were randomised in a 1:1 ratio to one of the following two treatment arms:

- Mannitol powder 100 g dissolved in 750 mL water to be drunk in 30 min on the colonoscopy day, with consumption completed at least 4 h before colonoscopy; following this treatment, patients could drink additional clear liquids (about 1 L) to prevent dehydrated.
- 2 L PEG-ASC administered according to a split-dose regimen: the first liter over 1–2 h the evening before colonoscopy, and the second liter the morning of the procedure, with consumption completed at least 4 h before the colonoscopy; patient should drink 500 mL of clear liquid after each dose. §In the course of this treatment, patients were encouraged to drink additional clear liquids (at least 1000 mL) to avoid feeling very thirsty and dehydrated.

Unblinded investigators assigned and reported the treatment groups as per randomization list. All endoscopists performing study colonoscopies were blinded to the treatment allocation. Experienced endoscopists underwent specific training to decrease interobserver variability in the evaluation of bowel cleansing, according to the Boston Bowel Preparation Scale (BBPS), and intestinal gas measurement techniques.

### 2.3. Selection of patients

The inclusion criteria were the ability of the patient to provide signed informed consent to participate in the study, age over 18

## PHASE III (NON-INFERIORITY)

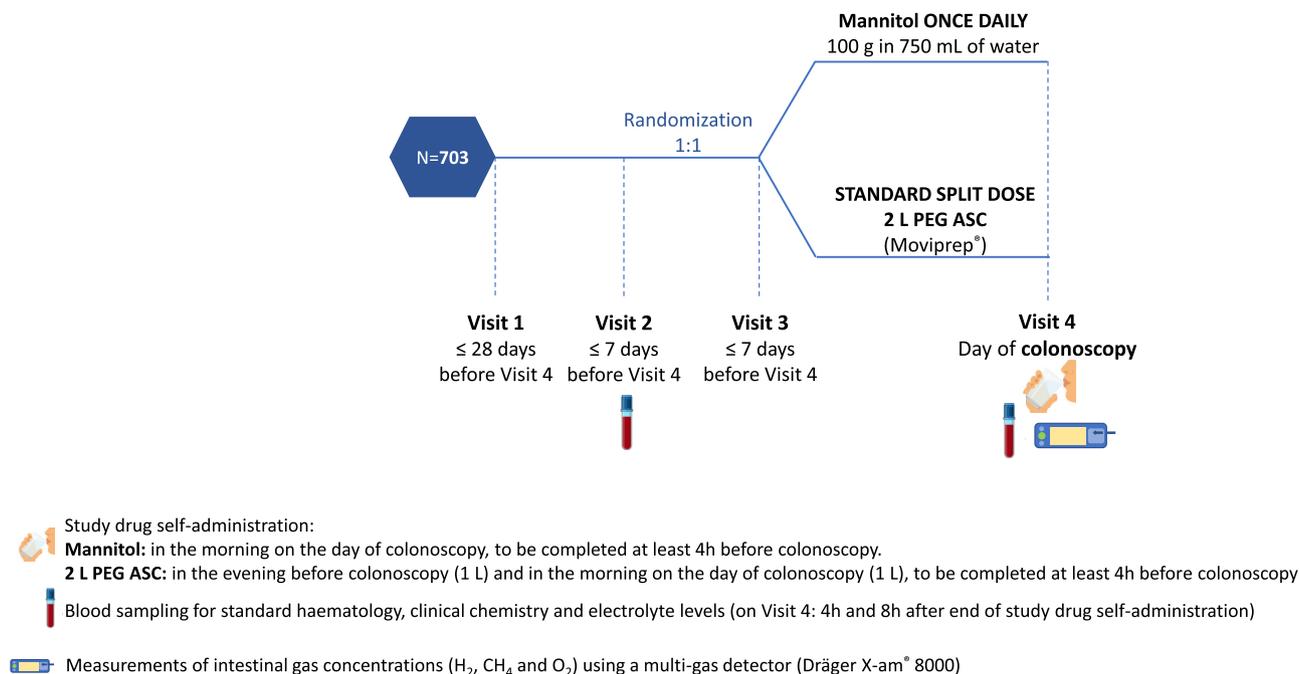


Fig. 1. Study design.

years, men and women scheduled for elective (screening, surveillance, or diagnostic) colonoscopy to be prepared and performed according to ESGE guidelines [3]. Patients had to be willing and able to complete the entire study and comply with instructions. The main exclusion criteria were pregnancy or breastfeeding, severe renal failure (eGFR <30 mL/min/1.73 m<sup>2</sup>), severe heart failure (NYHA Class III–IV), severe anemia (Hb <8 g/dL), clinically active inflammatory bowel disease, severe chronic liver disease (Child-Pugh class B or C), clinically significant electrolyte imbalance, recent (<6 months) symptomatic acute ischaemic heart disease, history of major gastrointestinal surgery, current use of laxatives and ongoing therapy affecting colonic motility. Further information on the experimental design is included in the supplementary material.

## 2.4. Study endpoints

### 2.4.1. Primary efficacy endpoint

The proportion of patients with adequate bowel cleansing, defined as a BBPS total score  $\geq 6$ , with a score for each of the three colon segments (right; transverse, including flexures; left, including the sigmoid and rectum)  $\geq 2$  during colonoscopy after standard washing and air insufflation for luminal distension [17].

### 2.4.2. Secondary efficacy endpoints

- adenoma detection rate, defined as the percentage of patients with at least one adenoma detected;
- caecal intubation rate, defined as the percentage of patients with the appendiceal orifice visible to the endoscopist;
- time to evacuation, calculated as the time from the start of the study treatment assumption to the first evacuation.

### 2.4.3. Adherence and acceptability endpoints

- adherence: study drug completely taken, partially taken (taken but not completely), not taken;
- taste: numeric rating scale (NRS) (0 = terrible to 10 = very good);

- ease of use: NRS (0 = very difficult to 10 = very easy);
- willingness to repeat the preparation with the same product (yes/no);
- satisfaction with bowel preparation (yes/no).

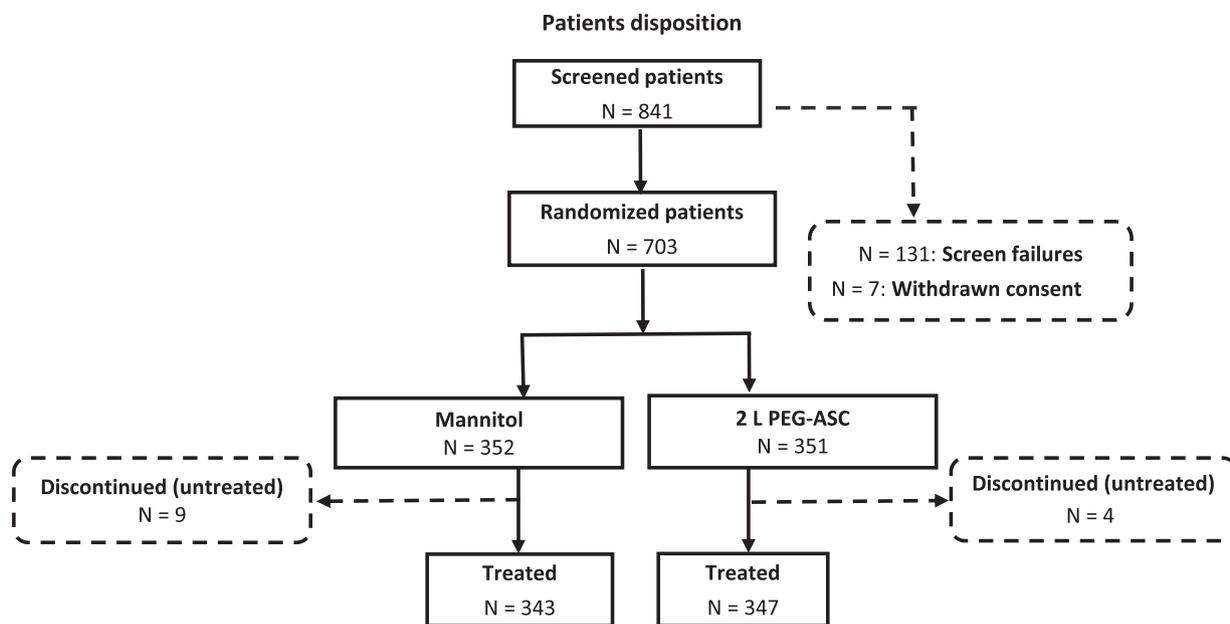
### 2.4.4. Safety endpoints

- intestinal gas concentration: the proportion of patients in a safe condition, defined as the absence in any colon segment of potentially critical levels of  $H_2$  and/or  $CH_4$  ( $>4$  % vol and  $>5$  % vol, respectively) before standard washing and air insufflation for luminal distension only in the rectosigmoid junction, and after standard washing and air insufflation for luminal distension in the right colon, transverse colon and rectosigmoid junction [11,18];
- adverse events (AEs): incidence of AEs related to treatment starting from the beginning of study drug administration;
- haematological and chemical parameters: proportion of patients with a clinically significant change from baseline in haematological and chemical parameters 4 h and 8 h after completion of study drug intake;
- vital signs: proportion of patients with a clinically significant change from baseline in pulse oximetry, blood pressure and heart rate measured during colonoscopy.

A change of a given parameter was considered clinically significant if it caused an additional control or a medical intervention.

### 2.4.5. Gas measurement

Measurements were made using a validated multi-gas monitor (X-am 8000, Dräger Safety AG & Co. KGaA) connected to an ERCP cannula through a three-way faucet valve and a connector. Hydrogen and  $O_2$  levels are measured as % of volume (%vol) and Methane is measured as % volume regarding Lower Explosive Limit, converted (LEL) in % volume during the analysis [18].



Study Populations

	Mannitol (N=352)	PEG-ASC (N=351)	Total (N=703)
Safety Set, n (%)	343 (97.44)	347 (98.86)	690 (98.15)
Full Analysis Set (FAS), n %	333 (94.60)	347 (98.86)	680 (96.73)
Per Protocol (PP) population, n %	325 (92.33)	332 (94.59)	657 (93.46)

**Safety set:** all patients who take the study preparation, even only partially.

**Full Analysis Set (FAS):** all randomized patients who take the study preparation, even only partially, undergo the colonoscopy, and have a BBPS available for at least one colon segment after standard washing and air insufflation for luminal distension.

**Per protocol (PP):** all randomized patients who take completely the study preparation, undergo the colonoscopy with no significant protocol violations.

Fig. 2. Analysis populations.

2.4.6. Statistical methods and ethics

Considering a percentage of efficacy of Moviprep equal to 85 % [19], non-inferiority has been assessed evaluating if the lower limit of the 95 % confidence interval for the difference between the two proportions was less than -8 %, corresponds to a relative risk of 0.906. The sample size resulted in 696 patients (348 for each treatment).

More details are reported in the supplementary material.

3. Results

Globally, 703 patients were randomised between March and July 2021. The analyzed populations are summarised in Fig. 2 and demographics in Table 1.

3.1. Primary efficacy endpoint

Adequate bowel cleansing was reported for 91.1 % of the mannitol group and 95.5 % of the PEG-ASC group (per protocol analysis). The between-group relative risk is 0.9539 (95 % CI 0.9121 to 0.9936), demonstrating the non-inferiority of mannitol in a single

dose compared to PEG-ASC in a split-dose regimen since the inferior 95 % CI did not cross the non-inferiority relative risk limit (0.9060). The one-sided p-value for the Farrington–Manning non-inferiority test was statistically significant (p = 0.0131).

Results for the complete analysis set population were very similar. Most patients presented adequate bowel cleansing in both groups: 90.4 % in the mannitol group and 94.8 % in the PEG-ASC group. The between-group relative risk is 0.9534 (95 % CI 0.9104 to 0.9945), confirming the non-inferiority of mannitol compared to PEG-ASC since the inferior 95 % CI did not cross the non-inferiority relative risk limit (0.9060, one-sided p-value p = 0.0158).

For the per-protocol (PP) population, the mean BBPS total score (range 0–9) was 7.7 ± 1.78 in the mannitol group and 7.9 ± 1.50 in the PEG-ASC group as reported in Table 2.

3.2. Secondary efficacy endpoints

3.2.1. Adenoma detection rate

The proportion of patients with at least one adenoma was similar in the two treatment groups: 0.29 (95 % CI 0.25 to 0.34) in the mannitol group and 0.30 (95 % CI 0.25 to 0.34) in the PEG-ASC

**Table 1**  
Demographics and baseline characteristics of enrolled patients; Randomized Set.

	Mannitol (N = 352)	PEG-ASC (N = 351)	Total (N = 703)
Age (years)			
Mean (SD)	54.8 (12.65)	54.6 (12.71)	54.7 (12.67)
Median	56.0	55.0	55.0
Q1; Q3	47.0; 65.0	47.0; 63.0	47.0; 64.0
Min; Max	20; 84	19; 86	19; 86
Sex, n (%)			
Male	133 (37.78)	155 (44.16)	288 (40.97)
Female	219 (62.22)	196 (55.84)	415 (59.03)
Ethnicity, n (%)			
Hispanic or Latino	4 (1.14)	4 (1.14)	8 (1.14)
Not Hispanic or Latino	343 (97.44)	344 (98.01)	687 (97.72)
Not reported	5 (1.42)	3 (0.85)	8 (1.14)
Patients who performed previous colonoscopies, n (%)	176 (50.00)	182 (51.85)	358 (50.92)
Indication for current colonoscopy, n (%)			
CRC Screening following positive FOBT	17 (4.83)	20 (5.70)	37 (5.26)
Surveillance post Polypectomy / Mucosectomy / ESD	43 (12.22)	40 (11.40)	83 (11.81)
Iron deficiency anemia	7 (1.99)	5 (1.42)	12 (1.71)
Rectal bleeding / melena	29 (8.24)	28 (7.98)	57 (8.11)
Abdominal pain/abdominal discomfort/bloating	64 (18.18)	64 (18.23)	128 (18.21)
Constipation	21 (5.97)	28 (7.98)	49 (6.97)
Bowel habit alterations different from constipation	26 (7.39)	23 (6.55)	49 (6.97)
Workup for suspected IBD or MC or other enterocolitis	6 (1.70)	5 (1.42)	11 (1.56)
Suspicious radiologic findings	3 (0.85)	0	3 (0.43)
Other	46 (13.07)	64 (18.23)	110 (15.65)
Comorbidities and risk factors for poor preparation, n (%)			
Patients with diabetes	18 (5.11)	14 (3.99)	32 (4.55)
Patients with dementia	0	0	0
Patients with cirrhosis	0	0	0
Patients with constipation	3 (0.85)	5 (1.42)	8 (1.14)
Patients with stroke	1 (0.28)	0	1 (0.14)
Patients who took narcotics	0	0	0
Patients who took tricyclic antidepressants	0	0	0
Enrolment Countries, n (%)			
Germany	51 (14.49)	49 (13.96)	100 (14.22)
France	6 (1.70)	7 (1.99)	13 (1.85)
Italy	244 (69.32)	244 (69.52)	488 (69.42)
Russia	51 (14.49)	51 (14.53)	102 (14.51)

Q1=1st Quartile; Q3=3rd Quartile; SD=Standard Deviation.

CRC=Colorectal Cancer; FOBT=Fecal Occult Blood Test; ESD=Endoscopic Submucosal Dissection; IBD=Inflammatory Bowel Disease; MC=Microscopic Colitis.

Percentages were computed on patients belonging to the Randomized Set.

group. The between-group difference was  $-0.003$  (95 % CI  $-0.071$  to  $0.066$ ), which was not statistically significant ( $p = 0.9423$ ).

### 3.2.2. Caecal intubation

The proportion of patients with positive caecal intubation was quite similar in the two treatment groups: 0.98 (95 % CI 0.97 to 1) in the mannitol group and 0.99 (95 % CI 0.99 to 1) in the PEG-ASC group. The between-group difference was  $-0.012$  (95 % CI  $-0.029$  to  $0.004$ ), which was not statistically significant ( $p = 0.1690$ ).

### 3.2.3. Time to evacuation

Time to first evacuation, calculated from the start of the study treatment to first evacuation, was much lower for mannitol ( $52.4 \pm 28.6$  min) than for PEG-ASC ( $116.2 \pm 95.4$  min). The difference between the two groups was statistically significant ( $p < 0.0001$ ).

After the end of the intake, the colonoscopy was performed 5.32 h ( $\pm 0.83$ ) in the Mannitol group and 5.10 ( $\pm 1.06$ ) in the Moviprep group.

## 3.3. Adherence and acceptability endpoints

### 3.3.1. Adherence

Treatment adherence was complete in the mannitol group: all patients took the drug completely at the prescribed dose and in

the prescribed manner. Six patients (1.7 %) in the PEG-ASC group assumed the treatment only partially.

### 3.3.2. Easy to use

The mean NRS for ease of use in the safety set population was  $9.3 \pm 1.41$  for mannitol and  $8.5 \pm 2.00$  for PEG-ASC. A maximum score of 10 was given by 65.4 % of the mannitol group versus 47.3 % of the PEG-ASC group (difference: 0.18 [95 % CI 0.11 to 0.25],  $p < 0.0001$ ) (Fig. 3, panel A). On a dichotomous scale of <8 versus 8–10 (i.e., less than good versus good), 92.7 % of the mannitol group versus 77.8 % of the PEG-ASC group gave a score from 8 to 10 (difference: 0.15 [95 % CI 0.10 to 0.20],  $p < 0.0001$ ).

### 3.3.3. Taste

The mean NRS for taste was  $8.3 \pm 1.74$  in the mannitol group and  $5.6 \pm 2.67$  in the PEG-ASC group. On a categorical scale, 31.1 % of the mannitol group versus 4.3 % of the PEG-ASC group gave taste a maximum score of 10 (difference: 0.27 [95 % CI 0.21 to 0.32],  $p < 0.0001$ ). On a dichotomous scale of <8 versus 8–10 (i.e., less than good versus good), 74.8 % of the mannitol group versus 28.8 % of the PEG-ASC group gave a score from 8 to 10 (difference: 0.46 [95 % CI 0.39 to 0.53],  $p < 0.0001$ ) (Fig. 3, panel B).

### 3.3.4. Willingness to use the study preparation

Of the patients in the safety set population, 97.1 % were willing to reuse mannitol and 78.4 % to reuse PEG-ASC. The difference in

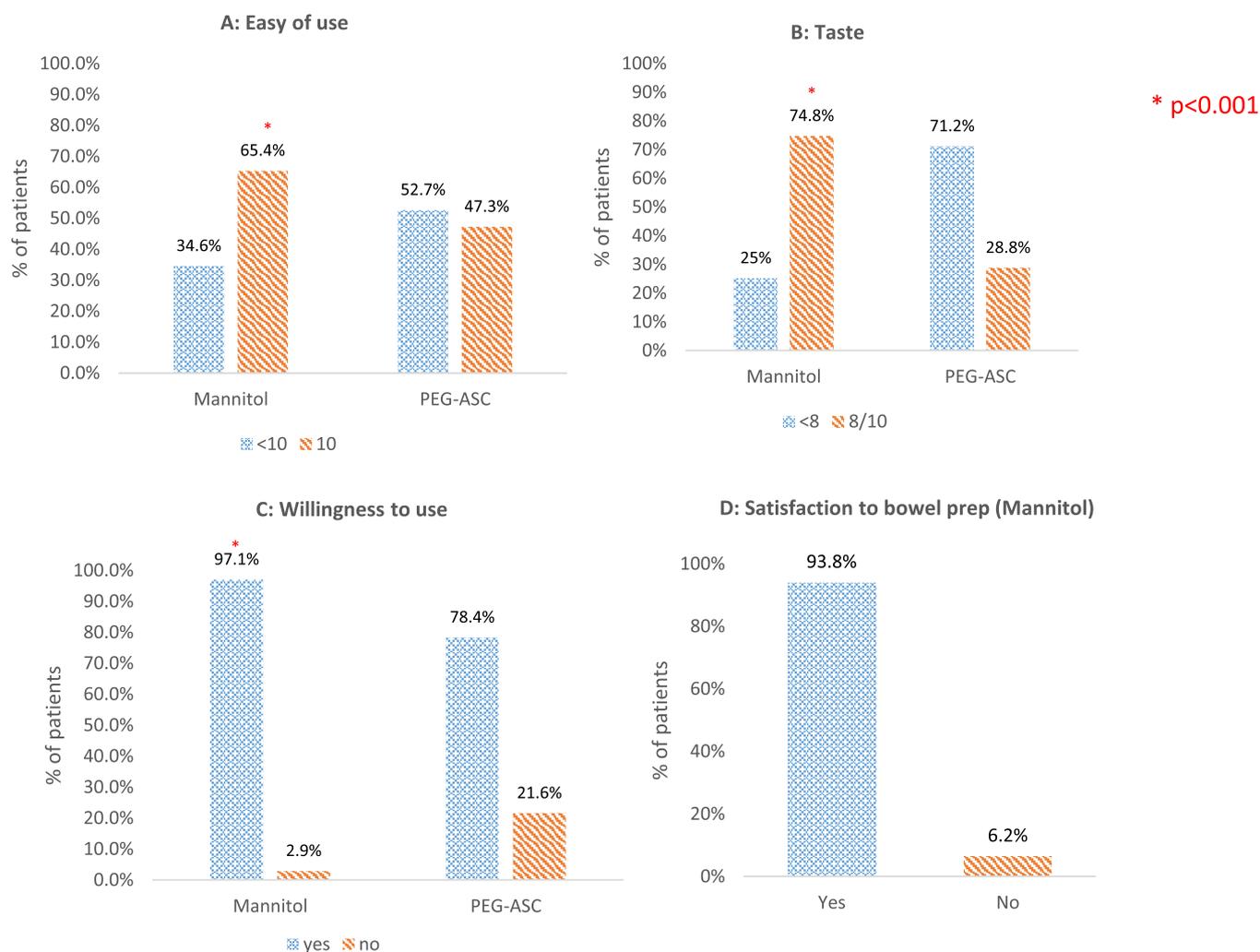


Fig. 3. Acceptability endpoints.

proportions was 0.19 (95 % CI 0.14 to 0.23;  $p < 0.0001$ ) (Fig. 3, panel C).

### 3.3.5. Satisfaction with bowel preparation

Roughly half (50.9 %) of the patients had undergone a previous colonoscopy, and most of them had undergone one (56.4 %), two (19.0 %) or three (11.5 %) colonoscopies. When available, the most common bowel cleansing preparation used during previous colonoscopy was PEG-ASC (24.3 %).

Of the patients treated with mannitol who had undergone a previous colonoscopy, 93.8 % preferred mannitol to the preparation used during their last colonoscopy (Fig. 3, panel D). Of the patients treated with mannitol who had previously undergone bowel preparation with PEG-ASC, 93.3 % stated that mannitol was better, whereas 93.9 % who had previously undergone bowel preparation with another product also said that mannitol was better.

## 3.4. Safety endpoints

### 3.4.1. Intestinal gas concentration

No patient in either the treatment or the standard group presented potentially critical levels of  $H_2$  (>4 % vol) or  $CH_4$  (>5 % vol). The complete results of statistical inference have been reported in detail in a recent publication [18].

### 3.4.2. Adverse events

Table 3 summarizes patients with treatment-emergent adverse events (TEAEs). No severe TEAE was observed in either group. The most common adverse events with mannitol were nausea (2.6 %), vomiting (4.4 %), and dizziness (1.2 %). Differences in the frequency of adverse events related to the drugs under study were not statistically significant.

### 3.4.3. Hematological and chemical parameters

No clinically relevant haematological and chemical abnormality occurred in either group. Two patients in the mannitol group had an abnormal hematological value (mild leucocytosis) 4 and 8 h after the completion of the study drug administration. Chemical parameters abnormal values were reported for twelve patients (3.5 %) in the mannitol group and five patients (1.4 %) in the PEG-ASC group. They mainly consisted of abnormal glucose values and liver function parameters in patients with abnormal values already at baseline. None of these alterations required specific measures. No modifications in plasma electrolytes were observed. Differences in the frequency of abnormal haematological values and chemical parameters between the two treatment groups were not statistically significant.

### 3.4.4. Vital signs

Before the colonoscopy, two patients in the mannitol group had abnormal values: one patient presented abnormalities in heart

**Table 2**  
Summary of BBPS scores and adequate bowel cleansing; PP population.

	Mannitol (N = 325)	PEG-ASC (N = 332)
Cecum BBPS sub-score, n (%)		
<2	19 (5.9)	10 (3.0)
≥2	303 (93.2)	321 (96.7)
Missing	3 (0.9)	1 (0.3)
Transverse colon BBPS sub-score, n (%)		
<2	14 (4.3)	8 (2.4)
≥2	308 (94.8)	323 (97.3)
Missing	3 (0.9)	1 (0.3)
Sigmoidal-rectum junction colon BBPS sub-score, n (%)		
<2	21 (6.5)	11 (3.3)
≥2	304 (93.5)	321 (96.7)
BBPS total score, n (%)		
n	325	332
Mean (SD)	7.7 (1.78)	7.9 (1.50)
Median	8.0	9.0
Q1; Q3	6.0; 9.0	7.0; 9.0
Min; Max	0; 9	0; 9
Adequate bowel cleansing a, n (%)		
Yes	296 (91.1)	317 (95.5)
No	29 (8.9)	15 (4.5)

Percentages were computed on patients belonging to the PP Population. A patient has adequate bowel cleansing if BBPS total score  $\geq 6$ , with a score for each of the three colon segments  $\geq 2$ . In case of at least one sub-score not available, the patient was considered as not having adequate bowel cleansing. BBPS=Boston Bowel Preparation Scale; CI=Confidence Interval; Q1=1st Quartile; Q3=3rd Quartile; SD=Standard Deviation. PP=Per Protocol.

rate and diastolic and systolic blood pressure and another in systolic blood pressure. One patient in the PEG-ASC group had augmented diastolic and systolic blood pressure. These abnormalities were mild and did not affect the colonoscopy's performance.

During the colonoscopy, two patients in the mannitol group had abnormal values: one had abnormal pulse oximetry and diastolic and systolic blood pressure; another had an abnormal heart rate and diastolic pressure. One patient in the PEG-ASC group had an abnormal heart rate and systolic blood pressure. These abnormalities were also mild and did not affect the colonoscopy's performance.

No clinically significant abnormalities were reported after the colonoscopy.

#### 4. Discussion

The study primarily shows that very low-volume mannitol administered in a single dose just 4 h before colonoscopy is very effective since it is not inferior to traditional split-dose of 2 L PEG-ASC: mannitol preparation resulted in a 91 % rate of patients with adequate bowel cleansing according to the BBPS, slightly lower but not significantly different compared to 94 % with PEG-ASC. This result is particularly relevant considering that early morning Mannitol was compared to PEG-ASC with a split regimen, which is the most effective method of colon preparation with PEG-based drug, as supported by solid scientific evidence [20,21].

Further evidence of the excellent performance of both mannitol and PEG-ASC in obtaining a good colon preparation was the very high adenoma detection and caecal intubation rates, two other important markers of colonoscopy quality, equally received by the two arms of the study. Notably, mannitol was very fast-acting compared with PEG-ASC: performing bowel cleansing a few hours before the endoscopic procedure might represent a significant advantage for both the patients and the endoscopy units, which would benefit from more on-demand and flexible procedure scheduling.

**Table 3**  
Summary of patients with treatment emergent adverse events (TEAEs) related to the study drug by system organ class and preferred term (Safety Set).

	Mannitol (N = 343) n (%)	PEG-ASC (N = 347) n (%)
Patients with at least one TEAE related to study drug	32 (9.33)	14 (4.03)
MedDRA System Organ Class/Preferred term		
Gastrointestinal disorders	24 (7.00)	8 (2.31)
Abdominal adhesions	1 (0.29)	0
Abdominal distension	0	1 (0.29)
Abdominal pain	0	2 (0.58)
Nausea	9 (2.62)	6 (1.73)
Vomiting	15 (4.37)	2 (0.58)
Hepatobiliary disorders	1 (0.29)	1 (0.29)
Hyperbilirubinaemia	1 (0.29)	1 (0.29)
Hypertransaminaemia	1 (0.29)	0
Investigations	2 (0.58)	2 (0.58)
Blood bilirubin increased	0	1 (0.29)
Blood creatine increased	1 (0.29)	0
Hepatic enzyme increased	1 (0.29)	0
Transaminases increased	0	1 (0.29)
Metabolism and nutrition disorders	2 (0.58)	0
Hyperglycaemia	2 (0.58)	0
Nervous system disorders	7 (2.04)	3 (0.86)
Dizziness	4 (1.17)	1 (0.29)
Headache	0	1 (0.29)
Presyncope	2 (0.58)	1 (0.29)
Syncope	1 (0.29)	0
Renal and urinary disorders	1 (0.29)	2 (0.58)
Leukocyturia	1 (0.29)	0
Proteinuria	0	1 (0.29)
Urinary retention	0	1 (0.29)
Respiratory, thoracic and mediastinal disorders	1 (0.29)	0
Hiccups	1 (0.29)	0
Vascular disorders	2 (0.58)	0
Hypotension	2 (0.58)	0

Percentages were computed on patients belonging to the Safety Set.

A TEAE is defined as an AE that occurs after the start of treatment administration. An AE is defined as related to the study drug if the relationship to the study drug is 'suspected'. If the relationship to the study drug is 'unknown' and the AE start date is on or after the study treatment self-administration date, the relationship of the AE is classified as suspected.

A second aim of the study also addressed the patients' overall experience with mannitol preparation compared to those treated with PEG-ASC. One of the ongoing problems pertinent to colonoscopy is patients' adherence to complex and unpleasant preparations. This issue is crucial because the lack of adherence to recommended preparations leads to challenging, low-quality colonoscopies. In the present large, randomized, controlled trial (RCT), several scores based on patients' evaluations show that tolerability was much more favourable with mannitol than with PEG-ASC. Notably, ease of use received the maximum score (10/10) in a larger number of patients treated with mannitol (92 %) than with PEG-ASC (65 %). This figure is likely the result of the very low volume of solution to be drunk with mannitol coupled with the single dose taken in the morning on the day of the colonoscopy, which avoids evening discomfort and sleep disturbances caused by the split-dose regimen with PEG-ASC. In addition, the mannitol taste was particularly pleasant, as 75 % of patients scored 8 to 10 (against 29 % of the PEG-ASC group). This aspect may be relevant since an unpleasant taste is among the main issues discouraging patients from undergoing bowel preparation and colonoscopy. Thanks to these considerations, 97 % of the patients treated with mannitol stated they were willing to reuse the preparation. Almost all (93 %) patients treated with mannitol who had undergone

previous colonoscopy preferred mannitol to the preparation used for the earlier procedure.

The SATISFACTION study also confirmed the good safety profile of bowel preparation with oral mannitol. TEAEs related to the study drug were uncommon and comparable in the two study groups. The rate of gastrointestinal drug-related TEAE appears slightly higher in patients receiving the same-day preparation with oral mannitol (7 % versus 2 %). Such difference was not statistically significant between the two study arms and was largely expected when comparing a same-day with a split dose regimen. Notably, only 9 % of patients treated with mannitol showed a drug-related TEAE. In most of them, it consisted of mild and transient vomiting, nausea, and dizziness that, in no case, compromised performing the colonoscopy. These data are particularly relevant when compared to recent literature where RCTs with split doses of very low volume or high-volume PEG have reported drug-related TEAE in 9–15 % and self-reported adverse events in up to 78 % of patients [22,23]. Nevertheless, a small proportion of patients treated with mannitol may show mild laboratory changes not requiring specific measures.

A specific feature of this study is evaluating gas production in all colonoscopies performed with oral mannitol or PEG-ASC. The vast data collected unequivocally shows that H<sub>2</sub> and CH<sub>4</sub> can be detected in both groups and that mannitol is not associated with higher concentrations [18]. In either group, no patient was found to have potentially critical levels of H<sub>2</sub> or CH<sub>4</sub>, and most patients had intestinal gas concentrations below the detectability levels, confirming the safety use of mannitol. The mean levels in patients with detectable intestinal gas concentrations were equal in the two treatment groups. No CO<sub>2</sub> insufflation or water-aided techniques were allowed, unlike ambient air insufflation, according to the study protocol, to test the safety of mannitol in less favourable conditions. It is well known that using CO<sub>2</sub> and water-aided techniques would decrease intestinal O<sub>2</sub> concentration below the threshold necessary for H<sub>2</sub> or CH<sub>4</sub> combustion, thus reducing the risk of intestinal gas explosion. Therefore, both CO<sub>2</sub> insufflation and water-aided injection can safely be used in oral mannitol preparation.

The findings of this study, to our knowledge, the largest randomized clinical trial ever performed, which included intestinal gas measurements, indicate that the presence of gases and their concentrations are not related to the type of drug used for bowel cleansing but rather to the colonoscopy procedure and to the degree of cleansing obtained [15].

The present randomized study has some strengths, including a large number of enrolled patients, the multicentre design, and the evaluation of gas levels in several colonic sites before and after standard endoscopic maneuvers of washing and air insufflation. However, a limitation of the study was that patients were not blinded, whereby their subjective scores could have been biased. Still, the blind condition was impossible due to the different methods for preparing and administering mannitol and PEG-ASC. However, the blinding of the endoscopists who performed the colonoscopies and the handling of the drugs by unblinded team members support the experimental design's validity and the results' reliability.

In conclusion, the results of the SATISFACTION Phase III study indicate that low-volume, single-dose mannitol may fully satisfy a currently unmet clinical need since it is not inferior to the split-dose regimen with PEG-ASC regarding bowel cleansing efficacy. It is also much more acceptable to the patient due to its low volume, ease of use, quick action, and pleasant taste: all these features should facilitate better adherence to the preparation, resulting in excellent colonoscopy performance. Furthermore, the willingness of patients to reuse mannitol expressed by most patients in this study could reduce reluctance to adhere to cancer screening and

surveillance programs, which could positively affect population health and health costs. Oral mannitol should be re-considered shortly as an optimal option for colon preparation.

### Grant support

This study was funded by NTC S.r.l., Milan, Italy.

### Funding

NTC S.r.l., Milan (Italy)

### Clinical trial

Trial registration: ClinicalTrials.gov (<https://clinicaltrials.gov/ct2/show/NCT04759885>) and EudraCT (eudract\_number:2019-002,856-18).

### Declaration of competing interest

AO is an employee of NTC. MC and MM are consultants with NTC. MV and GET received a consultant fee after the study end. The remaining Authors declare that there is no conflict of interest. NTC is developing a bowel cleansing preparation based on mannitol.

### Author contribution

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### Acknowledgment

The authors would like to thank the contract research organization OPIS (Desio, MB, Italy) for skillful management of the trial.

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## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2024.09.024.

## References

- [1] Johnson DA, Barkun AN, Cohen LB, et al. Optimizing adequacy of bowel cleansing for colonoscopy: recommendations from the US multi-society task force on colorectal cancer. *Gastroenterology* 2014;147(4):903–24.
- [2] Tontini GE, Prada A, Ferrazza S, et al. The unmet needs for identifying the ideal bowel preparation. *JGH Open* 2021;5(10):1135–41.
- [3] Hassan C, East J, Radaelli F, Spada C, et al. Bowel preparation for colonoscopy: european society of gastrointestinal endoscopy (ESGE) Guideline – update 2019. *Endoscopy*. 2019;51(8):775–94.
- [4] Bechtold ML, Mir F, Puli SR, Nguyen DL. Optimizing bowel preparation for colonoscopy: a guide to enhance quality of visualization. *Ann Gastroenterol* 2016;29(2):137–46.
- [5] Saltzman JR, Cash BD, Pasha SF, et al. ASGE standards of practice committee. Bowel preparation before colonoscopy. *Gastrointest Endosc* 2015;81(4):781–94.
- [6] Tian X, Shi B, Chen H, et al. Comparative efficacy of 2 L polyethylene glycol alone or with ascorbic acid vs. 4 L polyethylene glycol for colonoscopy: a systematic review and network meta-analysis of 12 randomized controlled trials. *Front Med (Lausanne)* 2019;6(August):1–13.
- [7] Minervini S, Alexander-Williams J, et al. Comparison of three methods of whole bowel irrigation. *Am J Surg* 1980;140(3):400–2.
- [8] Gilmore IT, Ellis WR, Barrett GS, et al. A comparison of two methods of whole gut lavage for colonoscopy. *Br J Surg* 1981;68(6):388–9.
- [9] De Paulo GA, Martins FPB, de Macedo EP, et al. Safety of mannitol use in bowel preparation: a prospective assessment of intestinal methane (CH<sub>4</sub>) levels during colonoscopy after mannitol and sodium phosphate (NaP) bowel cleansing. *Arq Gastroenterol* 2016;53(3):196–202.
- [10] Ladas SD, Karamanolis G, Ben-Soussan E. Colonic gas explosion during therapeutic colonoscopy with electrocautery. *World J Gastroenterol* 2007;13(40):5295–8.
- [11] Joseminders DFGM, Spillenaar Bilgen EJ, van Sorge AA, et al. Colonic explosion during endoscopic polypectomy: avoidable complication or bad luck? *Endoscopy* 2006;38(9):943–4.
- [12] de Sousa JB, Silva SME, Fernandes MBDL, et al. Colonoscopies performed by resident physicians in a university teaching hospital: a consecutive analysis of 1000 cases. *Arq Bras Cir Dig* 2012;25:9–12.
- [13] Monahan DW, Peluso FE, Goldner F. Combustible colonic gas levels during flexible sigmoidoscopy and colonoscopy. *Gastrointest Endosc* 1992;38:40–3.
- [14] Bond JH Jr, Levitt MD. Factors affecting the concentration of combustible gases in the colon during colonoscopy. *Gastroenterology* 1975;68:1445–8.
- [15] Spada C, Fiori G, Uebel P, et al. Oral mannitol for bowel preparation: a dose-finding phase II study. *Eur J Clin Pharmacol* 2022;78(12):1991–2002.
- [16] Fiori G, Spada C, Soru P, et al. Pharmacokinetics of oral mannitol for bowel preparation for colonoscopy. *Clin Transl Sci* 2022;15(10):2448–57.
- [17] Calderwood AH, Jacobson BC. Comprehensive validation of the boston bowel preparation scale. *Gastrointest Endosc* 2010;72(4):686–92.
- [18] Carnovali M, Spada C, Uebel P, et al. Factors influencing the presence of potentially explosive gases during colonoscopy: results of the SATISFACTION study. *Clin Transl Sci* 2023;16(5):759–69.
- [19] Bisschops R, Manning J, Clayton LB, Kweet Shing RN, Alvarez-Gonzalez M. Colon cleansing efficacy and safety with 1 L NER1006 versus 2 L polyethylene glycol + ascorbate: a randomized phase 3 trial. *Endoscopy* 2019;51(1):60–72.
- [20] Kilgore TW, Abdinoor AA, Szary NM, Schowengerdt SW, Yust JB, Choudhary A, et al. Bowel preparation with split-dose polyethylene glycol before colonoscopy: a meta-analysis of randomized controlled trials. *Gastrointest Endosc* 2011;73(6):1240–5.
- [21] Kilgore TW, Abdinoor AA, al Szaryet NM. Bowel preparation with split-dose polyethylene glycol before colonoscopy: a meta-analysis of randomized controlled trials. *Gastrointest Endosc* 2011;73:1240–5.
- [22] DeMicco MP, Clayton LB, Pilot J, Epstein MS. 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(3):677–87 e3.
- [23] Vassallo R, Maida M, Zullo A, et al. Efficacy of 1 L polyethylene glycol plus ascorbate versus 4 L polyethylene glycol in split-dose for colonoscopy cleansing in out and inpatient: a multicentre, randomized trial (OVER 2019). *Dig Liver Dis* 2024;56(3):495–501.