Thieme

Efficacy and safety of a new low-volume PEG with citrate and simethicone bowel preparation for pediatric elective colonoscopy: Phase 3 RCT

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ABSTRACT

Background and study aims Currently available polyethylene glycol (PEG)-based preparations continue to represent a challenge in children. The aim of this study was to compare the efficacy and safety of a new low-volume PEG preparation with a conventional PEG-electrolyte solution (PEG-ES) in children and adolescents.

Patients and methods This was a multicenter, randomized, observer-blind, parallel-group, phase 3 clinical trial, where patients were randomized between PMF104 (Clensia) and a conventional PEG-ES (Klean-Prep), and stratified by age stratum (2 to <6; 6 to < 12;12 to <18 years). The primary endpoint was to test the non-inferiority of PMF104 versus PEG-ES, in terms of colon cleansing. Safety, tolerability, acceptability, palatability, and compliance were also assessed. Efficacy endpoints were analyzed in the per protocol set (PPS) and full analysis set (FAS) and safety and tolerability endpoints in the safety set (SAF).

Results Of the 356 patients enrolled, 258 were included in the PPS, 346 in the FAS, and 351 in the SAF. Non-inferiority of PMF104 was confirmed for children aged > 6 years and for all age groups in PPS and FAS, respectively. Optimal compliance was reported more frequently in the PMF104

than in the PEG-ES group, in both PPS (86.1% vs. 68.4%) and FAS (82.9% vs. 65.3%).

Both preparations were equally safe and tolerable. Palatability and acceptability were considered better in the PMF104 group than in the PEG-ES group (27.1% vs. 15.3% and 15.3% vs. 3.5%, respectively).

Conclusions In children aged 6 to 17 years, the new low-volume product PMF104 is non-inferior to the reference PEG-ES in terms of bowel cleansing, safety, and tolerability, with slightly better results in compliance, palatability, and acceptability.

Introduction

Colonoscopy is an important diagnostic and therapeutic tool in evaluating and treating gastrointestinal tract pathologies [1]. Adequate visualization of the intestinal lumen is necessary for the detection of lesions [2, 3, 4], with bowel preparation, therefore, a key component of the process [5]. It is estimated that over 25% of pediatric patients undergo suboptimal bowel preparations [6], which can lead to longer procedure times, missed pathology, unsuccessful ileal intubation, and possibly a repeat procedure/anesthesia [7, 8, 9]. There are currently no standard methods for pediatric bowel preparation, but a wide variety of regimens have been used in clinical studies and clinical practice [10, 11]. According to current guidelines [1, 11, 12, 13], bowel cleansing preparation for colonoscopy in pediatric patients should be personalized based on the patient's age, clinical state, and anticipated willingness or ability to comply with the selected method [14].

In general, the major issue concerning bowel preparations in children is not related to the efficacy and safety of the products used, but to a child's lack of cooperation. Even the best efforts of medical staff may be futile. Method of administration, volume, and palatability are key aspects for tolerability, acceptance, and compliance. Improvement of these aspects should be expected or demonstrated in order to provide a significant therapeutic benefit.

Most of the many bowel preparation methods for colon cleansing prior to colonoscopy in children have been shown to be safe and effective. Stimulant laxatives and absorbable osmotic laxatives have been proven to be as effective as high-volume polyethylene glycol (PEG)-based solutions [1]. The limitation of PEG-electrolyte solutions (PEG-ES) for bowel cleansing is the high volume required to achieve adequate results and their unpleasant taste. In fact, most pediatric patients, especially the youngest, do not ingest enough PEG-ES, which can result in the need for hospitalization for 24 to 48 hours to cleanse the colon in an uncooperative child. In addition, most children are unable to take the PEG-ES orally and the only way to administer it may be by placing a nasogastric (NG) tube [15, 16]. Indeed, failure of bowel preparation in pediatric patients is mostly associated with non-compliance and not the efficacy or safety of the products used.

PMF104 is a new low-volume (2 L) PEG-ES that differs from existing PEG-ES in that it contains citrate (citric acid and sodium citrate) and simethicone and is mildly hyperosmotic. The PMF104 formulation was developed to improve patient compliance, by reducing the overall volume of liquid intake and limiting the incidence of adverse effects of standard PEG-ES (e. g., nausea, bloating, and abdominal pain) accordingly, without affecting efficacy, and with improved palatability and taste. While the equivalence of PMF104 to reference products for bowel cleansing prior to colonoscopy has been demonstrated in two large Phase 3 multicenter randomized studies in adults [17, 18], no studies have assessed its efficacy in the pediatric population. The aim of this multicenter, randomized, single-blind, non-inferiority study was to compare the efficacy and safety of PMF104 with a conventional, approved PEG-ES in children from 2 years of age and adolescents.

Patients and methods

Study design

This was a randomized, single-blind (endoscopist-blind), active-controlled, multicenter, non-inferiority trial to evaluate the efficacy, safety, tolerability, acceptability, palatability, and compliance of PMF104 compared with a conventional PEG-ES in children and adolescents aged 2 to < 18 years old requiring a diagnostic procedure of the colon.

The study protocol was reviewed and approved by the Italian, Belgian, and French competent authorities and by the ethics committees of the eight hospital clinics – in Rome (two sites), Bologna, Florence, Messina, Brussels, Lyon, and Paris – where the study was conducted.

All patients or their parents/legal representatives gave their written informed consent.

Study population

Children and adolescents aged 2 to < 18 years and scheduled for elective colonoscopy were considered eligible. The following patients were considered ineligible: patients needing an urgent colonoscopy, those with known or suspected hypersensitivity to the product ingredients, gastrointestinal obstruction, pseudo-obstruction or perforation, gastric retention, toxic colitis or toxic megacolon, previous intestinal resection, structural abnormality of the lower gastrointestinal tract, clinically significant electrolyte imbalance, end-stage renal insufficiency, known metabolic disease (particularly phenylketonuria), or known hepatic, renal, or cardiac disease. Pregnant and breastfeeding females were also excluded.

Based on the investigator's judgment, patients could be managed as outpatients, receiving the instructions to be followed for bowel preparation, and the questionnaire was to be completed on the day of bowel preparation; otherwise, the pa-

tients were managed as inpatients with bowel preparation performed at the trial center.

Patients were randomized on a 1:1 basis to receive PMF104 or conventional PEG-ES according to a computer-generated randomization list, with a block size of four. They were stratified by center and age stratum (2 to < 6 years; 6 to < 12 years; 12 to <18 years). These activities were performed by a physician who was not involved in the colonoscopy procedure. This study was single-blind and the endoscopists were unaware of the treatments assigned to the patients and had to avoid talking to the patients and staff.

Bowel cleansing agents

PMF104 is a new formulation of PEG 4000 and electrolytes, with citrates and simethicone (Clensia; Alfasigma S.p.A., Bologna, Italy). It comes as a powder in two separate sachets (sachet A and sachet B) to be dissolved in 0.5 L of water. A standard PEG-ES active comparator, with PEG 3350, sodium sulfate anhydrous, sodium bicarbonate, sodium and potassium chloride (Klean-Prep; Norgine, Amsterdam, the Netherlands), was chosen as the active control because it is well-known and widely used among the different age subsets.

Randomized patients had to start bowel preparation the day before the colonoscopy in the mid to late afternoon (4–6 p.m.). The solution had to be administered as a single dose by the oral route, leaving sufficient time for ingestion to ensure clear rectal effluent before bedtime. A nasogastric tube was inserted for inpatients unable to drink the required amount of solution.

Patients randomized to PMF104 had to receive a dose ranging from 500 to 1750 mL within 1 to 3 hours, based on their age range and body weight, as detailed in **Supplementary Table 1**. A volume of clear liquid (i. e., water, fruit juice, soft drinks, tea; no milk) equal to 50% of the volume of PMF104 administered had to be given at the same time for rehydration purposes.

Subjects randomized to PEG-ES had to receive a dose of the reference product based on their age range, of 70 to 90 mL/kg within 1 to 3 hours (up to a maximum volume of 4000 mL), as detailed in **Supplementary Table 1**. The dose had to be administered at a rate of 250 mL every 10 to 15 minutes until the total volume had been taken.

In both arms, if administration had to be performed via a nasogastric tube, the required rate was 20 to 30 mL/minute. An additional rescue dose had to be administered if the child did not have clear watery stools within 3 hours of completing the bowel solution. Neither osmotic nor stimulant laxatives were permitted in the last 3 days before the colonoscopy. A low-fiber diet was prescribed at least 48 hours before the start of bowel preparation. No solid food was allowed for at least 2 hours before, during, and after bowel preparation and until the colonoscopy was performed. Clear fluids were permitted up to 2 hours before sedation/anesthesia.

Efficacy assessment

The primary objective was to compare the efficacy of PMF104 versus PEG-ES in terms of colon cleansing according to the Boston Bowel Preparation Scale (BBPS) score on the day of the diagnostic procedure as blindly assessed by the endoscopist upon completion of the examination [19].

Secondary efficacy endpoints included time to reach clear watery stools, cecal intubation rate, proportion of patients with an acceptable BBPS score (≥ 5), and proportion of patients who needed a rescue dose. The time to reach clear watery stools was calculated using information from the questionnaires administered to children or parents/legal representatives on the day of the bowel preparation. Ileal intubation rate, which defines completeness of the examination, was assessed as "yes = ileocecal valve reached and crossed" or "no = ileum not reached".

Compliance, acceptability, and palatability

On the day of the procedure, before the colonoscopy, patients were asked about compliance (assessed by the amount of drug solution taken), acceptability (difficulty taking the solution), and palatability (taste of the solution). Compliance was evaluated on a three-point scale: optimal = the whole solution; good = 75% of the solution; poor = < 75% of the solution. The amount of additional clear liquids taken was recorded. Acceptability data were collected using a four-point scale (1 = very difficult; 4 = not difficult at all). Palatability was reported using a four-point scale from 1 (very bad) to 4 (very good). Acceptability and palatability were calculated in patients who took at least part of the preparation orally, excluding patients who took it exclusively via nasogastric tube.

Safety and tolerability

The safety of the bowel cleansing agents was evaluated by the occurrence of adverse events (AEs), which included abnormal laboratory findings. AEs were monitored throughout the study.

Time of onset, duration, severity, outcome, and seriousness of each event were recorded and the causal relationship with the study drugs was assessed by the investigators. Standard blood and urine tests were performed at enrollment and at the end of the study.

The occurrence and severity of gastrointestinal and systemic symptoms (i. e., nausea, vomiting, bloating, abdominal pain/cramps, anal irritation, and fatigue/weakness) were included in the tolerability evaluation. Children or their parents were asked to rate each of the above symptoms on a four-point scale (0 = no distress; 3 = severe distress).

Statistical analysis

The primary objective of this trial was to demonstrate the non-inferiority of PMF104 versus a conventional 4 L PEG-ES in colon cleansing. The non-inferiority margin was selected based on a combination of statistical reasoning and clinical judgment. Because an acceptable cleansing level is defined by a BBPS score of ≥ 5, the expected point estimate of the difference between the BBPS score of test and reference was 0; the non-inferiority margin for the BBPS score, therefore, was set to -1.5. Likewise, if an additional alternative analysis of variance (ANOVA) on square-root transformed data was required, the non-inferiority margin for the square-root transformed BBPS score was set to $-\sqrt{1.5}$.

Due to the lack of data in the literature about the variance of BBPS scores in the three age strata considered, the value of the variance for calculating the sample size was set to five. Sample size was calculated based on a -1.5-equivalence margin. The significance level was set at $\alpha = 0.1$ with a power of 80% in the "2 ≤ Age < 6" age group and at $\alpha = 0.025$ with a power of 96% in each of the other two age groups. Assuming a screening failure rate of 10%, considering an exclusion rate from the per protocol set (PPS) of about 20%, and according to the three age strata selected, the plan for screening and randomization was as follows: aged 2 to < 6 years: 60 children screened, 54 randomized, and 42 enrolled; aged 6 to < 12 years: 168 children screened, 152 randomized, and 126 enrolled; aged 12 to < 18 years: 168 children screened, 152 randomized, and 126 enrolled.

As recommended by the International Conference on Harmonization guidelines for equivalence trial design [20], all efficacy analyses, except for those regarding sensitivity, were applied to both the PPS and full analysis set (FAS). The PPS was the primary analysis population, while the FAS was the confirmatory one. Safety analyses were performed on the safety set (SAF). FAS, PPS, and SAF are defined in the supplementary material.

Three separate analyses were performed for the three age strata "2 ≤ age < 6", "6 ≤ age < 12", and "12 ≤ age < 18". The non-inferiority of PMF104 versus PEG-ES was evaluated for each age stratum independently of the results achieved in the other age strata. No multiplicity issues between the analyses of the three age strata were considered.

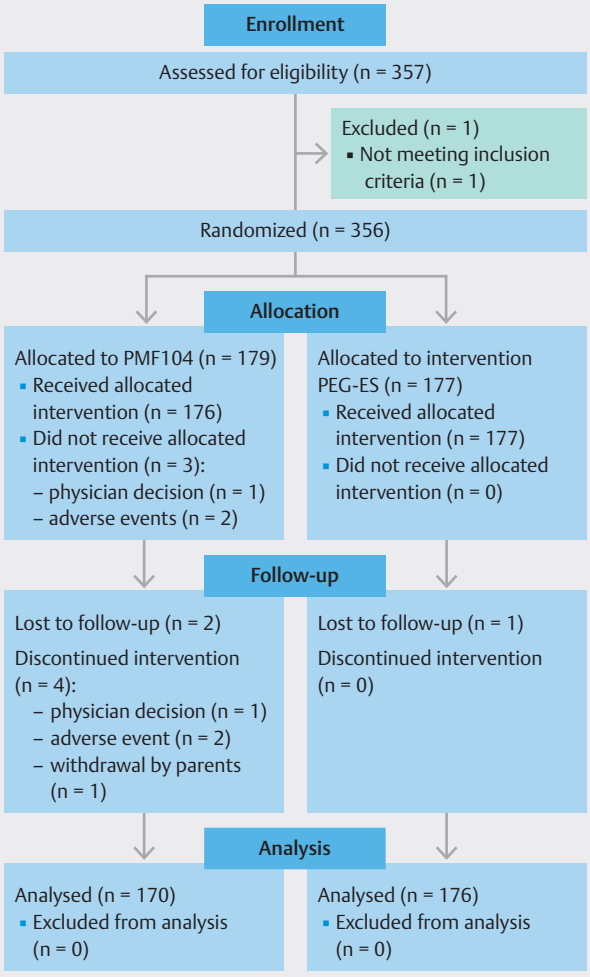
For each stratum, an ANOVA was used to compare the BBPS score of the two treatment groups. In addition, an overall exploratory analysis was performed on the pooled data from all three age strata.

With regard to the inability to reach the planned sample size in the aged 2 to < 6 years stratum, the primary efficacy analysis was replicated using supportive analysis (based on extrapolation methods).

Baseline characteristics were summarized using mean, standard deviation (SD), coefficient of variation (CV), minimum, median and maximum for continuous variables and counts and percentages for categorical variables. The statistical analysis was performed with SAS version 9.3 software.

Results

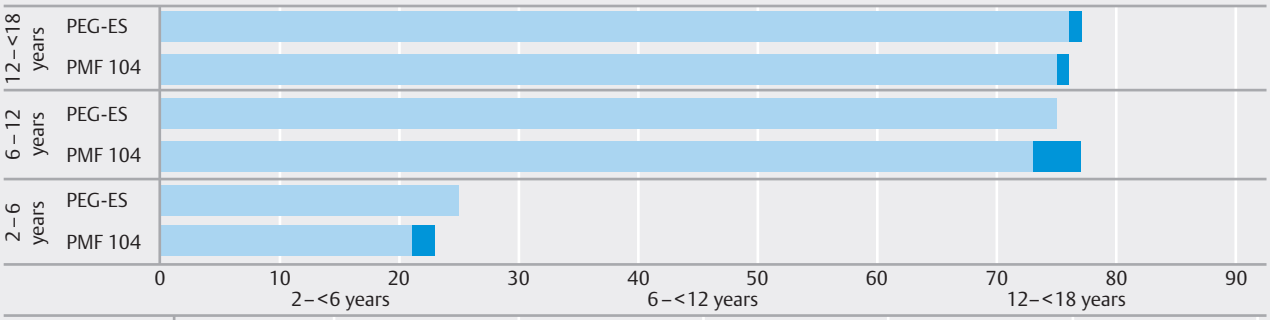
Patient flow is reported in ▶ **Fig. 1**. Three hundred and fifty-six children were randomized in the study as follows: 48, 153, and 155 children in the three age strata, respectively (2 to < 6; 6 to < 12; and 12 to < 18 years); 351 took at least one fraction of the dose of the study formulations and were included in the safety population. Indications for colonoscopy vary with age: in the under-6 age group, the main indication is lower gastrointestinal bleeding, while above 6 years of age, the proportion of colonoscopies performed as follow-up for chronic inflammatory bowel disease progressively increases (**Supplementary Table 2**). ▶ **Fig. 2** summarizes the number of completed subjects separately for PMF104 and PEG-ES treatments in each age stratum and overall.



▶ **Fig. 1** CONSORT flow diagram of the study.

Eight children, two in the aged 2 to < 6 years stratum (PMF104 treatment group only), four in the aged 6 to < 12 years stratum (PMF104 treatment only), and two in the aged 12 to < 18 years stratum (1 in each treatment group), discontinued the study after drug administration. Ninety-eight (98) patients incurred major protocol deviations (16 in the aged 2 to < 6 years stratum, 44 in the aged 6 to < 12 years stratum, and 38 in the aged 12 to < 18 years stratum). Therefore, 258 patients (mean age [SD]: 10.7 [3.8]; males [%]: 141 [54.7]) were included in the PPS population (▶ **Table 1**). Demographic and baseline characteristics were generally similar between treatment groups in each age stratum and overall (▶ **Table 2**). The most frequently reported medical history item in each age stratum and overall was "Gastrointestinal disorders" (**Supplementary Table 3**).

Forty-five endoscopists in eight centers were involved to do the colonoscopies. In all age groups, we observed similar colonoscopy duration for the two treatment groups: 28.2 ± 18.7 minutes and 30.2 ± 16.9 minutes for PMF104 and PEG-ES, respectively.



	PMF104	PEG-ES	PMF104	PEG-ES	PMF104	PEG-ES
Combined	21	25	73	75	75	76
Discontinued	2	0	4	0	1	1

▶ **Fig. 2** Graphical representation of study treated subjects. PEG-ES, polyethylene glycol-electrolyte solutions.

▶ **Table 1** Number of subjects in the SAF, FAS and PPS.

Age strata	Treatment	Data analysis sets – n (%)		
		SAF	FAS	PPS
2 to < 6 years N = 48	PMF104 N = 23	23 (100.0)	22 (95.7)	16 (69.6)
	PEG-ES N = 25	25 (100.0)	25 (100.0)	16 (64.0)
6 to < 12 years N = 153	PMF104 N = 78	77 (98.7)	73 (93.6)	50 (64.1)
	PEG-ES N = 75	74 (98.7)	74 (98.7)	59 (78.7)
12 to < 18 years N = 155	PMF104 N = 78	75 (96.2)	75 (96.2)	56 (71.8)
	PEG-ES N = 77	77 (100.0)	77 (100.0)	61 (79.2)
Overall N = 356	PMF104 N = 179	175 (97.8)	170 (95.0)	122 (68.2)
	PEG-ES N = 177	176 (99.4)	176 (99.4)	136 (76.8)

N, number of subjects; SAF, safety set; FAS, full analysis set; PPS, per protocol set; PEG-ES, PEG-electrolyte solution.

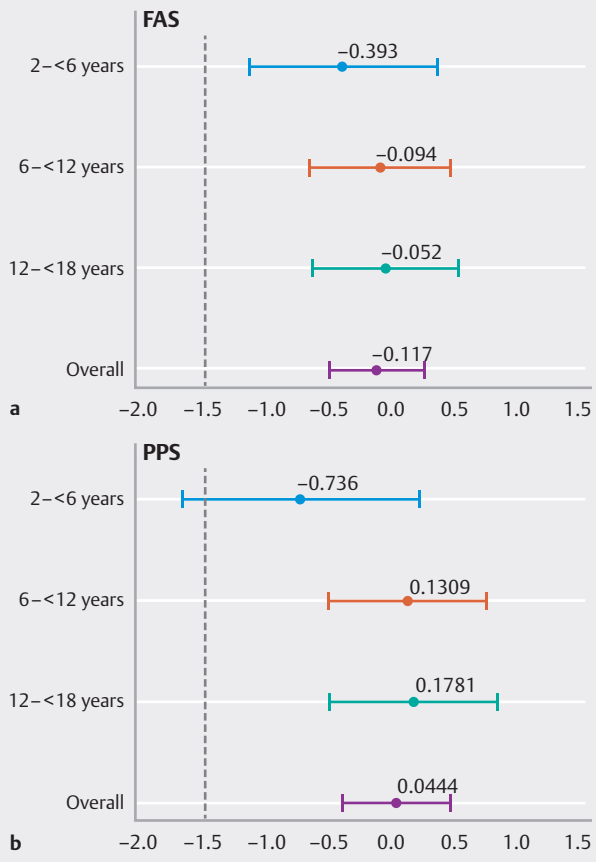
Efficacy

In the PPS, non-inferiority of PMF104 with respect to PEG-ES was confirmed for the aged 6 to < 12 years and 12 to < 18 years strata (▶ **Fig. 3**). Non-inferiority could not be confirmed, however, for the aged 2 to < 6 years stratum because the lower limit of the 90% one-sided confidence interval was slightly below the pre-established margin (▶ **Table 3**). The supportive analysis on the FAS demonstrated the non-inferiority of PMF104 with respect to PEG-ES for all three age strata, with the lower limit of the 97.5% (90% for the first stratum) one-sided confidence in-

▶ **Table 2** Demographic characteristics of the study participants in the PPS.

	Statistics	PMF104 N = 122	PEG-ES N = 136	Overall N = 258
Sex				
Female	n. (%)	60 (49.2)	57 (41.9)	117 (45.3)
Male	n. (%)	62 (50.8)	79 (58.1)	141 (54.7)
Race				
White	n. (%)	97 (79.5)	113 (83.1)	210 (81.4)
Missing	n. (%)	20 (16.4)	19 (14.0)	39 (15.1)
Asian	n. (%)	4 (3.3)	1 (0.7)	5 (1.9)
Other	n. (%)	1 (0.8)	2 (1.5)	3 (1.2)
Black or African American	n. (%)	0 (0.0)	1 (0.7)	1 (0.4)
Age (years)	N	122	136	258
	Mean	10.7	10.7	10.7
	SD	4.0	3.6	3.8
	CV%	37.3	33.9	35.5
	Min	2	2	2
	Median	11.0	11.0	11.0
	Max	17	17	17
Height (cm)	N	118	135	253
	Mean	142.6	143.4	143.0
	SD	22.7	21.9	22.3
	CV%	15.9	15.3	15.6
	Min	70	87	70
	Median	144.0	145.0	145.0
	Max	181	184	184

N, number of subjects; PPS, per protocol set; PEG-ES, PEG-electrolyte solution; SD, standard deviation; CV, coefficient of variation.



▶ **Fig. 3** Forest plot for BBPS for the three age strata in **a** full analysis set and **b** per protocol set. FAS, full analysis set; PPS, per protocol set.

terval above the pre-established non-inferiority margin in all three age groups (▶ **Table 3**).

The results of the overall exploratory analysis on both the PPS and FAS demonstrated the non-inferiority of PMF104 with respect to PEG-ES for the pooled age strata. Age stratum had no statistically significant impact ($P = 0.1805$ for the PPS and $P = 0.1924$ for the FAS).

With reference to the additional analyses described in the extrapolation plan for the aged 2 to < 6 years stratum in which the planned sample size was not reached, non-inferiority of PMF104 was obtained after extending the age range of the lowest stratum to aged 2 to < 7 years and aged 2 to < 8 years, but it was not obtained for the borrowed groups in the PPS.

Compliance, acceptability, and palatability

Considering compliance in both males and females (PPS) and in all three age strata (overall), "optimal" compliance was scored for considerably more patients in the PMF104 treatment group (86.1%) than in the PEG-ES group (68.4%). In terms of acceptability (overall), the PMF104 bowel solution was found to be "not difficult at all" and "slightly difficult" to drink by 15.3% and 18.8% of patients, respectively. In comparison, only 3.5% of patients found PEG-ES "not difficult at all" and 13.9% found it "slightly difficult" to drink. The palatability (overall) was "good" for 21.5% and 13.9% of patients with PMF104 and PEG-ES, respectively, whereas 5.6% of patients deemed PMF104 to be "very good" as opposed to 1.4% of patients for PEG-ES.

Solution taste was scored as "very bad" by 34% of patients in the PMF104 group and 50% of patients in the PEG-ES group. "Bad" taste was reported by 38.9% and 32.6% of the patients in the two treatment groups, respectively. **Supplementary Table**

▶ **Table 3** Analysis of variance (ANOVA) on BBPS score for the three age strata in the PPS and FAS.

Primary efficacy analysis – PPS				
Age group	**BBPS score Mean ± SD**		**Statistical analysis results**	
	PMF104	**PEG-ES**	**Adjusted mean difference**	**One-sided CI lower limit***
2 to <6 years	5.9 ± 2.2	6.6 ± 2.3	−0.7357	−1.6962
6 to <12 years	6.6 ± 1.9	6.5 ± 1.8	0.1309	−0.5097
12 to <18 years	6.1 ± 2.1	6.0 ± 2.0	0.1781	−0.5035
Overall	6.3 ± 2.0	6.3 ± 2.0	0.0444	−0.3989
Supportive efficacy analysis – FAS				
Age group	**BBPS score Mean ± SD**		**Statistical analysis results**	
	PMF104	**PEG-ES**	**Adjusted mean difference**	**One-sided CI Lower limit***
2 to < 6 years	6.3 ± 2.1	6.5 ± 2.2	−0.3926	−1.1545
6 to < 12 years	6.4 ± 2.1	6.6 ± 1.8	−0.0939	−0.6637
12 to < 18 years	6.0 ± 2.1	6.0 ± 1.9	−0.0522	−0.6420
Overall	6.2 ± 2.1	6.3 ± 1.9	−0.1166	−0.4994

BBPS, Boston Bowel Preparation Scale; PPS, per protocol set; FAS, full analysis set; PEG-ES, PEG-electrolyte solution; SD, standard deviation; CI, confidence interval.
*90% confidence interval (CI) for the first age stratum; 97.5% CI for the other two age strata.

▶ **Table 4** Treatment-emergent adverse events in the SAF.

	PMF104 n (%) [n AE]	PEG-ES n (%) [n AE]	Overall n (%) [n AE]
All TEAEs	122 (70.1) [341]	130 (73.4) [404]	252 (71.8) [745]
2 to < 6 years	14 (63.6) [23]	16 (61.5) [30]	30 (62.5) [53]
6 to < 12 years	49 (63.6) [139]	50 (67.6) [136]	99 (65.6) [275]
12 to < 18 years	59 (78.7) [179]	64 (83.1) [238]	123 (80.9) [417]
Related TEAEs	102 (58.6) [256]	109 (61.6) [301]	211 (60.1) [557]
2 to < 6 years	9 (40.9) [13]	11 (42.3) [21]	20 (41.7) [34]
6 to < 12 years	39 (50.6) [102]	42 (56.8) [99]	81 (53.6) [201]
12 to < 18 years	54 (72.0) [141]	56 (72.7) [181]	110 (72.4) [322]
Gastrointestinal symptoms	99 (56.9) [215]	107 (60.5) [245]	206 (58.7) [460]
Nausea	65 (37.4) [70]	69 (39.0) [76]	134 (38.2) [146]
Abdominal pain	50 (28.7) [52]	46 (26.0) [48]	96 (27.4) [100]
Abdominal distension	40 (23.0) [41]	45 (25.4) [46]	85 (24.2) [87]
Vomiting	34 (19.5) [36]	38 (21.5) [45]	72 (20.5) [81]
Anorectal discomfort	13 (7.5) [13]	25 (14.1) [27]	38 (10.8) [40]
Asthenia	9 (5.2) [9]	10 (5.6) [10]	19 (5.4) [19]
Headache	1 (0.6) [1]	0 (0.0) [0]	1 (0.3) [1]
Leading to discontinuation TEAEs	4 (2.3) [7]	5 (2.8) [5]	9 (2.6) [12]
2 to < 6 years	0 (0.0) [0]	1 (3.8) [1]	1 (2.1) [1]
6 to < 12 years	3 (3.9) [5]	0 (0.0) [0]	3 (2.0) [5]
12 to < 18 years	1 (1.3) [2]	4 (5.2) [4]	5 (3.3) [6]
SAEs	2 (1.1) [2]	5 (2.8) [9]	7 (2.0) [11]
2 to < 6 years	1 (4.5) [1]	1 (3.8) [1]	2 (4.2) [2]
6 to < 12 years	1 (1.3) [1]	0 (0.0) [0]	1 (0.7) [1]
12 to < 18 years	0 (0.0) [0]	4 (5.2) [8]	4 (2.6) [8]
Related SAEs	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Leading to discontinuation SAEs	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]

PEG-ES, PEG-electrolyte solution; SAF, safety set; TEAE, treatment-emergent adverse event; SAE, severe adverse event; AE, adverse event; n, number of subjects.

4 summarizes the results for compliance, acceptability, and palatability by age strata.

In the PMF-104, of 176 patients, 30 (17.0%) needed the NG tube since the beginning and another 12 (6.8%) needed it 1 hour after the start of preparation; in the PEG-ES, of 177 patients, 33 (18.6%) needed the NG tube since the beginning, and 15 (8.4%) needed it after 1 hour to complete the preparation.

Safety and tolerability

Overall, 745 treatment-emergent adverse events (TEAEs) were experienced by 252 patients (71.8%). ▶**Table 4** summarizes TEAEs for the two study arms. In general, clinical laboratory test results were within normal range or judged not clinically significant and/or were associated with concomitant diseases. No treatment-related clinically relevant changes in vital signs or body weight were observed throughout the study in any age stratum. Tolerability results in terms of the frequency of gastrointestinal and systemic symptoms are reported in ▶**Table 5**.

Discussion

This study demonstrated that PMF104 is non-inferior to a standard PEG-ES in achieving adequate cleansing of the bowel before colonoscopy in pediatric subjects aged 6 to < 18 years. Non-inferiority was not confirmed in the aged 2 to < 6 years age stratum, possibly due to the smaller-than-planned sample

▶ **Table 5** Tolerability score in the SAF for age range.

Symptom	Score*	Age strata – n (%)							
		2 to < 6 years		6 to < 12 years		12 to < 18 years		Overall	
		PMF104 N = 22	PEG-ES N = 26	PMF104 N = 77	PEG-ES N = 74	PMF104 N = 75	PEG-ES N = 77	PMF104 N = 174	PEG-ES N = 177
Nausea	**0**	17 (77.3)	21 (80.8)	46 (59.7)	48 (64.9)	40 (53.3)	31 (40.3)	103 (59.2)	100 (56.5)
	1	4 (18.2)	1 (3.8)	18 (23.4)	17 (23.0)	18 (24.0)	20 (26.0)	40 (23.0)	38 (21.5)
	2	0 (0.0)	4 (15.4)	8 (10.4)	5 (6.8)	11 (14.7)	16 (20.8)	19 (10.9)	25 (14.1)
	3	0 (0.0)	0 (0.0)	4 (5.2)	3 (4.1)	6 (8.0)	10 (13.0)	10 (5.7)	13 (7.3)
	Missing	1 (4.5)	0 (0.0)	1 (1.3)	1 (1.4)	0 (0.0)	0 (0.0)	2 (1.1)	1 (0.6)
Vomiting	**0**	17 (77.3)	19 (73.1)	57 (74.0)	59 (79.7)	59 (78.7)	56 (72.7)	133 (76.4)	134 (75.7)
	1	2 (9.1)	3 (11.5)	12 (15.6)	6 (8.1)	7 (9.3)	13 (16.9)	21 (12.1)	22 (12.4)
	2	2 (9.1)	4 (15.4)	5 (6.5)	6 (8.1)	9 (12.0)	6 (7.8)	16 (9.2)	16 (9.0)
	3	0 (0.0)	0 (0.0)	2 (2.6)	2 (2.7)	0 (0.0)	2 (2.6)	2 (1.1)	4 (2.3)
	Missing	1 (4.5)	0 (0.0)	1 (1.3)	1 (1.4)	0 (0.0)	0 (0.0)	2 (1.1)	1 (0.6)
Bloating	**0**	18 (81.8)	25 (96.2)	64 (83.1)	54 (73.0)	48 (64.0)	46 (59.7)	130 (74.7)	125 (70.6)
	1	3 (13.6)	1 (3.8)	9 (11.7)	12 (16.2)	13 (17.3)	12 (15.6)	25 (14.4)	25 (14.1)
	2	0 (0.0)	0 (0.0)	3 (3.9)	5 (6.8)	8 (10.7)	14 (18.2)	11 (6.3)	19 (10.7)
	3	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.7)	6 (8.0)	5 (6.5)	6 (3.4)	7 (4.0)
	Missing	1 (4.5)	0 (0.0)	1 (1.3)	1 (1.4)	0 (0.0)	0 (0.0)	2 (1.1)	1 (0.6)
Abdominal pain/cramps	**0**	15 (68.2)	20 (76.9)	58 (75.3)	51 (68.9)	41 (54.7)	53 (68.8)	114 (65.5)	124 (70.1)
	1	5 (22.7)	5 (19.2)	9 (11.7)	12 (16.2)	18 (24.0)	9 (11.7)	32 (18.4)	26 (14.7)
	2	1 (4.5)	1 (3.8)	9 (11.7)	9 (12.2)	11 (14.7)	11 (14.3)	21 (12.1)	21 (11.9)
	3	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)	5 (6.7)	4 (5.2)	5 (2.9)	5 (2.8)
	Missing	1 (4.5)	0 (0.0)	1 (1.3)	1 (1.4)	0 (0.0)	0 (0.0)	2 (1.1)	1 (0.6)
Anal irritation	0	19 (86.4)	25 (96.2)	71 (92.2)	67 (90.5)	65 (86.7)	60 (77.9)	155 (89.1)	152 (85.9)
	1	2 (9.1)	1 (3.8)	4 (5.2)	5 (6.8)	8 (10.7)	8 (10.4)	14 (8.0)	14 (7.9)
	2	0 (0.0)	0 (0.0)	1 (1.3)	1 (1.4)	0 (0.0)	5 (6.5)	1 (0.6)	6 (3.4)
	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.7)	4 (5.2)	2 (1.1)	4 (2.3)
	Missing	1 (4.5)	0 (0.0)	1 (1.3)	1 (1.4)	0 (0.0)	0 (0.0)	2 (1.1)	1 (0.6)
Fatigue/ weakness	**0**	19 (86.4)	22 (84.6)	54 (70.1)	53 (71.6)	53 (70.7)	43 (55.8)	126 (72.4)	118 (66.7)
	1	1 (4.5)	3 (11.5)	12 (15.6)	12 (16.2)	8 (10.7)	15 (19.5)	21 (12.1)	30 (16.9)
	2	1 (4.5)	1 (3.8)	8 (10.4)	4 (5.4)	10 (13.3)	14 (18.2)	19 (10.9)	19 (10.7)
	3	0 (0.0)	0 (0.0)	2 (2.6)	4 (5.4)	4 (5.3)	5 (6.5)	6 (3.4)	9 (5.1)
	Missing	1 (4.5)	0 (0.0)	1 (1.3)	1 (1.4)	0 (0.0)	0 (0.0)	2 (1.1)	1 (0.6)

PEG-ES, polyethylene glycol-electrolyte solutions; N, number of subjects; SAF, safety set.
*Score 0 = no distress; score 1 = mild distress; score 2 = moderate distress; score 3 = severe distress.

size for this age group. However, according to the extrapolation plan, the results of the additional analyses do not uniquely indicate that PMF104 is non-inferior to the low-volume PEG-ES also in this age group (these results are borderline). Better compliance was reported for PMF104 in all age groups, probably because this solution was found to be palatable and acceptable by a higher proportion of patients. Safety and tolerability were good and in line with the safety profiles of the comparator. As expected, the most reported tolerability findings and treatment-related AEs were gastrointestinal disorders.

The results of this study are notable for the following reasons. First, the low-volume PMF104 regimen tested was non-inferior to a standard PEG-ES in children aged ≥ 6 years in terms of bowel cleansing efficacy. PEG-ES regimens are often not well tolerated in children because of the quantity of liquid and their salty taste, meaning inpatient administration via a nasogastric tube is often required. PMF104 can represent an important alternative to the available regimens because it considerably reduces the total volume to be taken while maintaining the same efficacy. Second, PMF104 also scored higher in terms of palatability and acceptability. Combined with the non-inferior efficacy in children aged ≥ 6 years and the lower volume of bowel solution required, this result makes PMF104 a promising new regimen in children.

Similar results have previously only been obtained with sodium picosulfate preparations [21], but these regimens need to be studied extensively in multicenter trials before being considered as a reference.

Third, no safety-related issues emerged in the present study. Electrolyte measurement before and after preparation excluded clinically relevant alterations in sodium and potassium, acid-base balance, calcium, magnesium, and inorganic phosphorous homeostasis, offering reassurance as to the safety of PMF104 as a laxative especially for pediatric outpatient colonoscopy. Fourth, the rate of ileal intubation was similar between the groups, demonstrating that PMF104 (Clensia) enables the endoscopist to complete an ileocolonoscopy safely, which is always mandatory in children.

The clinical relevance of the present study should be integrated with the key findings of previous studies on Clensia in adults [17,18]. In detail, equivalence was demonstrated in terms of efficacy and safety between Clensia and high- and low-volume regimens, and this agent was shown to have better tolerability and acceptability. It may be included among the possible options for patients aged 6 years and older.

This study has some limitations. First, the sample size was not reached in the aged 2 to < 6 years stratum and the primary efficacy analysis did not confirm non-inferiority in this age stratum, unlike in the other two strata. However, because this population of children is the most fragile and difficult to recruit, it was agreed – after consulting the European Medicines Agency, which also took into account the impact of the COVID-19 pandemic on the enrollment rate in 2020 – to consider sufficient the number of patients enrolled at the end of the study period. As such, by performing additional analyses, it was possible to extrapolate the results even in the absence of the planned sample size.

Second, although the bowel cleansing was performed in both outpatient and inpatient settings, most of the procedures were performed on inpatients (approximately 86%), thus affecting the generalizability of the study results in the outpatient setting. Unfortunately, most sites preferred to perform inpatient procedures, due to the need to monitor patients for the safety profile by performing laboratory tests before and after the procedure.

Third, the association between the risk factors for inadequate bowel preparation – such as male sex, younger age, malnutrition or being overweight – and the level of bowel cleansing has not been investigated. Therefore, the effects of the two bowel cleansing agents on patients at risk of inadequate preparation remain unknown. Furthermore, previous a patient's experience with another bowel preparation (most likely a high-volume regimen) might favor their acceptance of a lower-volume preparation. This aspect has not been assessed.

Conclusions

In conclusion, in children aged 6 to 17 years, the low-volume preparation Clensia is non-inferior to a conventional 4 L PEG-ES regimen in terms of bowel cleansing, safety, and tolerability. Better compliance was reported for Clensia, probably because a higher proportion of subjects in each age group found this agent mostly palatable and acceptable. Clensia may be considered a good new "candidate" for a pediatric preparation regimen in children aged ≥ 6 years because it can offer a significant therapeutic benefit over certain existing treatments and it may satisfy the need to increase the tolerability, acceptance, and convenience of PEG-ES in children.

Conflict of Interest

AlfaSigma has funded this clinical trial with grants provided to the trial sites. Michela Padovani, Raffaella Tacchi and Fabio Cenci are Alfasigma employees. The remaining authors have no other conflict of interest to declare.

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Alfasigma SpA

Clinical trial

ClinicalTrials.gov (http://www.clinicaltrials.gov/)
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