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Original article

Tolerability and safety of a semi-elemental enteral formula with partially hydrolyzed guar gum (PHGG) in tube-fed children aged 1–4 years: An open-label, single-arm study

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SUMMARY

Background and aims: Partially hydrolyzed guar gum (PHGG) is a water-soluble fiber supporting digestive health with well-established safety and efficacy. This open-label, single-arm, multicenter trial aimed to assess the tolerability and safety of a semi-elemental enteral formula containing PHGG at 12 g/L in tube-fed young children.

Methods: Children aged 1–4 years with stable conditions requiring tube feeding to provide ≥80% of their nutritional needs received the study formula for seven days. Tolerability, safety, adequacy of energy/protein intake, and weight change were assessed.

Results: Of 24 children (mean age 33.5 months; 10 [41.7%] female), 23 (95.8%) commenced treatment and 18 (75%) completed the study. All children had underlying neuro-developmental disabilities, often in association with gastrointestinal comorbidities requiring treatment for constipation (70.8%) or gastro-esophageal reflux (66.7%). The formula was well-tolerated by 19 (82.6%) subjects, while 4 (17.4%; 95% CI: 5%, 39%) subjects withdrew early from the study due to gastrointestinal intolerance. The mean (SD) percentage energy and protein intake across the 7-day period were 103.5% (24.7) and 139.5% [50], respectively. Weight remained stable over the 7-day period ($p = 0.43$). The study formula was associated with a shift towards softer and more frequent stools. Pre-existing constipation was generally well controlled, and 3/16 (18.7%) subjects ceased laxatives during the study. Adverse events were reported in 12 (52%) subjects and were deemed 'probably related' or 'related' to the formula in 3 (13%) subjects. Gastrointestinal adverse events appeared more common in fiber-naïve patients ($p = 0.09$).

Conclusion: The present study indicates that the study formula was safe and generally well tolerated in young tube-fed children.

Clinicaltrials.gov identifier: NCT04516213.

1. Introduction

Dietary fiber is a crucial nutrient for humans [1]. Consumption of fiber confers benefits for digestive health, as well as benefits that extend beyond the gut [1,2]. Partially hydrolyzed guar gum (PHGG) is a water-soluble fiber produced by partial enzymatic hydrolysis of guar gum seeds. The seeds originate from *Cyamopsis tetragonolobus*, native to India and Pakistan [3,4]. Unlike guar gum which is highly viscous and difficult to incorporate in foods and solutions, PHGG is a non-viscous, non-gelling, water-soluble fiber with odorless and tasteless properties that can be easily added to nutritional supplements, enteral formulas, and other food products (as a thickener and emulsion stabilizer) [4,5]. The safety and efficacy of PHGG are well established in humans [4–13], and products containing PHGG have been in clinical use for over two decades. Several clinical studies have shown that PHGG supports digestive health by normalizing stool consistency in children and adults with constipation or diarrhea [3,9,11–16]. PHGG doses used in children ranged from 5 to 10 g per day when used as a supplement and in enteral formulas [3,9,14], and up to 15–20 g/L in oral rehydration

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solutions in young children [11,12]. PHGG confers prebiotic effects with the ability to stimulate the growth of beneficial bacteria, such as Bifidobacteria and butyrate-producing bacteria [17–19]. These effects on the microbiome can promote short-chain fatty acid (SCFA) production and good health [20].

Enteral feeding can be associated with gastrointestinal adverse effects, such as diarrhea or constipation [21,22]. Constipation is prevalent in non-ambulatory children, which may negatively impact their quality of life [23]. Intestinal dysbiosis in tube-fed subjects may contribute to the gastrointestinal symptoms [24,25]. Fiber supplementation has been proposed as a means of normalizing bowel function in patients receiving enteral nutrition. It may support the development of a healthy gut microbiome, which is of great clinical importance, particularly during early life [26]. Although the importance of dietary fiber in both health and disease is increasingly recognized, there are currently no evidence-based recommendations on fiber requirements in children receiving nutritional support. While it has been suggested that children receiving enteral nutrition may have the same fiber requirements as healthy children [22,27], fiber requirements during acute and chronic conditions are unknown.

The objective of the present study was to assess the tolerability and safety of a semi-elemental formula containing PHGG at 12 g/L in tube-fed children aged 1–4 years when provided as the main source of nutrition. The study formula was designed to suit the nutritional and fiber needs of a broad age range of children from 1 to 12 years. Currently, there is a clinical equipoise regarding the optimal fiber dose in young children, with recommendations ranging from 6 to 19 g/day for children aged 1–4 years [28–31]. The present study focused on this age group as their risk of developing adverse reactions may be increased due to the relatively high fiber content of the study formula. We hypothesized that the formula would be tolerated by at least 80% of study participants.

2. Materials & methods

2.1. Study design

A multicenter, open-label, single-arm study was conducted in three pediatric gastroenterology centers in the US from February 2020 to May 2021. The protocol was approved by the Copernicus Group Institutional Review Board (CGIRB, Triangle Park, North Carolina; Approval number 20200199). Written informed consent was obtained from all parents or legal guardians of participants. The trial was prospectively registered on ClinicalTrials.gov (NCT04516213).

2.2. Study participants

Children aged 12–48 months with clinically stable conditions requiring enteral tube feeding providing ≥80% of their nutritional needs for at least 7 days were eligible to participate in the study. Subjects with ongoing or intermittent significant gastrointestinal symptoms, gastrointestinal disorders or with a documented diagnosis of cow's milk protein allergy were excluded from participation. Subjects receiving parenteral nutrition or those with known hypersensitivity to PHGG or to any other ingredient contained in the study formula were also excluded.

2.3. Study product and procedures

The study formula (Peptamen Junior PHGG®; Nestlé Health Science, Switzerland) is a whey-based, nutritionally complete, semi-elemental enteral formula. The formula provides 1.2 kcal/mL of energy (12% protein, 51% carbohydrate, and 37% fat) and is supplemented with PHGG at 12 g/L, i.e., 10 g/1000 kcal. The formula is designed for the dietary management of pediatric patients aged 1–12 years receiving enteral nutrition. The nutritional profile is detailed in Table 1.

The study formula was administered at home by continuous or bolus infusion via a nasogastric tube or feeding gastrostomy for a 7-day period in replacement of the usual formula. The switch from the usual formula to the study formula was performed without grading over on Day 1. Nutritional intake targets were determined by the treating team prior to enrolment, based on age, gender, weight and growth trajectory. The rate and modality of administration were not changed when switching from the usual formula to the study formula.

After a baseline assessment at enrollment, subjects were assessed by their parent or caregiver for the presence or absence of a panel of gastrointestinal symptoms. Parents/caregivers kept a daily tolerance diary for 7 consecutive days, with the final study assessments occurring on Day 8. The following information was recorded: daily formula intake (feeding time, amount, bolus versus continuous feeding), any other nutritional intake, stool characteristics (consistency, frequency), gastrointestinal symptoms (vomiting, flatulence, abdominal pain), general health and mood.

The Bristol Stool Scale was used to characterize stool consistency [32]. Diarrhea was defined as watery stools (Bristol Stool Scale, type 7) at least three times per day. Constipation was defined as hard and infrequent stools (Bristol Stool Scale, types 1 or 2). Body weight was measured in kg on calibrated scales (to the nearest 100 g), with the child undressed. The change in weight over a 7-day period was defined as the change in body weight from baseline to Day 8. The World Health Organization (WHO) Child Growth Standards were used to assess anthropometric data [33]. The daily percentage of target energy and protein intakes were calculated as 100 × the actual caloric/protein intake divided by the estimated needs, as defined by the treating team. All adverse events occurring during the 7-day study period were collected, as reported by parents/caregivers or medical staff.

2.4. Study endpoints

The primary endpoint was the occurrence of gastrointestinal intolerance, defined as cessation of the study formula due to one or more of the following adverse reactions, as assessed by the investigator: diarrhea, change in stool characteristics deemed clinically significant, cessation of passage of stool or flatus for >48 h, overt vomiting, sudden or gradual increase in abdominal distension, or persistent abdominal pain/irritability >24 h with one of the above symptoms.

Secondary endpoints included 1) the frequency and nature of adverse events over a 7-day period 2) the daily percentage of energy and protein requirements met, and 3) the change in weight over the 7-day study period.

Table 1
Nutritional profile of the study formula.

Nutritional content	Per 1000 mL
Energy, kcal	1200
Protein, g	36
Carbohydrate, g	160
Total Fat, g	52
Medium-chain triglycerides, g	32
PHGG, g	12
Osmolality, mOsm/kg	394

2.5. Statistical considerations

No formal sample size calculations were performed for this single-arm tolerance study. A sample size of 35 subjects (30 completers) was deemed appropriate for the objectives of the study. Descriptive summary statistics were performed for all primary and secondary study endpoints/outcome measures. Means, standard deviations, medians and range were used to summarize continuous data. Frequency counts and percentages were used to summarize categorical data. Statistical significance was defined as a p-value <0.05.

3. Results

3.1. Patient characteristics

Twenty-four subjects were screened and enrolled between February 2020 and May 2021 at three US pediatric gastroenterology centers. The enrollment target of 30 subjects was not achieved due to recruitment barriers related to the COVID-19 pandemic. Of 24 subjects enrolled, 23 (95.8%) commenced treatment with the study formula and 18 (75%) completed the study. Among the 6 subjects who did not complete the study, 5 (20.8%) subjects withdrew due to adverse events. One subject did not commence treatment and was excluded as the age at enrollment was >48 months. Figure 1 shows the summary of subject disposition.

Baseline characteristics of subjects are described in Table 2. All subjects had neuro-developmental disabilities. Gastrointestinal comorbidities were prevalent in a large proportion of subjects, with 70.8% (17/24) of subjects being treated for constipation, and two-thirds (16/24) receiving medications for gastroesophageal reflux (GERD) or vomiting. Almost two-thirds of subjects were 'fiber-naïve' and did not receive a fiber-containing formula before enrollment into the trial. All children received minimal dietary fiber from oral foods before and during the trial. A summary of formulas used by study participants at the time of enrollment into the study is provided in Table S1 (Supplementary materials).

3.2. Gastrointestinal tolerance

The study formula was generally well tolerated: 19 (82.6%) subjects completed the 7-day study period and did not experience any significant gastrointestinal adverse effects that would have warranted discontinuation of the formula. Four (17.4%; 95% CI: 5%, 39%) subjects discontinued the study early due to gastrointestinal intolerance symptoms (Table 3). Three of these subjects presented with vomiting, of whom two were being treated with anti-reflux medications. Among subjects who discontinued the study formula prematurely, two were previously managed with an amino acid-based formula.

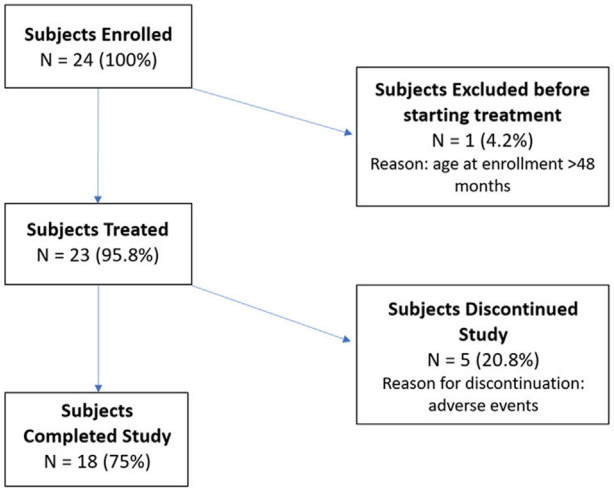

Fig. 1. Summary of subject disposition.

Table 2
Summary of demographics and baseline data (Intent-to-treat analysis set; n = 24).

Baseline characteristics	Number of subjects
Median age (range), months	35.5 (16, 57)
Age group, n (%),	
<12 months	0
12–23 months	6 (25)
24–35 months	6 (25)
36–47 months	10 (41.6)
48–60 months	2 (8.3)
Sex, female, n (%)	10 (41.6)
Race/ethnicity, n (%)	
Black or African American	19 (79.2)
White	5 (20.8)
Primary diagnosis n (%),	
History of extreme prematurity	14 (58.3)
Genetic condition	4 (16.6)
Hypoxic ischemic encephalopathy	3 (12.5)
Feeding disorder of unknown etiology	3 (12.5)
Gross Motor Function Classification System (GMFCS) level V	24 (100)
Gastrointestinal co-morbidities n (%),	
Constipation	17 (70.8)
Documented gastroesophageal reflux disease	5 (20.8)
Non-documented gastroesophageal reflux disease/ treatment with antireflux medications or antiemetics	11 (45.8)
Anthropometric measurements	
Weight, median (range), kg	13.6 (7.6, 17.6)
Weight-for-age Z-score, median (range)	−0.8 (−3.2, 1.4)
Length-for-age Z-score, median (range)	−2.0 (−4.8, 1.4)
Weight-for-length Z-score, median (range)	0.4 (−3.1, 3.1)
Previous formula, n (%)	
Standard polymeric formula	14 (58.3)
Partially hydrolyzed formula	5 (20.8)
Amino acid-based formula	3 (12.5)
Whole food-based (real-food) formula	2 (8.3)
Fiber-containing formula, n (%)	
Yes	9 (37.5)
No	15 (62.5)

3.3. Daily nutritional intake and PHGG dose

The daily intake of the study formula by the subjects ranged between 700 and 1360 mL/day. Based on the energy and protein targets established by the treating team, the mean (SD) percentage of the daily target energy intake achieved during the 7-day study period was 103.5% (24.6), corresponding to a mean actual energy intake of 1093.6 (281.9) kcal/day from the study formula. The mean percentage of protein intake across the 7-day-period was 139.5% (49.9) of the estimated target protein requirements, with a mean actual protein intake of 32.8 (8.5) g/day.

The mean PHGG intake from the study formula was 12 (2.4) g/day, with a range of 7.8 g/day to 16.3 g/day, depending on the amount of formula received.

3.4. Changes in body weight

The mean body weight at baseline was 12.5 (2.8) kg, corresponding to a weight-for-age z-score (WAZ) of −0.77; and the mean body weight at Day 8 (or last value prior to end of treatment) was

Table 3
Summary of characteristics of subjects who prematurely discontinued the study product.

Subjects and symptoms	Relationship to study product as per investigators	Outcome	Formula used before enrollment
Subject 1, aged 22 months			
Vomiting	Unrelated[a]	Early termination of SF at Day 2	Polymeric formula without fiber
Subject 2, aged 24 months			
Vomiting	Unrelated[b]	Early termination of SF at Day 2	Amino acid-based formula without fiber
Subject 3, aged 36 months			
Abdominal pain			Amino acid-based formula without fiber
Diarrhea	Probably related[c]	Early termination of SF at Day 5	
Subject 4, aged 30 months			
Viral bronchopneumonia with superimposed bacterial pneumonia	Unrelated	Early termination of SF at Day 5	Semi-elemental formula without fiber
Subject 5, aged 47 months			
Fussiness	Probably related	Early termination of SF at Day 3	Polymeric formula with 13 g/L of fiber
Vomiting			

SF: Study formula.
[a] Vomiting continued after the study product was discontinued and after switch to usual formula; subject suffering from gastroesophageal reflux.
[b] Subject previously on an amino acid-based formula; subject suffering from gastroesophageal reflux.
[c] GI intolerance may be due to switch from amino acid-based formula to semi-elemental formula, as well as possible adverse reaction to fiber.

12.5 (2.6) kg, corresponding to a WAZ of −0.78. There was no significant change in weight during the 7-day trial, with a mean and median change in WAZ of −0.05 (p = 0.43) and −0.03 (p = 0.41), respectively.

3.5. Stool characteristics

The distribution of stool consistency and summary of stool characteristics are displayed in Fig. 2 and Table 4. Overall, the participants had more regular and softer stools while on the study formula. Starting from Day 4, no participant experienced very hard or hard stools (Bristol Stool Scale type 1 or 2). Three subjects out of 16 (18.7%) ceased laxatives without rebound constipation during the study period. The percentage of subjects with normal stools (Bristol Stool Scale type 3, 4 or 5) went from 21.8% (5/23) on Day 1 to 38.9% (7/18) on Day 7; while the percentage of subjects with no daily stools went down from 39.1% (9/23) on Day 1 to 16.7% (3/18) on Day 7. Around 4% (1/23) of subjects experienced watery stools (Bristol Stool Scale type 7) on Day 1 against 16.7% (3/18) on Day 7.

3.6. Other gastrointestinal and general tolerance data

Fifteen (64.7%) subjects experienced no episodes of vomiting during the 7-day period, and five (19.8%) had 1–2 episodes of vomiting per day. Ten (41.9%) subjects had baseline flatulence, seven (30.7%) had no change in flatulence and five (22.2%) had little to no flatulence. In one subject (5.2%), the flatulence was assessed as clinically significant (significant discomfort). As per diary information, about two-thirds of subjects had no abdominal pain during the trial, three (12.9%) subjects complained about mild pain, three (12%) subjects had discomforting pain, one subject reported distressing pain, and another subject experienced intense or excruciating pain. Three-quarters of study participants were happy or content, four (18%) were fussy with or without crying, and two subjects (6.6%) reported history of being irritable/crying.

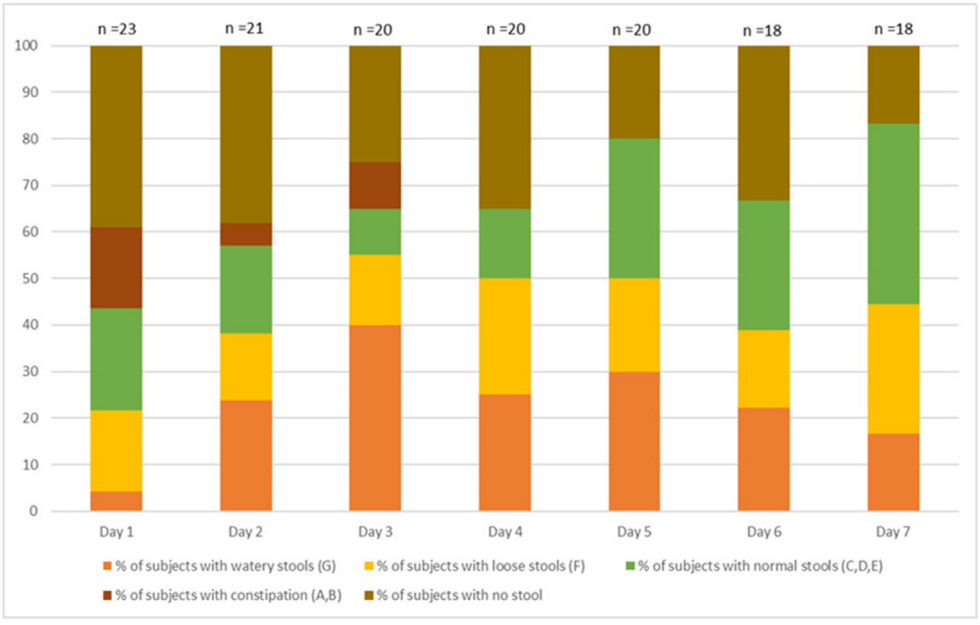

Fig. 2. Distribution of stool consistency during the 7-day study period.

Table 4
Summary of stool characteristics.

Stool Characteristics	
Number of stools per day, mean (SD)	
Day 1	1.2 (1.1)
Day 7	1.8 (1.2)
Subjects with no bowel movements for 24 h, *n* (%)	
Day 1	9/23 (39.1)
Day 7	3/18 (16.7)
Subjects with constipation [a], *n* (%)	
Day 1	4/23 (17.4)
Day 7 [b]	0 (0)
Subjects who stopped laxatives during the 7-day trial, n (%)	3/16 (18.7)
Subjects with diarrhea [c], n (%)	
Day 1	0/23 (0)
Day 7	1/18 (5.6)
Over the 7-day period	5/23 (21.7)

[a] Defined as stools of Bristol Stool Scale, type 1 or 2.
[b] No cases of constipation reported from Day 4.
[c] Defined as at least 3 watery stools (Bristol Stool Scale, type 7) per day.

3.7. Safety

Overall, 12 (52.1%) subjects reported at least one treatment-emergent adverse event (TEAE), and a total of 31 TEAEs were reported in the study. These included 29 non-serious TEAEs. In addition, one subject reported two serious adverse events (SAEs) that were deemed unrelated to the study formula as assessed by the investigator. This subject had fever on Day 1 of the study and was hospitalized on Day 5 due to a viral bronchopneumonia with superimposed bacterial pneumonia; this subject withdrew from the study on Day 5. The subject had a medical history of chronic lung disease with recurrent respiratory infections.

Five subjects withdrew from the study due to TEAEs. The most common TEAE was vomiting (n = 9; 39.1%), followed by diarrhea (n = 5; 21.7%) and abdominal pain (n = 4; 17.3%). The TEAEs were deemed 'related' to the study formula by the investigators in one subject who nonetheless was able to complete the trial to Day 8. Two other subjects reported TEAEs that were deemed 'probably related' to the study formula and discontinued the treatment before Day 8. There was a trend suggesting a higher risk of developing adverse reactions in fiber-naïve subjects compared to those who were consuming a fiber-containing formula prior to enrollment (10/12 vs. 2/12; Fisher's exact test, p = 0.09). Among the three subjects with TEAEs related/probably related to the study formula, two did not have fiber in their usual formula. Table 5 summarizes all TEAEs.

Table 5
Summary of All Treatment-Emergent Adverse Events (Safety Analysis Set, n = 23).

Treatment-Emergent Adverse Events (TEAEs)	Events, *n*	Subjects, *n* (%)
Total number of TEAEs	31	12 (52.2)
Gastrointestinal disorders:	22	11 (47.8)
Abdominal pain	5	4 (17.4)
Flatulence/malodorous stool	2	2 (8.6)
Diarrhea	5	5 (21.7)
Vomiting	10	9 (39.1)
Non-gastrointestinal disorders (infections, pyrexia, irritability, hiccups, rhinorrhea)	9	8 (34.7)
Serious Adverse Events (SAEs) [a]	2	1 (4.3)
Parainfluenza pneumonia with secondary bacterial pneumonia		
TEAEs Leading to Study Discontinuation	7	5 (21.7)
Relationship of TEAEs to the study formula:		
'Related'	1	1 (4.3)
'Probably related'	7	2 (8.6)
'Unlikely related' or 'Unrelated'	23	20 (86.9)

[a] No serious adverse events (SAEs) were deemed related to the study formula.

4. Discussion

This study evaluated the safety and tolerability of a semi-elemental enteral formula containing 12 g/L of PHGG in tube-fed young children. The findings indicate that, overall, the formula was well tolerated, with a shift towards softer stools in the majority of subjects. While PHGG has a long history of safe use when administered as a supplement to children and adults, particularly in those with functional gastrointestinal disorders [3,10,14,34], this study is the first to assess the safety of a PHGG-containing enteral formula in tube-fed children.

In our study population, about 70% of subjects received laxative treatment for constipation prior to enrollment in the study. Constipation was well controlled in all children within 3 days of formula intake, and the number of subjects without regular daily bowel movements dropped by more than half. These findings are consistent with published data that support the role of PHGG in the prevention and treatment of constipation in both children [3,9,14] and adults [13,35–40]. Several studies found that supplementation with PHGG was as effective as conventional laxative treatments in relieving stool-withholding and constipation-associated abdominal pain which allowed a reduction in the use of laxatives in children and adults [3,35,36]. In the present study, about one in five subjects was able to discontinue laxative treatment during the 7-day study period. This finding is clinically relevant as constipation and fecal retention are common co-morbidities in children with neuro-developmental disorders [23].

In subjects with constipation, PHGG increases fecal moisture and output [34,38,41,42]. The resulting softer and bulkier stools promote colonic peristalsis and facilitate defecation [43]. This was in keeping with observations in participants of the present study who developed softer and more frequent stools with an increase in the mean defecation frequency from 1.2 at enrollment to nearly two bowel movements per day at Day 7. PHGG has been shown to modulate colonic transit time (CTT) [37,39,44]. In a study involving 49 adult patients with chronic constipation, a PHGG intake of 5 g/day for 4 weeks significantly accelerated colonic transit by 12 h [37]. This effect was more prominent in patients with slower transit who achieved a reduction in CTT by approximately 22 h. In another study involving 68 adults with constipation-predominant irritable bowel syndrome, PHGG supplementation for 4 weeks reduced CTT by 7 h [39]. By contrast, healthy men (without constipation) fed a liquid diet supplemented with 15 or 21 g/L PHGG showed a prolonged CTT compared to those fed a fiber-free liquid diet [44,45], suggesting a normalizing effect of PHGG on bowel function and colonic transit.

During the study period, almost half of the children developed one or more loose or watery stools at some stage. However, diarrhea defined as ≥3 watery stools per day, occurred in 5 (21.7%) subjects. Its occurrence was, however, confounded by several factors, including concurrent use of laxatives and/or intercurrent infections. In addition, prior nutritional management with an amino acid-based formula in three children may indicate previous gastrointestinal issues or intolerance to semi-elemental formula. In studies involving young children, PHGG added to the WHO Oral Rehydration Solution at 15–20 g/L, proved to be effective in decreasing the duration of diarrhea and stool output, and enhancing weight gain in malnourished children aged 4–36 months with acute and persistent diarrhea [11,12,16].

The mode of action of PHGG in the presence of diarrhea may be related to the effects of SCFA. PHGG is fermented in the colon to SCFA, specifically butyrate, acetate and propionate, which promote the absorption of sodium and water by colonocytes [21,43]. This process of water absorption is important in improving stool consistency in subjects with diarrhea [18,34,46]. PHGG showed the

greatest production of SCFA compared to other fiber sources including soy oligosaccharides, fructo-oligosaccharides and inulin [43,47]. SCFA are a major player in gut health, providing the main energy source for the colonocytes, stimulating the growth of Lactobacilli and Bifidobacteria by lowering the colonic pH, and preventing the growth of pathogenic bacteria [48]. The modulating effects of PHGG on gut microbiota are likely to help shape a healthy microbiome from an early age. PHGG also has beneficial effects beyond the gut, including lowering of hyperglycemia and hyperlipidemia without loss of minerals nor micronutrients in feces [18,40,42].

Gastrointestinal side effects during tube feeding can be attributed to a diverse range of causes, including gut dysbiosis, infectious processes, medications, or to the underlying disease [21,22]. Fiber-containing formula can help normalize bowel function and improve microbiota profiles in tube-fed individuals [25]. In tube-fed adult patients, formula supplemented with PHGG was associated with a reduction in the frequency and duration of diarrhea compared with fiber-free feeds in both general wards and intensive care settings [21,49,50]. In a case series in children, PHGG-containing formula (6 g/L of PHGG) contributed to reducing gastrointestinal symptoms (diarrhea and constipation) and improved weight gain in two tube-fed children with cerebral palsy [14]. Enteral formulas containing other types of fiber have also shown beneficial effects on gastrointestinal symptoms. This includes, for instance, formulas containing real-food ingredients [51,52], and formulas containing other sources of fiber such as blend of soluble and insoluble fibers and short-chain fructo-oligosaccharides [53]. Despite the beneficial effects of fiber, fiber-free formulas are historically used 'by default' as a first-line formula in children requiring nutritional support. This may be mainly due to concerns regarding the tolerance of fiber in sick children or knowledge gaps among health care professionals regarding the importance of fiber in health and disease. In addition, evidence-based guidelines on fiber administration in children receiving nutritional support are currently lacking, and the optimal fiber amount and type designed to meet the requirements of tube-fed children is unknown. It is unclear whether fiber intake in tube-fed children should be similar to that of healthy children. Fiber recommendations for healthy children vary greatly between nutrition societies, ranging between 8.4 and 14 g/1000 kcal or 6–19 g/day in children aged 1–4 years [28–31]. PHGG intake in our study, which averaged 12 g/day, is aligned with these recommendations. The amount of fiber varies between marketed enteral formulas, and the study product has one of the highest fiber contents. A mixture of dietary fiber sources is generally recommended for healthy children, but there are no guidelines for tube-fed patients. While some enteral formulas contain more than one type of fiber, PHGG represents a single source. However, PHGG seems to fulfill the two main functional effects of a fiber with effects on fermentation, as well as acting as a bulking agent as shown in several studies [4–7,13,34,42].

The safety profile of PHGG is well documented in the literature [4–13]. Although in our study, among the TEAEs, vomiting was reported most frequently (39%), the investigators considered it 'probably related' to the study formula in only one subject. In fact, two-thirds of children enrolled in this study had either a documented diagnosis of GERD or were treated for vomiting/GERD prior to enrollment. This finding is in keeping with reports of GERD in up to 70% of children with neurological impairment [23]. These children represent a vulnerable population prone to gastrointestinal symptoms such as vomiting, abdominal discomfort and constipation [23]. In clinical practice, a minimal change in the volume, energy, type of formula or mode of administration may trigger gastrointestinal symptoms in sensitive children, suggesting that the TEAEs observed in the present study were likely multifactorial and not limited to the effects of PHGG alone.

Gastrointestinal symptoms appeared more likely to occur in the fiber-naïve children. In some of the subjects, these symptoms appear to be transient; however, the short study duration did not allow an assessment of the evolution of symptoms over a longer period. Mild-to-moderate bloating and flatulence have been reported during PHGG administration in some studies [21,35,38], particularly during the first week of administration, before it gradually decreased in the subsequent weeks. Based on the observations made in this study, fiber-naïve children, or those usually consuming low-fiber diets, may benefit from a gradual introduction of fiber, including PHGG. This approach may facilitate progressive gastrointestinal adaptation and less risk for developing gastrointestinal intolerance symptoms [27].

The present study had several limitations, including a relatively small sample size, absence of a control group and a short intervention period. Despite the relatively small sample size, the number of patients is a common standard for initial safety/tolerance assessments of this nature. The 7-day treatment period was likely not sufficient to fully assess the tolerability and benefits of the study formula, and some observed adverse symptoms may have been transient due to gastrointestinal adaptation. A significant proportion of study subjects was treated for constipation which made an assessment of the effect of the PHGG-containing study formula on diarrhea difficult. The presence of some confounders (simultaneous use of laxatives, concomitant infections, previous use of an amino acid-based formula) may have affected the readout of the stool characteristics results, although only five subjects had diarrhea. Detailed data on stool consistency and frequency before enrollment were not available, however, subjects with significant gastrointestinal symptoms at the time of screening were not included as per exclusion criteria. Changes in gut microbiota were not assessed in this safety and tolerability study and should be evaluated in future studies.

5. Conclusions

This is the first study to assess the safety and tolerability of a PHGG-enriched formula in young tube-fed children aged 1–4 years. The study formula was generally well tolerated and provided adequate nutrition. The formula was associated with a shift towards softer and more frequent stools in a population with a high prevalence of constipation. Therefore, the formula may have a role in the clinical management of chronic constipation and may enable a reduction in laxative treatment in some patients. A gradual introduction of the formula may reduce the risk of gastrointestinal intolerance symptoms, especially among 'fiber-naïve' patients. A follow-up study conducted over a longer intervention period in children with tube feeding-associated diarrhea or constipation would provide additional data to document the safety and benefits of this novel PHGG-enriched formula.

Author contributions

RGH was involved in study conceptualization and methodology; RGH and BZ were responsible for formal data analysis; GM and TS were involved in study investigation; BZ prepared the original draft manuscript; all authors were responsible for reviewing and editing subsequent drafts of the manuscript; GM, TS, BZ and RGH were involved in study supervision. All authors have read and agreed to the published version of the manuscript.

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Institutional review board statement

The study was conducted in accordance with the Declaration of Helsinki and approved by a centralized Institutional Review Board, Copernicus Group - CGIRB, Triangle Park, North Carolina, USA; Approval No. 20200199.

Informed consent statement

Informed written consent was obtained from all parents or legal guardians of subjects involved in the study.

Data availability statement

Data are available on request from the Chief Science & Medical Officer, Nestlé Health Science, 1800 Vevey, Switzerland.

Declaration of competing interest

All participating institutions received funding from Nestlé Health Science to complete the study. GM has given lectures for Nestlé Health Science and participated in another study funded by Nestlé Health Science. RGH and BZ are employees of Nestlé Health Science. TS declared no conflict of interest.

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Appendix A. Supplementary data

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