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ORIGINAL RESEARCH

Energy- and protein-enriched formula improves weight gain in infants with malnutrition due to cardiac and noncardiac etiologies

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Abstract

Background: We aimed to assess safety, tolerability, and improvement in weight gain with an energy- and protein-enriched formula (EPEF) in infants with poor growth.

Methods: Infants aged 1–8 months with poor growth received EPEF for 16 weeks. Our primary objective was improvement in weight as measured by change in weight-for-age *z*-score (WAZ) and weight gain velocity (grams per day) ≥ median for age. Secondary objectives included improvement in other anthropometric *z*-scores, formula tolerance, and safety.

Results: Twenty-six patients with poor growth due to congenital heart disease ($n = 15$), other organic causes ($n = 9$), and nonorganic causes ($n = 2$) completed the study per protocol. Mean daily energy intake was 123 ± 32 kilocalories per kilogram of body weight, with >90% of energy coming from EPEF. Weight gain velocity exceeded the median for 83% (20 of 24) and 67% (16 of 24) of infants at ≥1 time point and for the overall study period, respectively. Mean ± SD WAZ improved from −2.92 ± 1.04 at baseline to −2.01 ± 1.12 at 16 weeks ($P = 0.0001$). Z-scores for weight-for-length and head circumference ($P = 0.0001$) and for length-for-age ($P = 0.003$) improved significantly at 16 weeks. Compared with baseline, stool consistency was different at 2, 4, and 16 weeks ($P < 0.05$). There were no significant differences in vomiting, fussiness, or daily number of stools while there was a decrease or no change in spit-up, flatulence, crying, or gassiness.

Conclusion: EPEF is safe, well tolerated, and improves weight gain in infants with poor growth.

KEYWORDS
cardiac disease, enteral nutrition, malnutrition, pediatrics

CLINICAL RELEVANCY STATEMENT

Our study demonstrated that in infants with poor growth, an energy- and protein-enriched formula (EPEF) had a positive impact on growth, with appropriate rates of growth achieved by most infants. EPEF was found to be safe and well tolerated.

BACKGROUND

In the United States, malnutrition occurs in 5%–13%[1,2] of children in primary care settings and in 4% of hospitalized infants.[3] It is more common in children with medical conditions, including congenital heart disease (CHD).[4–8] These children may have increased nutrition requirements while concomitantly having impaired ability to consume adequate nutrition because of feeding difficulties, poor appetite, or their clinical status.[4,8–10] Inadequate nutrition intake should be corrected quickly, as undernutrition in early life can lead to growth failure and may adversely affect cognitive development and health outcomes throughout the life span.[11–13]

Nutrition support of infants with growth failure aims to provide additional energy and nutrients that exceed recommendations for healthy infants to promote catch-up growth. Increasing energy provision to infants is typically done by concentrating and/or fortifying infant formula (ie, preparing with a higher ratio of powder to water and/or adding glucose polymer powders and fat emulsions).[8,9,14] This may increase the risk of mistakes during preparation,[15] result in intolerance because of increased osmolality of the formula,[16] and/or result in suboptimal energy distribution from macronutrients (ie, decreasing the percentage of energy from protein).[17]

Previous clinical studies have shown that a ready-to-feed, energy- and protein-enriched formula (EPEF) is well tolerated, improves energy and nutrient intake, and promotes growth and protein anabolism.[17–24] EPEF formula may provide a viable alternative to concentrating and/or fortifying standard infant formulas to provide adequate nutrients and energy for infants with malnutrition and/or growth failure. We aimed to assess safety, tolerability, and improvement in weight gain with EPEF in infants with growth failure.

METHODS

Study design and participants

This prospective, open-label, single-arm growth, safety, and tolerance study was conducted across six sites in the United States. The study was approved by the Children's Wisconsin Institutional Review Board (1173875-16) and at each participating site. Participants were recruited from January 2018 through January 2020 after informed consent was obtained. Inclusion criteria were infants aged 1–8 months (and achieved term gestation) with malnutrition, defined as either weight-for-length *z*-score (WHZ) ≤ -1.0 or weight gain velocity *z*-score ≤ -2.0 over the previous 4–8 weeks, and expected to obtain ≥80% of total energy intake from EPEF for 16 weeks. Infants with Down syndrome were enrolled using only the WHZ criteria for malnutrition, not weight gain velocity. Exclusion criteria included small- and large-for–gestational age infants; gastrointestinal (GI), hepatic, or renal dysfunction; inherited metabolic disorders; congenital neurological insults; malabsorption; systemic or congenital infections; cow milk protein allergy and/or genetic conditions (except Down syndrome) known to interfere with growth or body dysmorphology; and children feeding directly at the breast more than twice per day.

Feeding regimen

Participants were fed EPEF for up to 16 weeks or until meeting criteria for "early success" (WHZ ≥ 0 or weight velocity > +2 *z*-score for age at two consecutive visits). The early success criteria were included to avoid potential negative impacts of excessive catch-up growth.[25] EPEF is an energy-dense formula providing (per 100 ml): 100 kcal of energy, 2.6 g of protein, and 5.4 g of fat, with an osmolarity of 305 mOsm/L (Fortini Infant, Nutricia North America, Rockville, MD). EPEF contains a prebiotic fiber blend of nine parts galactooligosaccharides to one part fructooligosaccharides (detailed information about the formula is provided in Table S1). Specific intake targets were deferred to site primary investigators because of the individual needs, varying ages, and medical conditions of the study population. Participants could be fed EPEF orally, by tube feeding, or by a combination or oral and tube feeding. Infants who met criteria for early success were to be switched to a lower energy density feed after exiting the study.

Anthropometric data

Participants were seen at visit 1 (baseline), visit 2 (2 weeks), visit 3 (4 weeks), visit 4 (8 weeks), visit 5 (12 weeks), and visit 6 (16 weeks). A phone call was conducted on day 3 to confirm full transition to the EPEF feeding regimen. At each visit, weight, length, and head circumference were obtained by the same trained researcher according to standard anthropometric procedures (details reported in the supporting information).[26] *z*-scores for weight-for-age (WAZ), length-for-age (HAZ), WHZ, and head circumference (HCZ) were obtained using the World Health Organization (WHO) Anthro software program (WHO, Anthro 3.2.2, 2011).[27] Corrected age was used for all infants who were born <37 weeks' gestational age.

Nutrition intake and EPEF tolerance

Diaries on EPEF and other food or formula intake (for 7-day periods) and 3-day records of stool characteristics (stool color, number, and consistency) and formula tolerance (episodes of spit-up, vomiting, gassiness, flatulence, fussiness, and crying) were kept by caregivers prior to visits 2–6. EPEF and food intake diaries were analyzed using

ESHA Food Processor Nutrition Analysis Software (The Food Processor 11.7.217, database structure version 11.7.1).[28]

Safety

Adverse effects (AEs) and severe AEs (SAEs) were monitored and investigated throughout the study following a standardized safety protocol. Details of the AEs and SAEs, including number and types of events, onset, duration, nature of the event, severity, and action taken were recorded throughout the study. The relationship of the AE and SAE to the study product was assessed and documented. Further details of the safety protocol and framework for evaluation of AEs and SAEs are included in the supporting information.

Data analysis

Data sets

The per protocol (PP) data set was used to report all growth, intake, and tolerance parameters. Infants were excluded from the PP group if they were noncompliant with the feeding regimen and/or enrolled in violation of inclusion or exclusion criteria without an approved exemption. The all-patients-treated data set, including all patients who were enrolled in the study, was used for all safety parameters.

Our primary objective was improvement in weight from baseline through 16 weeks, as measured by change in WAZ and attainment of weight gain velocity (grams per day) greater than or equal to median weight gain velocity for age.[26] Secondary study objectives included improvements in WHZ, HAZ, and HCZ, as well as weight and length gain velocities.

Assessment of the primary objective

Statistical evaluations (paired *t*-tests) were performed to establish differences between WAZ at baseline and at the end of study. Weight gain velocity was assessed for baseline and end of study and for each of the following 4-week intervals: visits 1–3 (weeks 1–4), visits 3–4 (weeks 4–8), visits 4–5 (weeks 8–12), and visits 5–6 (weeks 12–16). Actual weight gain velocity was compared with the target (median weight gain velocity for age). The Kaplan-Meier survival analysis method was used to determine whether each patient's rate of weight gain met this target and the earliest time point when this occurred.

Assessment of the secondary objectives and other outcomes

Statistical evaluations were performed (paired *t*-test for continuous metrics, Fischer exact test for 2 × 2 contingency tables, and chi-square test for tables with more than two rows and/or more than two columns) to identify differences in measures between baseline and follow-up visits, as required, for each of the secondary parameters. In addition, generalized linear mixed-effects model via PROC GLIMMIX of SAS (ref- SAS/STAT Software version 9.4, 2020; SAS Institute, Cary, NC)[29] was used to conduct repeated-measures analysis of covariance.

The growth measures assessed were as follows: weight in grams, WAZ and WHZ; length in centimeters and HAZ; HC in centimeter and HCZ. Data are presented at each study visit and the change from baseline. Summary statistics (means, SD, median, 5th to 95th percentiles, and minimum to maximum) for all growth measures (actual measurements and *z*-scores) for the PP population (for all infants and two subgroups: infants with CHD and non-CHD infants) were generated.

Summary statistics (means, SD, median, and minimum to maximum) were generated for baseline demographics, feeding history, and tolerance. Diary data were compared with reported prestudy levels and breastfed reference groups for stool characteristics.[30,31] The energy intakes (kilocalories per kilogram per day) achieved by infants were compared with a scientifically appropriate reference for the promotion of catch-up growth in infants of 120 kcals/kg/day.[9,32–35]

RESULTS

Participants

Twenty-four of the 30 enrolled infants completed the study, including four infants (13%) who met criteria for early success and finished the study prior to visit 6 (week 16). The leading cause of growth failure was a CHD (58%), followed by other organic causes (35%) and nonorganic causes (8%). Mean length of the intervention period was 94 ± 35 days. The flow of participants through the study is illustrated in Figure 1. Baseline characteristics are summarized in Table 1 and feeding history in Table 2.

Evaluation of primary objective

Change in WAZ

Mean (±SD) WAZ was −2.92 (±1.04) at baseline and −2.01 (±1.12) at week 16 (see Figure 2). Mean (SD) improvement in WAZ was 0.79 (±0.76) between baseline and end of study participation ($P = 0.0001$) and 0.86 (±0.74) between baseline and week 16 ($P = 0.0001$).

Weight gain velocity

Two infants in the PP group withdrew early and are not included in this analysis. Eighty-three percent (20 of 24) of participants achieved weight gain velocity greater than or equal to median weight gain

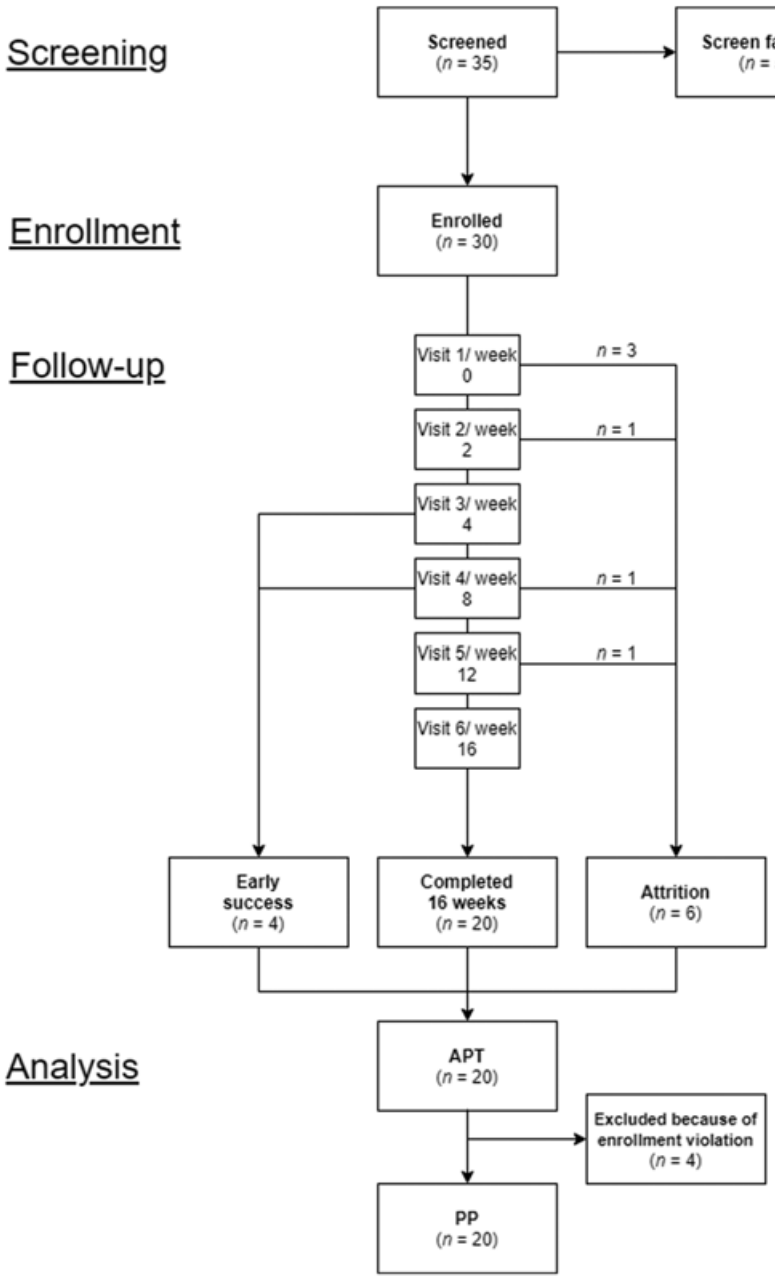

FIGURE 1 Participant flowchart. APT, all patients treated; PP, per protocol group

velocity for age on at least one visit interval during the study. The number of infants meeting the primary objective at each time point and the cumulative number of infants having met this criterion are summarized in Table 3.

Sixteen infants achieved the weight gain velocity (greater than or equal tomedian weight gain velocity for age) for the overall study period. The remaining eight infants gained weight during the study period, although at rates below the WHO median. This group included four infants who achieved target weight gain velocity on at least one occasion. These infants had experienced intermittent illnesses (8 of 8) and/or had surgical procedures (6 of 8) during the study period. All except two of these infants had CHD.

Evaluation of secondary objectives: growth outcomes

WAZ, WHZ, and HCZ all increased significantly from baseline to end of study and from baseline to 16 weeks (Table 4). HAZ increased significantly from baseline to 16 weeks and trended upward from baseline to end of study; however, this increase did not achieve significance (Table 4).

Nutrition intake

Total energy intake across the study period was 123 ± 32 kcals/kg/day (123 ± 32 ml EPEF/kg/day), of which the majority (94.3 ± 7.5%) was

TABLE 1 Demographics and anthropometric characteristics at baseline, PP group

Parameter/categories	Statistics	Grow-in, PP (*N* = 26)
Age at Visit 1 (weeks)	*n*	26
	Mean (SD)	22.2 (10.5)
	Min, max	5, 39
Sex		
Male	*n* (%)	16 (61.5)
Female	*n* (%)	10 (38.5)
Race		
White	*n* (%)	11 (42.3)
Black	*n* (%)	12 (46.2)
Hispanic/Latino	*n* (%)	3 (11.5)
Gestational age (weeks)	*n*	26
	Mean (SD)	37.4 (3.2)
	Min, max	28.4, 41.1
Birth weight (g)	*n*	26
	Mean (SD)	2920 (672)
	Min, max	980, 3880
Weight-for-age *z*-score at birth	*n*	20
	Mean (SD)	−0.19 (0.70)
	Min, max	−1.37, 1.33
Weight-for-age *z*-score at visit 1	*n*	26
	Mean (SD)	−2.92 (1.04)
	Min, max	−6.43, −1.05
Weight-for-length *z*-score at visit 1	*n*	26
	Mean (SD)	−2.02 (0.75)
	Min, max	−3.75, −0.39
Length-for-age *z*-score at visit 1	*n*	26
	Mean (SD)	−2.06 (1.31)
	Min, max	−5.64, 1.20
Head circumference–for-age *z*-score at visit 1	*n*	26
	Mean (SD)	−1.50 (1.23)
	Min, max	−4.05, 0.55
Cause of growth failure		
Congenital heart disease	*n* (%)	15 (57.7)
Ventricular septal defect	*n* (%)	5 (19.2)
Tetralogy of Fallot	*n* (%)	1 (3.8)
Pulmonary stenosis	*n* (%)	1 (3.8)
Atrial septal defect, ventricular septal defect	*n* (%)	2 (7.7)
Complete atrioventricular septal defect	*n* (%)	2 (7.7)
Complex heart defects[a]	*n* (%)	4 (15.4)
Other (organic)	*n* (%)	9 (34.6)
Feeding difficulty	*n* (%)	1 (3.8)
History of prematurity	*n* (%)	2 (7.7)
Pierre Robin syndrome	*n* (%)	1 (3.8)

(Continues)

TABLE 1 (Continued)

Parameter/categories	Statistics	Grow-in, PP (*N* = 26)
Tongue tie, chronic congestion, and inadequate oral intake	*n* (%)	1 (3.8)
Unknown	*n* (%)	4 (15.4)
Other (nonorganic)	*n* (%)	2 (7.7)
Infants with Down syndrome	*n* (%)	6 (23.1)

Abbreviations: max, maximum; min, minimum; PP, per protocol.
[a]Complex heart defects included atrial septal defect, patent ductus arteriosus, and ventricular septal defect (*n* = 1); complete atrioventricular septal defect and patent ductus arteriosus (*n* = 1); congenital anomaly of aortic arch, tetralogy of Fallot, and persistent left superior vena cava (*n* = 1); and patent ductus arteriosus and ventricular septal defect (*n* = 1).

TABLE 2 Baseline feeding history, PP group

Parameter/categories	Statistics	Grow-in, PP (*N* = 26)
Mode of feeding at study entry		
Oral	*n* (%)	21 (80.8)
Tube fed	*n* (%)	0
Combination (oral and tube fed)	*n* (%)	5 (19.2)
Feeding at study entry		
Breast feeding	*n* (%)	0 (0)
Formula feeding	*n* (%)	26 (100.0)
Combination	*n* (%)	0 (0)
Energy density of feed at study entry		
20 kcal/fl oz	*n* (%)	8 (30.8)
22 kcal/fl oz	*n* (%)	1 (3.8)
24 kcal/fl oz	*n* (%)	7 (26.9)
25 kcal/fl oz	*n* (%)	0
26 kcal/fl oz	*n* (%)	2 (7.7)
27 kcal/fl oz	*n* (%)	7 (26.9)
28 kcal/fl oz	*n* (%)	1 (3.8)
Feeding type at study entry	*n*	25
Standard IF	*n* (%)	8 (32.0)
Standard IF (GI concern)	*n* (%)	8 (32.0)
Protein hydrolysate formula	*n* (%)	4 (16.0)
Premature (postdischarge) formula	*n* (%)	6 (24.0)
Partially hydrolyzed whey protein	*n* (%)	2 (8.0)
Number of formulas prior to study entry	*n*	25
	Mean (SD)	4.0 (2.6)
	Median	3.0
	Min, max	1, 10

Abbreviations: GI, gastrointestinal; IF, infant formula; max, maximum; min, minimum; PP, per protocol.

from EPEF (116 ± 32 kcals/kg/day or 116 ± 32 ml EPEF/kg/day). There was a small increase in energy intake from complementary foods for some infants toward the end of the study; however, EPEF was the main energy source (>90% on average) at all time points.

Tolerance

Diary-reported tolerance outcomes throughout the study are shown in Table 5. Compared with baseline, percentage of feedings resulting in spit-up significantly decreased from visit 3 onward. The reported mean number of feeds resulting in vomiting did not change throughout the study. Reported levels of gassiness, flatulence, fussiness, and crying were generally similar or lower during the study compared with baseline. At some visits, levels were significantly lower ($P < 0.05$) for gassiness and crying than at baseline.

No changes in the mean number of stools were reported. No prestudy data on stool color were available and no observable differences throughout the study were seen. More stools were reported as watery during the study (57.1%–69.6%) compared with visit 1 (13.6%) and fewer were reported as soft (68.2% at visit 1 compared with 13%–30% throughout the study). Stool consistency was statistically different ($P < 0.03$) at visits 2 and 3 compared with baseline. Stool consistency of the infants in the study (>80% watery or soft) is comparable to infants being breastfed.[30,31] Feed intolerance requiring discontinuation of EPEF was reported for one infant (withdrew on day 1 because of vomiting and diarrhea).

Safety

At least one AE was reported for 28 infants (93%) during the study. The most frequent AE classification was GI (23 infants, 77%) followed by infections (16 infants, 53%). Most of the GI AEs reported were vomiting 53% (16 of 30), increased spit-ups 20% (6 of 30), and diarrhea 30% (9 of 30); these were mild/moderate and resolved without intervention. The majority (60%) of the AEs were classified as "not related" and an additional 16% as "unlikely" to be related to the product. Of those "probably related," all five cases were GI (vomiting, diarrhea, or spit-up), and of those "possibly related," 13 of 15 AEs were GI (vomiting, diarrhea,

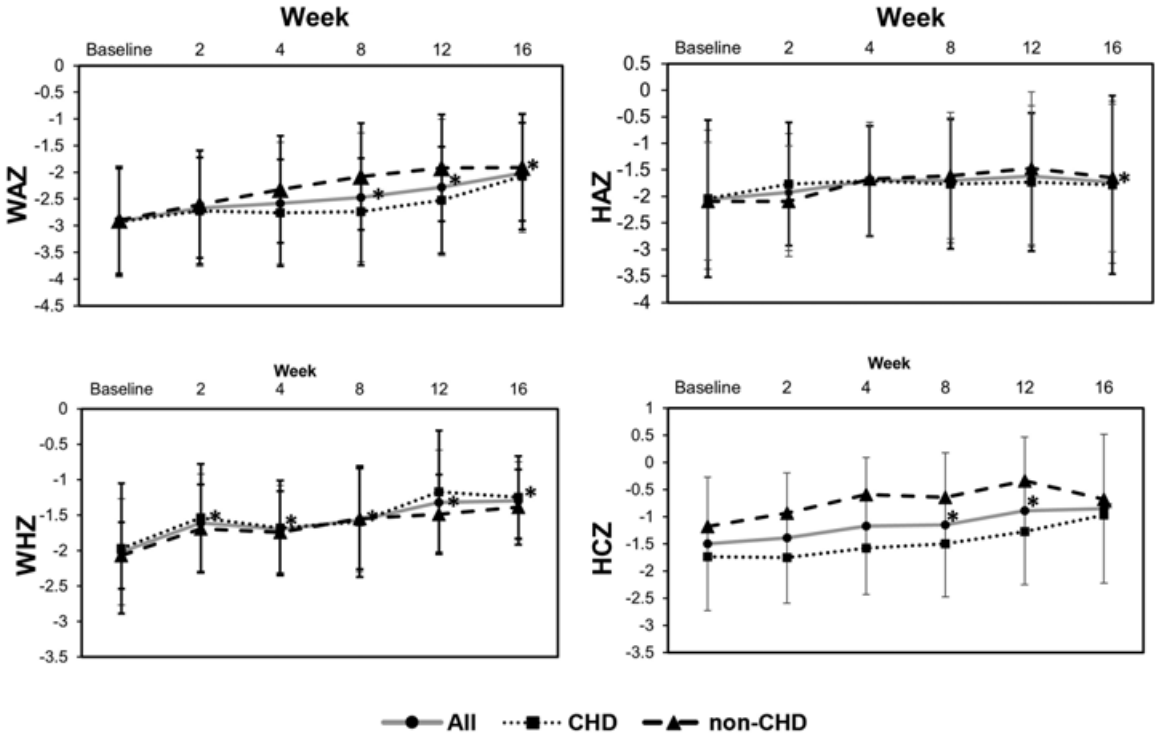

FIGURE 2 Mean (SD) *z*-scores by cause of growth failure from baseline to week 16 (per protocol group). *Indicates *P*-value for change from baseline < 0.05. HAZ, length-for-age *z*-score; HCZ, head circumference–for-age *z*-score; WAZ, weight-for-age *z*-score; WHZ, weight-for-length *z*-score

TABLE 3 Number of participants meeting weight gain velocity target (greater than or equal to WHO growth standards median weight gain velocity for age) at each visit and cumulative totals

Visit (time in weeks)	*n*	Number and proportion (%) of infants who met success at visit[a]	Cumulative number and proportion (%) of infants who met success[b]
By visit 3 (week 4)	24	14 (58)	14 (58)
By visit 4 (week 8)	22	8 (36)	15 (63)
By visit 5 (week 12)	20	10 (50)	18 (75)
By visit 6 (week 16)	18	12 (67)	20 (83)

Abbreviations: *n*, total number of participants who provided a measure at that visit; WHO, World Health Organization.
[a]Number and proportion (%) of infants who met success at visit: the number of participants at that visit who met the criteria for success and the percentage of the participants who provided a measure at that visit.
[b]Cumulative number and proportion (%) of infants who met success: the cumulative number of participants who met the criteria for success up to and including that visit and the percentage of the participants who provided a measure up to and including that visit.

increased spit-ups); 1 of 15 was dermatologic (perioral skin rash); and 1 of 15 was hepatic, lymphatic/hematologic (elevated aspartate aminotransferase, alanine aminotransferase, and platelet levels).

The majority of AEs (65%) were assessed as mild and the remainder (35%) as moderate. A total of six SAEs were reported for five (16.6%) infants during the study, all of whom had CHD as cause of growth failure. Four of the SAEs were classified as not related to the study product and two as unlikely related to the study product. In two of the infants, the SAEs were due to confirmed viral infections (2 of 2 classified as not related), and the study formula was stopped temporarily while an oral rehydration solution was administered. Three of the SAEs were due to poor oral intake associated with deteriorating cardiac function (1 of 3 classified as not related and 2 of 3 classified as unlikely related), all of which necessitated placement of a nasogastric or gastrostomy tube. The final SAE was reported in an infant, after completion of the study, who required repair of an inguinal hernia (classified as not related).

DISCUSSION

Our prospective study provides evidence that EPEF supports improvements in growth in infants with various underlying causes of malnutrition and is well tolerated and safe.

TABLE 4 Growth *z*-scores at baseline, week 16, and end of study and change from baseline

	n	Mean (SD)	*P*-value for difference with baseline
Weight-for-age *z*-scores			
Baseline	26	−2.92 (1.04)	
Week 16	18	−2.01 (1.12)	
Change from baseline to week 16	18	0.86 (0.74)	0.0001
Final study visit[a]	24	−2.18 (1.07)	
Change from baseline to final visit	24	0.79 (0.76)	0.0001
Length-for-age *z*-scores			
Baseline	26	−2.06 (1.31)	
Week 16	18	−1.73 (1.53)	
Change from baseline to week 16	18	0.25 (0.61)	0.003
Final study visit[a]	23	−1.84 (1.42)	
Change from baseline to final visit	23	0.28 (0.68)	0.06
Weight-for-length *z*-scores			
Baseline	26	−2.02 (0.75)	
Week 16	18	−1.30 (0.55)	
Change from baseline to week 16	18	0.77 (0.81)	0.0001
Final study visit[a]	23	−1.31 (0.59)	
Change from baseline to final visit	23	0.74 (0.73)	0.0001
Head circumference–for-age *z*-scores			
Baseline	26	−1.50 (1.23)	
Week 16	17	−0.85 (1.37)	
Change from baseline to week 16	17	0.54 (0.68)	0.0001
Final study visit[a]	23	−1.04 (1.23)	
Change from baseline to final visit	23	0.47 (0.61)	0.001

[a]Final study visit represents the last visit during the study, which for some infants was not week 16 (ie, those who met the early success criteria and those who withdrew from the study before the 16-week visit). Two infants did not provide complete anthropometric data at the final study visit because of withdrawing early from the study ($n = 1$) and because of changes to the final study visit due to institutional policies during the coronavirus disease 2019 pandemic ($n = 1$). Two participants did not provide any anthropometric measures at the final study visit because of withdrawing early from the study ($n = 1$) and because of changes to the final study visit due to institutional policies during the coronavirus disease 2019 pandemic ($n = 1$).

Despite *z*-scores well below population references at study entry, most infants in our study achieved the primary objective of obtaining an adequate rate of weight gain to achieve catch-up growth. A few of these infants responded particularly well to the nutrition intervention, and the correction of their growth deficits was rapid (3 of 26 met criteria for early success). All infants gained weight over the study period, including the four infants (17%) who did not meet the target weight gain velocity at any time point in the study. Gains in length, weight-for-length, and head circumference were also achieved over the course of the intervention with all *z*-scores (WAZ, HAZ, WHZ, and HCZ) improving significantly from baseline to 16 weeks.

Improvements in weight gain for infants fed EPEF have previously been reported in randomized controlled trials[17,24] and a retrospective review of case records[22]; however, our study is the first to report significant improvements in length. Length gains are important in that they reflect accretion of skeletal mass rather than muscle, fat, and other tissue mass.[34] Clarke et al reported significantly improved WAZ and a nonsignificant decrease in HAZ for infants fed EPEF for 6 weeks. In our study, improvements in HAZ were significant at 16 weeks despite the inclusion of infants with Down syndrome (6 of 26 participants), who are usually significantly shorter than healthy infants.[36] Length gains in infants are typically more slowly achieved than weight gains; therefore, shorter duration of the feeding intervention may have limited the observation of length gains by Clarke et al.[17] This may also explain why HAZ improvements were not significant from baseline to final visit in our study, as this measure included infants with final observations at <16 weeks due to meeting criteria for early success or withdrawing at earlier time points. Our findings suggest that infants with growth failure may benefit from continued nutrition intervention with EPEF after initial improvements in weight if catch-up length gains are required to correct growth failure.

TABLE 5 Tolerance parameters by visit, per protocol group

		Prestudy	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
Infant formula intake							
Number of daily formula feedings	*n*	NA	23	24	22	19	15
	Mean (SD)	NA	6.1 (1.8)	6.3 (1.6)	6.5 (1.9)	6.0 (1.6)	6.5 (1.4)
	Median	NA	6.2	6.0	6.0	5.6	6.9
	Min, max	NA	1.0, 9.5	4.0, 10.0	4.4, 10.0	4.4, 10.0	3.7, 8.7
Percentage of formula feedings resulting in spit-up	*n*	26	23	24	22	19	15
	Mean (SD)	28.2 (42.0)	16.8 (25.1)	15.6 (24.7)	13.2 (23.1)[a]	9.1 (11.8)[a]	7.4 (15.0)[a]
	Median	1.5	9.2	4.0	4.2	2.9	0.0
	Min, max	0.0, 50.0	0.0, 100.0	0.0, 100.0	0.0, 100.0	0.0, 41.6	0.0, 57.7
Percentage of formula feedings resulting in vomiting	*n*	26	23	24	22	19	15
	Mean (SD)	3.8 (13.6)	6.8 (12.1)	5.5 (10.3)	2.1 (4.4)	5.5 (7.1)	3.2 (7.3)
	Median	0.0	0.0	0.0	0.0	2.4	0.0
	Min, max	0.0, 50.0	0.0, 47.5	0.0, 42.9	0.0, 18.4	0.0, 25.0	0.0, 23.8
Stool characteristics							
Average number of stools per day	*n*	26	23	23	21	18	15
	Mean (SD)	2.2 (1.3)	2.2 (1.8)	2.4 (2.0)	2.0 (1.0)	2.1 (1.4)	2.2 (1.3)
	Median	2.0	1.7	1.7	1.7	2.0	2.0
	Min, max	0.0, 4.0	0.7, 8.0	0.3, 8.0	0.7, 5.0	0.0, 5.7	0.0, 5.7
Average stool-consistency score	*n*	22	23	23	21	17	14
Watery	*n* (%)	3 (13.6)	16 (69.6)[a]	15 (65.2)[a]	12 (57.1)	10 (58.8)	9 (64.3)
Soft	*n* (%)	15 (68.2)	3 (13.0)[a]	7 (30.4)[a]	6 (28.6)	4 (23.5)	2 (14.3)
Formed	*n* (%)	4 (18.2)	4 (17.4)[a]	1 (4.3)[a]	2 (9.5)	3 (17.6)	3 (21.4)
Hard	*n* (%)	0	0	0	1 (4.8)	0	0
Assessment of stool color	*n*	NA	23	23	21	17	14
Yellow (I and II)	*n*	NA	4	1	2	2	4
Green (III)	*n*	NA	10	10	6	5	2
Brown (IV and VI)	*n*	NA	6	6	7	6	5
Black (V)	*n*	NA	3	6	6	4	3
Tolerance diaries							
Assessment of gassiness	*n*	26	23	22	21	18	15
	Mean (SD)	2.6 (1.1)	2.3 (1.0)	2.2 (0.9)	2.1 (0.9)	1.9 (0.6)[a]	1.9 (0.9)[a]
None	*n* (%)	5 (19.2)	5 (21.7)	5 (22.7)	6 (28.6)	5 (27.8)	5 (33.3)
1–2 times per day	*n* (%)	9 (34.6)	6 (26.1)	6 (27.3)	4 (19.0)	8 (44.4)	6 (40.0)
3–4 times per day	*n* (%)	4 (15.4)	7 (30.4)	6 (27.3)	10 (47.6)	5 (27.8)	3 (20.0)
>4 times per day	*n* (%)	8 (30.8)	5 (21.7)	5 (22.7)	1 (4.8)	0	1 (6.7)

(Continues)

TABLE 5 (Continued)

		Prestudy	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
Assessment of flatulence	*n*	26	23	22	21	18	15
	Mean (SD)	2.5 (1.2)	1.9 (1.0)	2.0 (1.0)	1.9 (1.0)	2.0 (1.1)	1.9 (0.9)
None	*n* (%)	7 (26.9)	8 (34.8)	8 (36.4)	9 (42.9)	8 (44.4)	6 (40.0)
1–2 times per day	*n* (%)	7 (26.9)	7 (30.4)	6 (27.3)	5 (23.8)	1 (5.6)	5 (33.3)
3–4 times per day	*n* (%)	5 (19.2)	4 (17.4)	4 (18.2)	4 (19.0)	6 (33.3)	3 (20.0)
>4 times per day	*n* (%)	7 (26.9)	4 (17.4)	4 (18.2)	3 (14.3)	3 (20.0)	1 (6.7)
Assessment of fussiness	*n*	26	23	22	21	18	15
	Mean (SD)	2.0 (0.9)	1.9 (0.8)	1.7 (0.6)	1.9 (0.8)	1.9 (0.8)	1.6 (0.7)
None	*n* (%)	9 (34.6)	7 (30.4)	6 (27.3)	6 (28.6)	5 (27.8)	5 (33.3)
<1 h/day	*n* (%)	10 (38.5)	11 (47.8)	11 (50.0)	7 (33.3)	4 (22.2)	7 (46.7)
1–3 h/day	*n* (%)	5 (19.2)	4 (17.4)	4 (18.2)	7 (33.3)	6 (33.3)	2 (13.3)
>3 h/day	*n* (%)	2 (7.7)	1 (4.3)	1 (4.5)	1 (4.8)	3 (16.7)	1 (6.7)
Assessment of crying	*n*	26	23	22	21	18	15
	Mean (SD)	2.2 (1.0)	1.8 (0.7)[a]	1.6 (0.6)	1.9 (0.8)	1.7 (0.6)	1.5 (0.8)[a]
None	*n* (%)	8 (30.8)	8 (34.8)	8 (36.4)	7 (33.3)	5 (27.8)	9 (60.0)
<1 h/day	*n* (%)	9 (34.6)	10 (43.5)	10 (45.5)	7 (33.3)	8 (44.4)	3 (20.0)
1–3 h/day	*n* (%)	6 (23.1)	5 (21.7)	4 (18.2)	6 (28.6)	3 (16.7)	1 (6.7)
3–6 h/day	*n* (%)	3 (11.5)	0	0	0	1 (5.6)	2 (13.3)
>6 h/day	*n* (%)	0 (0.0)	0	0	1 (4.8)	1 (5.6)	0

Abbreviations: max, maximum; min, minimum; NA, not applicable.
[a] *P*-value < 0.05 compared with prestudy.

Consistently achieving adequate growth can be difficult for infants with underlying medical conditions because of the clinical course of their disease. In some severe cases, prevention of further weight loss rather than an improved growth rate may be a reasonable outcome.[37] The majority (93%) of participants in our study had an underlying medical condition, with more than half of our study population (58%) having a CHD. CHDs can significantly impact growth because of frequent and disruptive surgical interventions, fluid restriction necessitating reduced volumes of formula, and increased nutrition requirements to support recovery from surgery.[4,8,9] In our study, infants with CHD and non-CHD infants had similar WAZ at baseline and similar weight gain over the duration of the study. At the end of the study, mean WAZ were similar in both the CHD and non-CHD groups. Therefore, our study shows that EPEF can support improved growth outcomes in a medically challenging patient population.

To promote catch-up growth, infants with malnutrition need more energy, protein, and other nutrients than their healthy counterparts while assuring GI tolerance.[7,20,35,38] A target intake of 105–126 kcal/kg/day is often recommended to promote catch-up growth.[34,35] However, many infants do not consume the requisite energy (and other nutrients) to enable improved weight gain.[39,40] In our study, a diverse group of infants consumed, on average, 123 ± 32 kcals/kg/day. The majority of this energy came from EPEF that contributed, on average, >90% of total energy intakes across the study. Thus, not only did the infants in our study meet energy intake recommendations, but they also demonstrated improvements in all growth parameters through this intake despite significant underlying illnesses.

Infants with illness-related growth failure, such as much of our study population, often have feeding difficulties, GI symptoms, and/or feeding intolerance that impact nutrition intake. This may have been one reason for the multiple formula changes (4 ± 2.6 formulas) prior to enrollment reported for our study population. To assess tolerance of the EPEF, achievement of target dietary intake, outcomes of site-reported GI AEs and SAEs, ongoing clinical assessments, and tolerance diary outcomes have been reviewed.

In approximately half (53%) of the participants, vomiting adverse effect was reported, which is reflected in the tolerance diaries as an increase in vomiting that was reported initially (visit 2) but resolved over the course of the study. Feeding and GI problems, such as reflux, swallowing difficulties and vomiting are frequently reported in infants with CHD,[8–10] and as CHD was the cause of growth failure in 58% of participants, this condition may have contributed to the number of vomiting AEs. A change in stool consistency from baseline was also reported for infants, with more parents reporting watery stools from visit 2 onward. This is potentially due to infants changing to the prebiotic containing–EPEF. This change in stool consistency toward more

watery/soft stool is acceptable and is in line with the stool consistency reported for healthy breastfed infants.[30,31] These changes in stool consistency were not related to diarrhea, as it was not reported as a significant AE in the study. Other tolerance parameters reported (gassiness, flatulence, crying, or spit-ups) were unchanged or reduced from those reported at baseline or throughout the study.

Assessment of feeding tolerance is multifactorial, and a recent study in critically ill infants proposed a standard definition of feeding intolerance to include an inability to achieve enteral nutrition targets, in combination with the presence of GI symptoms (presence of repeated vomits and diarrhea or severe GI symptoms [eg, abdominal pain or distension]).[41] Considering this definition, we conclude that tolerance of the EPEF was acceptable, as the required formula intakes were achieved, GI symptoms resolved, and tolerance was not cited by the study sites as a reason for withdrawal except for one participant (withdrawn on day of enrollment).

For most infants, at least one mild/moderate AE was reported during the study, which may be influenced by symptoms related to their underlying clinical condition. However, most AEs (76%) were considered not related or unlikely to be related to the study product. Of the AEs possibly/probably related to the study product, these generally resolved with no action. There were a small number of SAEs reported in the study, all of which were considered not or unlikely to be related to the study product. Previous studies on EPEF have similarly reported the formula to be safe and overall well tolerated, with limited side effects.[17–21,23,24]

Traditionally, there have been concerns about concentrating infant formula beyond 27 kcal/oz (0.9 kcal/ml) solely by decreasing the amount of water used to make the formula. These concerns are based on changes in macronutrient concentration, especially increased protein and solute delivery that could be deleterious in young infants. Beyond this concentration, modular products (either solely carbohydrate or solely lipid additives) have been used. Such additives change the macronutrient composition, suffer from lack of miscibility, and increase potential for preparation errors, both by milk laboratory personnel and caregivers.

In this study, the increased energy and nutrient intakes provided by EPEF had a positive impact on growth while being found to be well tolerated and safe. The performance of EPEF in this and other studies[17–24] should put to rest any reservations about using 30 kcal/oz (1 kcal/ml) formula in infants. We should also note that EPEF provides a higher percentage of energy as protein (10.4%) than standard infant formula, and this should enable more appropriate gain of lean body mass to fat.[34]

Limitations

Although not directly a limitation, there were difficulties in recruitment, resulting in closing the study prior to meeting enrollment targets. Increased breastfeeding rates and utilization of protein hydrolysate or elemental formulas for infants with poor growth limited the number of infants suitable for inclusion in this study. Despite the reduction in sample size, our study was sufficiently powered to show significant improvements in growth parameters.

In our study, we did not limit the enrollment of infants with CHD to infants postcardiac repair surgery. This resulted in a mixed group, with nine infants in the PP group having cardiac repair surgery during the study (60% of infants with a CHD), with surgery occurring at varying times from week 2 up through week 13. Corrective surgery can improve growth failure in infants with CHD and was likely a factor in the growth improvement of some infants in our study. However, the immediate postoperative period poses challenges to nutrition intake that can temporarily delay restoration of growth in the short-term,[4,10,32,42] and the benefits of CHD repair on weight gain and growth are usually seen several months or up to a year after surgery.[43] Therefore, the wide range of timing of CHD surgery in our small ($n = 15$) population of infants with CHD limited our ability to assess the impact of CHD repair on the improvements in growth reported in our study.

A control group would have enabled comparison of the growth, safety, and tolerance of the EPEF to current approaches used for increasing energy intake of term infants in the United States. Previous randomized controlled trials have reported that EPEF is as well tolerated as energy-supplemented formula and standard infant formulas and helps infants meet nutrient targets sooner.[19,20,23] Clarke et al reported similar improvements in weight of infants fed EPEF compared with infants fed energy-supplemented formula,[17] and Scheeffer et al reported improved weight gain in infants postoperative for CHD repair surgery fed EPEF compared with normocaloric formula (20 kcal/fl oz or 0.67 kcal/ml).[24] However, none of these studies compared EPEF to concentrated infant formulas, which is a more common approach in the United States, as previously described, than normocaloric formula or infant formula at the standard concentration with added modular energy. Although formulas are often concentrated, the final energy level and addition of modular varies by patient population and institutional practices, complicating the selection of an appropriate control protocol.

Conclusion

This study joins other studies to show that this EPEF is a safe and effective alternative for infants with poor growth. EPEF has a nutrition composition designed to promote catch-up growth and has been found to support appropriate rates of catch-up growth and to be safe and well tolerated in infants with growth failure due to CHD, other organic causes, or nonorganic causes. EPEF is a sterile, liquid formula that requires no modification before use; it can therefore be safely administered to meet nutrition targets for infants with or at risk of growth failure, with increased energy requirements and/or fluid restrictions.

CONFLICT OF INTERESTS

Praveen S. Goday received research funding from Nutricia for this study. Praveen S. Goday also serves as a member of a Data and Safety Monitoring Board for Shire Pharmaceuticals. Caitlin Krekel was an employee of Nutricia North America at the time this work was done

and a consultant for Nutricia North America at the time of writing this article.

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This study was funded by Nutricia North America, Rockville, MD, USA.

AUTHOR CONTRIBUTIONS

Praveen S. Goday and Anand Seth equally contributed to the conception and design of the research; Caitlin Krekel contributed to the design of the research; Praveen S. Goday, Jeffery D. Lewis, Charlie J. Sang Jr, Donald E. George, Katherine E. McGoogan , and Anca M. Safta contributed to the acquisition of the data; Anand Seth contributed to the analysis of the data; Praveen S. Goday and Caitlin Krekel contributed to the interpretation of the data; and Praveen S. Goday and Caitlin Krekel drafted the manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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