

Hypoallergenicity and Effects on Growth and Tolerance of a New Amino Acid-Based Formula with Docosahexaenoic Acid and Arachidonic Acid

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Objective In study 1, to compare the effect on growth in healthy infants of a new amino acid–based formula (AAF) and a control extensively hydrolyzed formula (EHF), with both docosahexaenoic acid (DHA) and arachidonic acid (ARA) at levels similar to those in human milk worldwide. In study 2, to evaluate the hypoallergenicity of this new AAF in infants and children with confirmed cow’s milk allergy (CMA).

Study design In study 1, a total of 165 healthy, full-term, formula-fed infants randomly received the new AAF or control formula. Anthropometric measurements, tolerance, and adverse events were recorded throughout the study. Plasma amino acid profiles were evaluated in a subset of the infants. In study 2, the hypoallergenicity of the new AAF was evaluated in 32 infants and children using a double-blind, placebo-controlled food challenge; an open challenge; and a 7-day feeding.

Results In study 1, overall growth, tolerance, and safety outcomes were similar in both groups. In study 2, 29 of the 32 subjects completed both challenges; no allergic reaction was seen in any of the 32 subjects.

Conclusions The new AAF with DHA and ARA at levels similar to those in human milk worldwide is hypoallergenic. It also is safe and supports growth in healthy, term infants. (*J Pediatr* 2008;153:266-71)

The American Academy of Pediatrics (AAP) recommends breast-feeding as the ideal source of nutrition for infants and cow’s milk–based formula (CMF) as an appropriate alternative for infants who are not breast-fed.¹ Approximately 2.5% of infants are allergic or intolerant to CMF and require an alternative formula.^{2,3} Infants with cow’s milk allergy (CMA) frequently develop allergic reactions to other foods as well.² Some infants with poorly managed food allergy may experience growth failure.^{4,5} Soy-based formulas (SFs) have been used as alternatives for infants allergic to CMF but, depending on the type of CMA, concomitant allergy to SF can be seen in 14% of infants with IgE-mediated CMA and in up to 60% of infants with non-IgE-mediated CMA.^{6,7} Consequently, SFs are not recommended for infants with non-IgE-mediated reactions because of the high frequency of infant sensitivity to both cow’s milk and soy proteins.⁷

The AAP recommends extensively hydrolyzed formula (EHF) to manage infants who are allergic or intolerant to CMF.⁸ But although most of these infants are successfully managed with EHF, a small subset do not improve when fed EHF. Some of them have multiple food allergies and may exhibit poor growth.⁴ EHF may contain small peptide fragments capable of provoking allergic reactions.⁹⁻¹¹ Consequently, alternative formulas are occasionally needed.

Amino acid–based formulas (AAFs) are fed to infants who are highly sensitive to cow’s milk and cannot be managed using EHF.⁸ AAFs also have been fed to infants with multiple food protein intolerances, resulting in reduced allergic symptoms^{10,12-16} and improved growth.^{12,14,15,17} A new AAF has been developed that provides a mixture of essential and nonessential amino acids similar to that in human milk, along with added docosahexaenoic acid (DHA) and arachidonic acid (ARA) at levels similar to those in human milk worldwide.¹⁸⁻²⁰

The present studies were designed to evaluate the effects of this new formula on overall growth and tolerance in healthy, term infants. Furthermore, the hypoallergenicity

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AAF	Amino acid–based formula	DHA	Docosahexaenoic acid
ARA	Arachidonic acid	EHF	Extensively hydrolyzed formula
CMA	Cow’s milk allergy	IgE	Immunoglobulin E
CMF	Cow’s milk–based formula	SE	Standard error
DBPCFC	Double-blind, placebo-controlled food challenge	SF	Soy-based formula

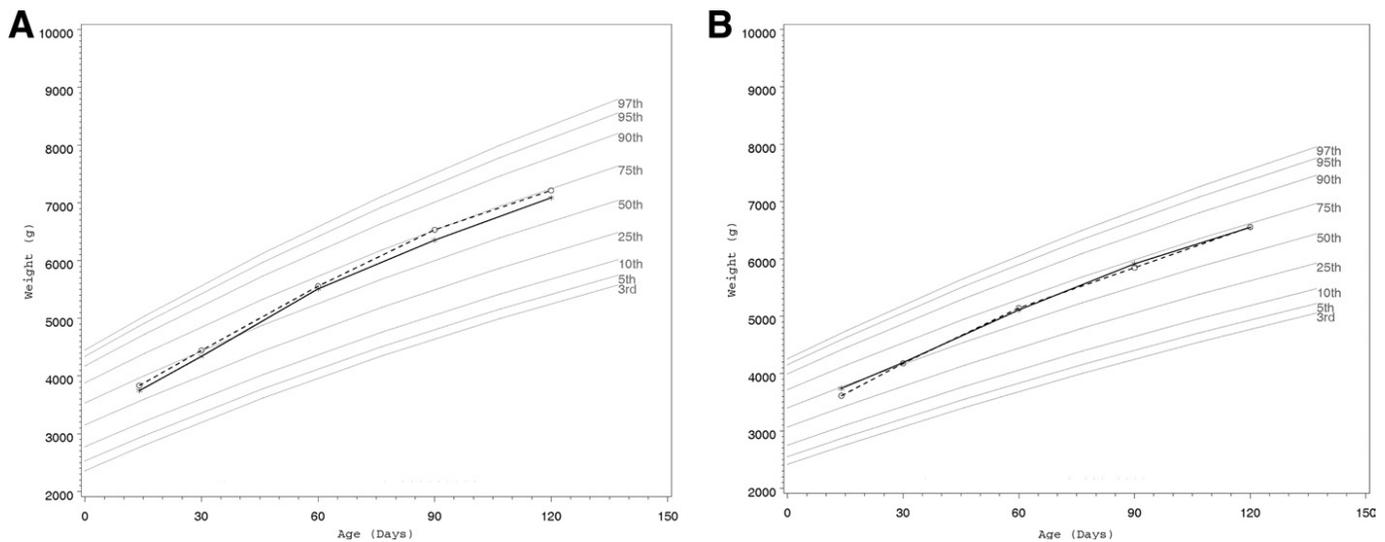


Figure 1. Study 1: Mean achieved weight of male subjects (A) and female subjects (B) from 14 to 120 days of age with CDC reference percentiles (3 to 97). The control group is represented as a solid line; the experimental group, as a dashed line.

of the new AAF was evaluated in infants and children with documented CMA based on criteria developed by the AAP's Subcommittee on Nutrition and Allergic Diseases.^{8,21}

METHODS

Study 1: Growth and Tolerance Study

STUDY DESIGN AND POPULATION. This double-blind, randomized, controlled, parallel-design, prospective trial was conducted at 14 clinical sites in the United States. Healthy, term infants 14 ± 2 days of age who were fed only formula for at least 24 hours before randomization were stratified by sex and randomly assigned to 1 of 2 study groups: the control group, who received a casein EHF (Nutramigen LIPIL; Mead Johnson Nutritionals, Evansville, Indiana), and the experimental group, who received the new AAF, which was of identical nutrient composition to the control formula, differing only in the protein equivalent source. The amino acid composition of the experimental formula was similar to that reported for human milk.²² Both formulas contained 2.8 g of protein equivalent/100 kcal, had added DHA (0.32% of total fatty acids; 17 mg/100 kcal) and ARA (0.64% of total fatty acids; 34 mg/100 kcal), and were provided in powdered form. The formulas were fed from 14 ± 2 through 120 ± 4 days of age.

Growth, acceptance, tolerance, and the occurrence of adverse events were compared between the 2 groups. Formula acceptance was determined by formula intake, whereas tolerance was based on the number and consistency of bowel movements, whether the infant was unusually fussy or gassy, and whether diarrhea or constipation occurred. A parent or caregiver was required to bring the infant to the study site 5 times for data collection, at age 14 ± 2 days, 30 ± 3 days, 60 ± 3 days, 90 ± 3 days, and 120 ± 4 days. Body weight, length, and head circumference were recorded at each study visit. The parent or caregiver was instructed to record the

amount of formula that the infant had consumed in the 24 hours before each study visit. Adverse events were recorded throughout the study as they occurred. A blood sample was obtained by venipuncture from a subset of infants (16 in the experimental group and 15 in the control group) at approximately 90 days of age. All blood samples were frozen and shipped on dry ice to the laboratory (Children's Hospital and Regional Medical Center, Seattle, Washington) for determination of plasma amino acid concentrations. The study design was approved by a central or site-specific institutional review board for each clinical site, and all parents and guardians who agreed to let their infant participate provided written informed consent.

Statistical analysis

We determined that 51 subjects per group completing the study would provide 80% power to detect a clinically relevant difference of a 3 g/day weight gain from 14 to 120 days when testing at an α level of 0.05 (1-tailed). Analysis of variance was used to analyze anthropometric measurements, growth rate, and stool frequency. Study formula intake and plasma amino acids were analyzed using the van Elteren test. The proportion of infants in each group who had adverse events or who discontinued participation in the study was compared using Fisher's exact test. All testing was conducted at an α level of 0.05. One-tailed tests were used when analyzing weight growth rates; 2-tailed tests were used for all other analyses.

Study 2: Hypoallergenicity Challenge Study

STUDY DESIGN. The hypoallergenicity of the new AAF used in study 1 was evaluated in a separate study of 32 infants and children age ≤ 10 years with documented CMA at 3 clinical sites in the United States. Study 2 was designed to assess

the hypoallergenicity of the new AAF using criteria developed by the AAP's Subcommittee on Nutrition and Allergic Diseases.²¹ Using these criteria, a formula must be tested in infants and children with hypersensitivity to cow's milk or CMF, with findings verified by elimination-challenge tests under double-blind, placebo-controlled conditions. For a formula to be considered hypoallergenic, these tests should show with at least 95% confidence that 90% of allergic individuals will not react to the formula.^{8,21} Statistically, studying at least 29 patients with documented CMA and detecting negative challenges are required to meet these criteria.

Consequently, we evaluated the hypoallergenicity of the new AAF using a double-blind, placebo-controlled food challenge (DBPCFC), with formulas fed in randomized order after a prechallenge elimination period, followed by an open challenge if the response to the DBPCFC was negative. Subjects were monitored by direct observation for any indication of allergy (extent and severity of rash, pruritus, or urticaria/angioedema; upper or lower respiratory symptoms; or gastrointestinal symptoms) and adverse events throughout the double-blind and open challenges. If the open challenge response was also negative, then a 7-day home feeding period followed. During this 7-day period, the child's parent or guardian kept a daily diary of acceptance and tolerance measures and any adverse events, including a record of formula volume intake, number of bowel movements, doctor visits due to illness, and medication usage during home feeding. A final evaluation was completed at the end of the 7-day home feeding period or on withdrawal from the study.

The placebo formula used in this DBPCFC was another commercially available AAF (Neocate; Nutricia, North America [formerly SHS North America], Gaithersburg, MD), also provided as a powder. History and information on allergic disease status were obtained and a baseline physical examination and skin prick testing with a negative control (saline), a positive control (histamine), cow's milk extract, Neocate, and the new AAF were completed before the subjects underwent the DBPCFC. The study design was approved by a central or site-specific institutional review board, and all parents and guardians who allowed their child to participate provided written informed consent.

STUDY POPULATION. Infants and children age ≤ 10 years were considered eligible for the study if they had documented CMA and their allergic disease was under good control. Infants and children with atopic dermatitis were included if it was under sufficient control to allow recognition of a positive response to the challenge. Infants and children using a beta-blocker within 12 hours of the challenge, an antihistamine more than once within 3 days to 6 weeks of the challenge (depending on the type of antihistamine), or an oral steroid medication within 3 weeks of the challenge were excluded from study.

Confirmation of CMA was required before study entry by either a positive DBPCFC to cow's milk or a positive CAP RAST (ImmunoCAP; Phadia [previously Pharmacia Diagnostics], Uppsala, Sweden), with diagnostic value for cow's

milk, defined as ≥ 5 kU_A/L for subjects age ≤ 2 years or ≥ 15 kU_A/L for subjects age > 2 years, within 90 days of study entry, along with either a convincing or suggestive history of an allergic reaction to cow's milk. A convincing history was defined as an immediate allergic reaction to cow's milk within the previous 2 years developing after isolated ingestion of cow's milk and requiring emergency management by a physician. A suggestive history was defined as an immediate allergic reaction to cow's milk that was not necessarily in isolation occurring on 1 or more occasions but not requiring emergency management by a physician, or a convincing history occurring more than 2 years earlier.^{23,24}

RESULTS

Study 1

Of the 165 infants enrolled (1 infant who enrolled but dropped out before consuming any study formula was not included in any analyses) between October 2004 and June 2005, 110 (58 in the experimental group and 52 in the control group) completed the study. The infants in the 2 groups were similar in terms of mean (\pm standard error) weight, length, and head circumference at birth and at study entry (entry weight, 3742.4 \pm 61.2 g in the control group, 3716.7 \pm 61.1 g in the experimental group; length, 52.6 \pm 0.3 cm in the control group, 52.2 \pm 0.3 cm in the experimental group; head circumference, 36.3 \pm 0.2 cm in both groups).

Infants in the 2 groups were similar in terms of rate of weight increase from day 14 to days 30, 60, 90, and 120 (36.2 \pm 2.1 g/day in the control group vs 37.1 \pm 2.0 g/day in the experimental group at day 30, 34.4 \pm 1.4 g/day vs 34.3 \pm 1.4 g/day at day 60, 31.1 \pm 1.2 g/day vs 32.2 \pm 1.1 g/day at day 90, and 29.1 \pm 1.0 g/day vs 29.8 \pm 1.0 g/day at day 120). The similarities in growth rate were reflected in similarities in achieved body weight (Figure 1A, B). An isolated difference was seen between the 2 groups in rate of length increase from 14 to 120 days (0.113 \pm 0.003 cm/day in the control group vs 0.107 \pm 0.003 cm/day in the experimental group; $P = .030$) and achieved length at 120 days (64.3 \pm 0.4 cm in the control group vs 63.4 \pm 0.4 cm in the experimental group; $P = .031$); however, this difference was not considered clinically relevant. There were no statistically significant differences between the 2 groups in head circumference growth rate or achieved head circumference. Parents and guardians reported similar volumes of formula intake in both groups throughout the study. A significant difference was observed between the 2 groups only in terms of fussiness ($P = .028$) and fussiness relative to normal ($P = .039$) at age 90 days, with parents of infants in the experimental group reporting more fussiness.

No difference between groups was detected in the number of subjects who experienced at least 1 adverse event. A statistically significant difference in diarrhea reported as an adverse event was detected between the 2 groups, with diarrhea reported for 9 infants in the control group versus no infants in the experimental group ($P < .001$). No significant differences in incidence of serious adverse events were observed between the 2 groups when analyzed by body system or individual event.

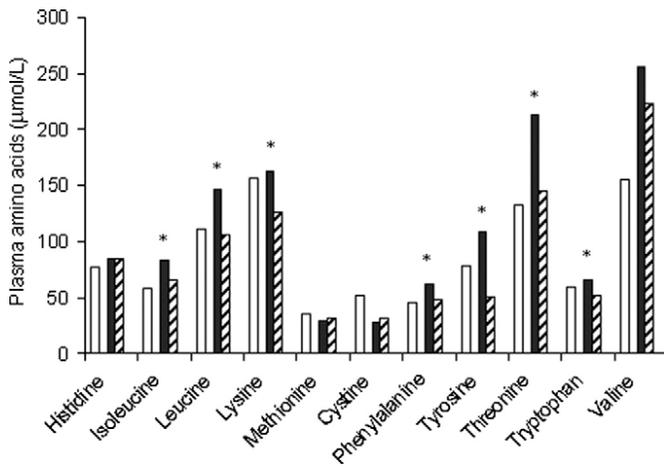


Figure 2. Study 1: Plasma concentrations ($\mu\text{mol/L}$) of essential amino acids in the experimental and control groups (median) and in 1-month-old reference breast-fed infants (mean).²⁶ The breast-fed reference infants are represented as the white column; the experimental group, as the black column; and the control group, as the dashed column. *Significantly higher in the experimental group than in the control group ($P < .05$).

In the subset of infants with plasma amino acid evaluation at age 90 days, the experimental group had significantly higher ($P < .05$) concentrations of the essential amino acids isoleucine, leucine, lysine, phenylalanine, tyrosine, threonine, and tryptophan compared with the control group. None of these differences was considered clinically relevant, however. The plasma amino acid concentrations in the 2 study groups were similar to those in breast-fed infants (Figure 2).

Study 2

Of the 32 infants and children (age range, 8 months to 10 years) recruited, 29 completed both the DBPCFC and open challenge. One of the 32 subjects never consumed any study products; 2 other subjects withdrew after only 1 challenge formula (1 after receiving placebo and 1 after receiving the new AAF), with no allergic reactions observed. Of the 29 subjects completing both the DBPCFC and open challenge, 27 completed the full 7-day feeding period on the new AAF; 1 subject completed 3 of the 7 days, and 1 was lost to follow-up during the 7-day feeding period.

CMA was confirmed in all 29 subjects who completed both the DBPCFC and open challenge; 24 of these subjects had positive diagnostic milk-specific IgE values to cow's milk, as described earlier, and 5 had positive DBPCFC to cow's milk, all of whom had a history of allergy to cow's milk. All of these subjects also had positive skin prick reactions to histamine and cow's milk but negative responses to the new AAF and placebo formula.

Of the 29 subjects who completed both challenges, 23 (79%) had multiple food allergies as reported by a parent or guardian. Nineteen subjects (66%) had 2 or more food allergies in addition to CMA. Other common food allergies reported at study entry included allergies to eggs, peanuts, soy, wheat, tree nuts, and beef. Twenty-four of the 29 subjects

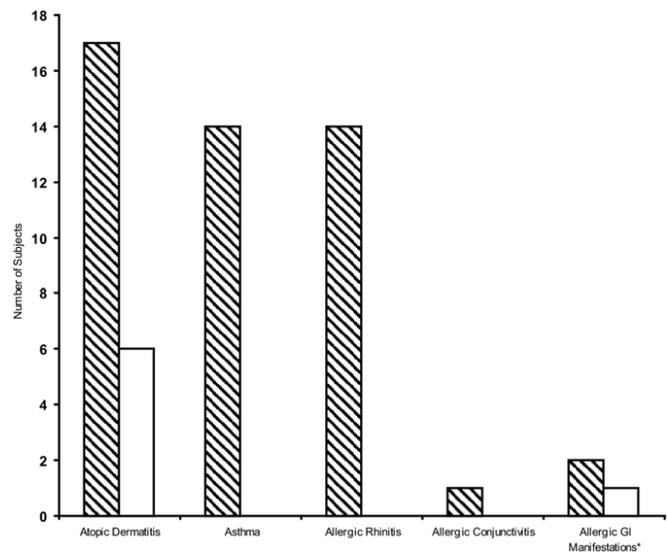


Figure 3. Study 2: History of allergic manifestations at study entry in the 29 subjects completing both challenges. Ongoing is represented as the dashed column; resolved, as the white column. Ongoing allergic manifestations were noted in 24 of 29 subjects at study entry. *Allergic GI manifestations included allergic enterocolitis, esophagitis and gastroesophageal reflux.

who completed both challenges (83%) had ongoing allergic manifestations at study entry, including atopic dermatitis, asthma, allergic rhinitis, allergic conjunctivitis, or gastrointestinal manifestations (Figure 3).

All of the 29 subjects who completed both the DBPCFC and open challenge had negative responses to both tests. As determined by daily parental record, acceptance and tolerance of the new AAF were generally good. No serious adverse events occurred during the DBPCFC, open challenge, or extended 7-day feeding period on the new AAF. The study provided 95% confidence that at least 90% of infants and children allergic to cow's milk would have no reaction to the new AAF, thus demonstrating the hypoallergenicity of the new AAF in infants and children with documented CMA, many of whom had multiple food allergies.

DISCUSSION

The AAP states that infants who develop symptoms of food allergy may benefit from the use of an EHF or an AAF.⁸ Preclinical in vitro studies have demonstrated the absence of any detectable cow's milk protein in the experimental AAF tested in the current studies (data on file). Our 2 studies were designed to evaluate the safety and tolerability of the new AAF and to demonstrate its hypoallergenicity in vivo. The results of these studies demonstrate that the new AAF is hypoallergenic, safe, well tolerated, and promotes normal growth when fed to healthy term infants from 14 to 120 days of age.

Overall acceptance and tolerance of the new AAF in these studies was good. In study 1, no differences were noted between the experimental and control groups in terms of mean achieved weight, rate of weight increase, achieved head circumference, or rate of head circumference increase. A sig-

nificant difference between the 2 groups was observed in rate of length increase and achieved length at 120 days, but this difference was not considered clinically relevant, because the mean length measurements in both groups were between the 50th and 90th percentiles on the Centers for Disease Control and Prevention (CDC) reference charts at age 120 days and throughout the study.

In study 2, all 29 infants and children who completed both the DBPCFC and the open challenge had negative responses to challenges with both the new AAF and placebo. Of these 29 infants and children, 79% had multiple food allergies. Diagnostic values of cow's milk-specific IgE have been established to facilitate the diagnosis of CMA and were used as part of the inclusion criteria for most of the subjects in this study. We considered that it would be excessively interventional and potentially traumatic to perform 2 DBPCFCs in this population of infants and children, with 1 challenge done to confirm the diagnosis of CMA in a subject who had not undergone a DBPCFC in the previous 90 days and the other done to test the hypoallergenicity of the new AAF. A similar inclusion criterion was used by Sicherer et al¹³ in a study to evaluate the hypoallergenicity of an AAF currently on the market. They reported 22 successfully completed DBPCFCs and 9 successfully completed single-blind challenges that demonstrated the hypoallergenicity of the tested AAF. Sampson et al²⁵ characterized another AAF currently on the market as hypoallergenic after conducting DBPCFCs and open challenges in 26 children with CMA.

Previous studies conducted in infants with intolerance to CMF have demonstrated that AAFs are safe and effective in infants with documented allergy to cow's milk protein and promote acceptable growth when fed for varying periods.^{4,10,12-17} Unlike most previous studies, however, the AAF in our study 1 was the primary source of nutrition for these healthy term infants, with only 6% to 15% of infants consuming anything other than formula during the 24 hours before the study visits. The findings of study 1 support the conclusion that acceptable growth occurs in infants fed the new AAF, which is hypoallergenic in infants and children with CMA.

The significantly higher plasma amino acid levels detected in the experimental group compared with the control group generally reflects the higher concentrations of these amino acids in the AAF compared with the EHF, but they are not considered clinically relevant, especially because growth was similar across groups and tracked in a normal range on the CDC growth charts. The plasma amino acid concentrations in the experimental and control groups were similar to those seen in breast-fed infants.²⁶

Past studies with different AAFs also suggest that AAFs are safe and effective and may be particularly well suited for infants with non-IgE-mediated or multiple food allergies. In a study of 74 infants with CMA, a whey-based EHF was compared with an AAF. Growth was promoted in infants receiving the AAF but declined in infants fed the whey-based EHF.¹² Similarly, an AAF fed to 31 children

with cow's milk and multiple food allergies was shown to be hypoallergenic and effective in maintaining normal growth.¹³ That study was unique in that 14 of the 31 children had allergic eosinophilic gastroenteritis and were followed up for growth over an extended period on the new AAF. Blood eosinophil counts declined significantly during feeding with the AAF, indicating reduced allergic inflammation. Children with allergic eosinophilic gastroenteritis may especially benefit from AAFs, and an AAFs are recommended for infants and children with poor growth and multiple food allergies on highly restricted diets.¹³

In a previous study of 52 infants with CMA who did not tolerate EHF, AAF used for a mean duration of 11.4 months proved to be safe in all cases, with infants exhibiting overall gains in weight and length.¹⁴ Of the 52 infants studied, 65% had multiple food allergies. In this study, an earlier diagnosis of intolerance to EHF was associated with a better prognosis, shorter duration of symptoms, and a decreased number of food allergies.

In a previous study of infants with multiple food protein intolerance, 18 infants (median age, 7.5 months) were given an AAF for 2 months, then underwent a DBPCFC, followed by a 7-day observation period with the previously best-tolerated formula.⁴ The AAF formula promoted stabilization of symptoms in all of the infants. The formula challenge produced increased irritability, vomiting, diarrhea, and/or eczema flares in 8 of the 12 infants. Six infants had an adverse reaction to soy formula, 2 had an adverse reaction to whey hydrolysate formula, and 4 had an adverse reaction to casein hydrolysate formula.

The results of these studies highlight the importance of early detection and treatment of intolerance to EHF, manifested mainly as digestive symptoms, and the therapeutic potential of AAFs in treating infants with eosinophilic gastroenteritis or multiple food allergies. Of note in our study, ongoing multiple food allergies were reported in 23 subjects, 19 of whom had 2 or more types of food allergy in addition to CMA, as reported by parents and guardians. These subjects had a negative DBPCFC to the experimental AAF tested, as well as no allergic exacerbations during the 7-day feeding period with this formula.

Standard infant formulas and specialty formulas with added DHA and ARA are available to feed healthy infants and infants with special nutritional needs, respectively. Adding DHA and ARA to these types of formulas to achieve near-median worldwide human milk levels has been shown to promote normal infant growth and enhance visual and mental performance.²⁷⁻³⁰ The new AAF with added DHA and ARA may provide infants with CMA the benefits of improved visual and mental development. Furthermore, the addition of DHA to this formula may provide some anti-inflammatory effects,³¹ which could be potentially beneficial for infants with CMA and other food allergies. To the best of our knowledge, this is the first study to demonstrate the efficacy of an AAF with added DHA and ARA at near-median worldwide human milk levels.

In summary, the new AAF promoted appropriate growth in healthy term infants from 14 to 120 days of age and was well accepted and tolerated. This formula also was demonstrated to be hypoallergenic and safe in infants and children with CMA and multiple food allergies.

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