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Randomized Trial of a Yogurt-type Amino Acid–based Formula in Infants and Children With Severe Cow's Milk Allergy

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ABSTRACT

Objectives: Evaluation of a spoon-fed amino acid–based formula (AAF) with a yogurt-type texture compared to the reference oral liquid formula (Neocate).

Methods: Phase III/IV, prospective, randomized (1:1), open-label, multicenter study in infants/young children (6–36 months) with severe cow's milk protein allergy (CMA) who had consumed AAF for ≥1 month before the study. Patients received reference+test formula (Neocate with a yogurt-type texture for spoon-feeding: group 1) or reference formula (group 2) for 28 days. The study formulae were integrated into the patients' usual daily diet. Efficacy on Day 0, 14, and 28 was assessed primarily in terms of symptoms associated with CMA. The evolution of symptoms, amount of formula consumed, nutritional and energy intake, anthropometric data, and tolerability were also assessed.

Results: The incidence of CMA symptoms was similar in each group ($P > 0.05$) on day 0, 14, and 28. For specific symptoms, there was little change from day 0 and no significant difference between groups for incidence on day 0 or evolution at day 14 or 28. There was no difference in formula consumption (day 0–day 28) between groups ($P = 0.90$), but nutritional value was generally higher for group 1 and calcium intake was statistically higher for group 1 ($P < 0.05$). Weight-for-height, weight-for age, and body mass index-for-age z scores were higher for group 1 than group 2 ($P < 0.05$). Both formulae were well tolerated.

Conclusions: There was no difference in efficacy, formula consumption, and tolerability between the new spoon-fed yogurt-type AAF formula and the reference formula, whereas significantly higher calcium intake was achieved with the new formula.

Key Words: adherence, cow's milk protein allergy, efficacy, nutritional therapy, symptoms

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What Is Known

- Infant liquid formula consumption reduces with age, presenting a challenge for cow's milk allergy management using exclusively liquid formulae.
- Cow's milk allergy has an incidence of 2% to 3% in infants and young children.
- Hypoallergenic formulae are not tolerated by 10% of patients with cow's milk protein allergy, that is, infants with severe cow's milk protein allergy, for whom amino acid–based formulae are the only alternative.
- Commonly, amino acid–based formulae taste is a complaint that reduces compliance.

What Is New

- A new amino acid–based formulae with a yogurt-type texture and improved taste had similar efficacy and tolerability compared to amino acid–based formulae alone.
- Consumption of the new amino acid–based formulae resulted in improved calcium intake.

Cow's milk allergy (CMA) is characterized by a combination of dermatological, gastrointestinal, and respiratory clinical symptoms, which can lead to feeding difficulties (1,2). In infants and young children CMA is one of the most common food allergies with an incidence of 2% to 3% (3). Although it can be associated anaphylactic shock or even death, there is no medicinal treatment for CMA and its management is based on the elimination of cow's milk protein from the diet and treatment of symptoms (4–6). For breast-fed infants with CMA, mothers should be encouraged to continue breast-feeding while avoiding milk proteins from their own diet (5). If breast-feeding is, however, not possible or cannot be maintained in patients with CMA, a hypoallergenic formula should be provided that contains <1% immune-reactive protein in relation to the total nitrogen content (extensive hydrolysate formula [eHF])

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(7). Such substitute formulae can only be recommended for CMA if tolerated by at least 90% of children with CMA (8–10), which is the case for most eHF (11–13). However, 10% of children with CMA do not tolerate eHF (11–17); for these children, an amino acid–based formula (AAF) is the only alternative (4,18) with proven efficacy and tolerability (16). Neocate is an established liquid AAF that promotes growth and development of this population (11–15,17,19,20), is well tolerated (17,21), and has proven efficacy against cutaneous (11,17) and gastrointestinal (14,22) symptoms. The taste of AAF is, however, a common complaint from parents and children and can have an adverse impact on compliance to the feeding regimen, leading to reduced efficacy (23). There is, therefore, a desire from healthcare professionals to provide AAF formulae with a yogurt-type texture to allow spoon feeding and better taste, improving compliance and acceptance. This is of particular interest given that severe forms of CMA can be prolonged due to delayed acquisition of oral tolerance to cow's milk protein. The modified texture of the yogurt-type formula is also likely to be of interest for oral eating development (24). The consumption of liquid formula tends to decrease in an age-dependent manner, paralleling an increasing consumption of solid food. Cow's milk exclusion diets without appropriate substitution may induce nutritional deficiencies, especially in calcium, which can adversely affect bone development in infants with severe CMA (19,25).

The present study was therefore performed to investigate the efficacy, adherence to treatment, nutritional intake, and tolerability of a new Neocate preparation with a yogurt-type texture and calcium-supplemented compared to the currently available liquid preparation in infants with severe CMA.

METHODS

Study Design and Participants

This phase III/IV, prospective, randomized, open-label study was conducted in 8 centers in France. The protocol and 1 amendment were approved by an ethics committee (Comité de Protection des Personnes Sud-Est III, Lyon, France) and by the French National Health Authority (ANSM: reference number 131476B-32). The study conformed to Good Clinical Practice (ICH-E6) and the ethical principles of the Declaration of Helsinki (Fortaleza revision, 2013), and was conducted in accordance with applicable national regulatory requirements. Before enrolment, written informed consent was obtained from at least 1 parent/legal representative of each patient. The study took place from March 2014 to January 2016.

Infants and young children aged between 6 and 36 months, with a documented diagnosis of severe CMA, defined as persistence of symptoms with eHF, and who had consumed AAF for at least 1 month before the study with observed clinical efficacy were eligible. Those with a multiple food allergy were also eligible, and all were capable of consuming the minimum required quantity of test or reference formula for the duration of the study. The main exclusion criteria were birth weight <2500 g, prematurity (<37 weeks) with specific feeding requirements, history of potentially fatal severe acute reactions to ingestion of cow's milk (stage III or IV anaphylaxis), one or more severe additional pathologies or congenital malformations, intolerance to lactose, or any component of the test or reference formulae, any indication that could compromise study completion, and participation in any other clinical study in the 2 weeks before the study and for the duration of the study.

After the inclusion visit (day-21 to d-7) patients were randomized by the investigator using an interactive Web response system on day 0 in a 1:1 ratio to a reference+test formula (Neocate with a yogurt type texture for spoon-feeding: group 1) or reference formula alone (group 2) for 4 weeks (28 ± 2 days). The study formulae were integrated into the patients' usual daily diet which was not otherwise affected by the study protocol. Patients were allocated a unique identification number during the randomization to ensure the confidentiality of personal data. Parents/legal representatives were contacted by telephone 2 weeks later (14 ± 2 days) and visited the site for an end-of-study visit after 4 weeks (28 ± 2 days).

Study Products

The reference formula was Neocate (infants aged <1 year) and Neocate Advance (young children aged 1–3 years). Both are oral liquid AAFs used in the treatment of severe CMA. Once reconstituted with water, the formulae contain a mixture of essential and nonessential amino acids, carbohydrates, lipids, vitamins, and minerals; they do not contain glucose, lactose, sucrose, fructose, galactose, or soya oil.

The test formula was Neocate with a yogurt-type texture for spoon-feeding obtained by the addition of highly purified rice starch as a texturing agent.

The nutrient composition of each study formula is presented in Supplementary Table 1 (Supplemental Digital Content, *http://links.lww.com/MPG/B182*).

Group 1 received the reference+test formula as needed, and ideally including 100 g/day (patients aged 6–12 months) or 200 g/day (patients aged 12–36 months) of test formula (ie, yogurt texture and spoon-fed). Group 2 received the reference formula but no test formula.

Study products were supplied in powdered form, stored <25°C, and reconstituted precisely with the volume of water specified in the manufacturer's recommendations for both test and reference formulae within 1 hour of use.

Efficacy Assessments

Primary Criterion: Cow's Milk Protein Allergy Symptoms

A clinical evaluation of symptoms associated with severe CMA was performed by the Investigator during the visits on day 0 and day 28 and during the telephone call on day 14 using evaluation scales (absence, mild, moderate, or severe) for cutaneous, gastrointestinal, and respiratory symptoms combined. Between evaluations, parents/legal representatives recorded symptoms daily and classified their severity using standard scales.

Secondary Criteria: Adherence to Nutritional Therapy and Evolution of Cow's Milk Protein Allergy Symptoms

From day 0 to day 28, parents/legal representatives measured the total volume of AAF (groups 1 and 2) and the quantity of spoon-fed yogurt AAF (group 1) consumed daily. Two 3-day food diaries (1 in the week before day 0 and a second in the week before day 28) were completed by the parents/legal representatives. These served to monitor any major modifications in the feeding habits of the patients, which could have had an impact on the study results. The mean nutritional content (calcium, iron, vitamin D, and protein equivalent) for each group was calculated over 28 days based on the quantity consumed and the respective composition of each formula, and assessed for the overall population as well as for infants <12 months of age and >12 months of age.

The evolution of dermatological (angiodema, eczema, lip edema, urticaria, and other), gastrointestinal (constipation, diarrhea, gastroesophageal reflux, vomiting, and other), and respiratory (asthma, cough, laryngeal edema, rhinitis, and other) symptoms of CMA was evaluated on day 0, day 14, and day 28 by the investigators. The presence and severity of symptoms were recorded daily by parents/legal representatives.

Third Criterion: Anthropometric Data

Weight, height, and body mass index (BMI) were reported and z scores for weight-for-height, weight-for-age, height-for-age, and BMI-for-age were calculated for each group at enrollment and day 28 using WHO references (WHO Anthro) (26).

Safety Assessment

Adverse events (AEs) were recorded by the investigator during the visits on day 0 and day 28 and during the telephone call on day 14, and throughout the study by the parents/legal representatives.

Statistical Analyses

The primary efficacy objective of the present study was to evaluate the clinical efficacy of the test formula in terms of the number of patients with combined CMA symptoms at day 14 and day 28. Secondary objectives included an evaluation of adherence to the nutritional therapy in each group in terms of the volume of AAF consumed daily, and further description of specific CMA symptoms on days 0, 14, and 28 and their evolution (appearance, no change, or disappearance of symptoms). For anthropometric data, z scores were calculated based on WHO growth data (27). The change from baseline (day 0) was compared between groups by analysis of covariance using age at baseline as a covariate. AEs were also assessed as a secondary safety objective.

The normality of quantitative data was assessed using the Shapiro-Wilk test and comparisons performed using the Student t test if the distribution for each group was normal and using the Wilcoxon Mann-Whitney test if at least one of the distributions was not normal. Qualitative comparisons were performed using the Chi^2 or Fisher exact test. In addition, a generalized estimating equations model was used to compare the evolution of qualitative data taking into account covariates of formula, time, and formula∗time, and the nature of the parameter (binary or ordinal) and other factors including age, treatment duration, and nature of the CMA. All statistical comparisons used a 5% significance threshold ($P = 0.05$).

The evaluation of CMA symptoms, adherence to treatment, nutritional intake, and anthropometric data was performed using the per protocol (PP) set (all included patients who were randomized and completed the study with no major protocol deviation). The assessment of AEs was performed using the safety set (SS) (all included patients who had at least one administration of the test or reference formula). The intent-to-treat (ITT) set was used to evaluate patient characteristics and demography (all included patients who were randomized).

Based on previous clinical studies (11,13,17,20,28–30), for an alpha level of 0.05 for statistical significance and a power of 80%, a sample size of 48 patients (24 patients per group) was considered sufficient to detect a significant difference in the number of patients presenting CMA symptoms between groups. Assuming an attrition rate of 10%, an overall sample size of 54 patients was appropriate to meet the primary objective of the study.

The statistical analyses were done using SAS Version 9.3 (SAS Institute, Cary, NC).

RESULTS

Patients Studied

Thirty-four patients were enrolled in the study and randomized to group 1 (N = 17) or group 2 (N = 17) (Fig. 1). All patients had CMA, with the incidence of symptoms at baseline being 42.9% and 50.0% in group 1 and group 2, respectively, which was mainly non–IgE-mediated (76.5% of patients in each group). The median (range) time since the start of AAF treatment was similar in each group (21.5 [5–52] weeks in group 1 and 26.0 [5–100] weeks in group 2). In group 1, 2 patients discontinued the study (1 due to an AE and 1 due to an SAE), and 15 patients in group 1 and all patients in group 2 completed the study as planned. In groups 1 and 2, respectively, 14 and 16 patients were included in the PP set (Fig. 1) of whom CMA was still symptomatic for 6 and 8 patients in groups 1 and 2, respectively, at baseline. Overall in group 1 (PP set) patients consumed 60.05 ± 38.45 g of the test product per day.

Baseline demographic and anthropometric characteristics were similar in each group—for the ITT set in group 1 and group 2, respectively, the median (range) age at inclusion was 13.0 (6–25) months and 13.0 (5–35) months, gestation was 39.0 (35–41) weeks and 38.0 (35–40) weeks, weight was 3.50 (1.7–4.2) kg and 3.10 (1.8–3.6) kg, height was 0.495 (0.43–0.52) m and 0.490 (0.43–0.53) m, and head circumference was 35.0 (30–36) cm and 34.0 (29–36) cm. In each group there were more boys than girls (76.5% and 58.8% boys in group 1 and group 2) and most were born by vaginal delivery (76.5% in each group). The demographic data were similar for the PP and ITT sets.

Efficacy Assessments

Primary Criterion: Cow's Milk Protein Allergy Symptoms

The incidence of patients with CMA symptoms (PP set) was similar in group 1 and group 2 at day 0 (6/14 patients [42.9%] and 8/16 patients [50.0%]), day 14 (7/14 patients [50.0%] and 7/16 patients [43.8%]), and day 28 (6/14 patients [42.9%] and 9/16 patients [53.3%]). Statistical comparison (Fisher exact test) confirmed no difference ($P > 0.05$) between groups on any occasion (Fig. 2).

Regarding the evolution of overall CMA symptoms during the study in patients who had symptoms, at day 14 most patients in each group had no change in symptoms (4/7 patients [57.1%] and 6/7 patients [85.7%] in group 1 and group 2); 1/7 patients (14.3%) in group 2 showed an improvement and 3/7 patients (42.9%) in group 2 showed worsening. At day 28, of those who had symptoms, most patients in each group had no change in symptoms (4/6 patients [66.7%] in group 1 and 5/9 patients [55.6%] in group 2) or an improvement (1/6 patients [16.7%] in group 1 and 4/9 patients [44.4%] in group 2); 1 patient [16.7%] in group 1 showed worsening of symptoms at day 28.

Statistical analysis using the generalized estimating equations model showed a visit effect with more symptom improvement on day 28 than day 14 ($P = 0.0183$); there was no effect ($P > 0.05$) based on sex, group, type of CMA (ie, IgE-mediated and non–IgE-mediated), age, or duration of AAF treatment at baseline.

Secondary Criteria: Adherence to Nutritional Therapy, Nutritional Value, Evolution of Cow's Milk Protein Allergy Symptoms

The mean ± SD consumption of AAF powder from day 0 to 28 was 2834 ± 532.4 g in group 1 and 2801 ± 805.6 g in group 2, with no statistical difference ($P = 0.90$, Student t test) between groups. The mean nutritional daily intake for calcium overall ($P = 0.012$) and for patients <12 months of age ($P = 0.006$) was statistically higher in group 1 than group 2. There were no significant differences for iron, vitamin D, protein intake, and energy for any age group (Table 1). From the food diary data there were no major modifications to the usual feeding habit for any patient.

Dermatological, gastrointestinal, and respiratory symptoms were absent in most patients on day 0 and there was little change at day 28.

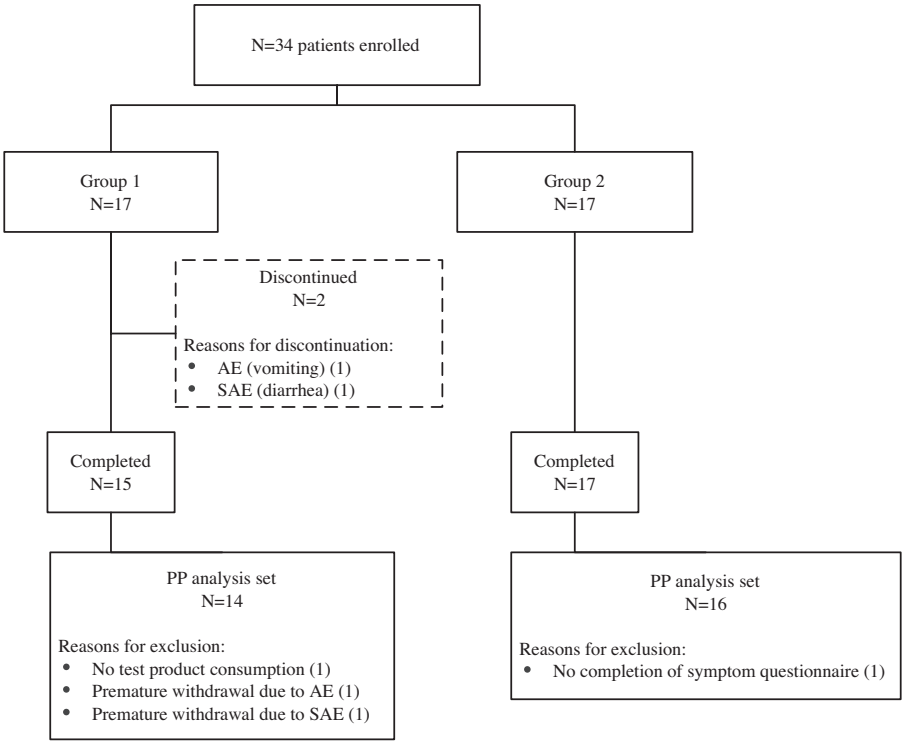
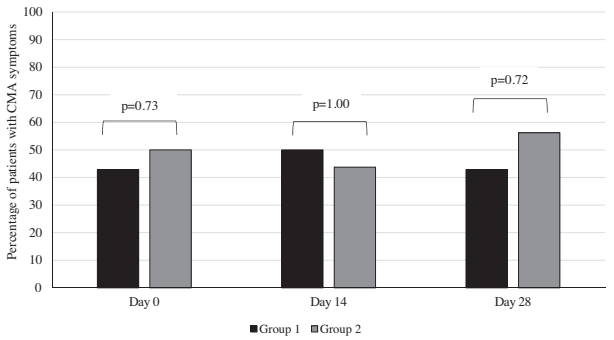


FIGURE 1. Study participation flowchart.

Anthropometric Data

Compared with baseline (day 0), *z* score at day 28 was significantly higher for group 1 than group 2 for weight-for-height ($P = 0.021$), weight-for-age ($P = 0.022$), and BMI for age ($P = 0.023$), and was similar between groups for height-for-age ($P = 0.487$) (Fig. 3).



p was considered significant when<0.05
Group 1=Reference+test formula
Group 2=Reference formula only

FIGURE 2. Percentage of patients with severe CMA symptoms at day 0, day 14, and day 28 (PP set).

Safety Assessment

The incidence of treatment-emergent AEs (TEAEs) was slightly higher in group 1 (14/17 patients [82.4%] experienced 29 TEAEs) and group 2 (10/17 patients [58.8%] experienced 16 TEAEs). In group 1, 7 TEAEs were considered to be related to the study formula (2 episodes of vomiting [2 patients], 2 episodes of diarrhea [2 patients], and single episodes of gastroenteritis with abdominal pain and anorexia); no TEAE in group 2 was considered to be related to the reference formula. Most lasted 1 to 7 days, were mild or moderate in severity, and resolved after treatment.

Episodes of severe diarrhea (1 patient) and severe vomiting (1 patient), which occurred 1 day and 8 days after the first intake of study formula and lasted 27 days and 8 days, respectively, led to the discontinuation of 2 patients in group 1.

There were 2 SAEs (diarrhea in group 1 and gastroenteritis in group 2). The diarrhea necessitated discontinuation of treatment, and the gastroenteritis resulted in hospitalization and treatment with Motilium (domperidone) and Gaviscon (alginate).

DISCUSSION

In children with severe CMA, the therapeutic objective of the spoon-fed yogurt-type AAF is not to provide a superior clinical efficacy to that of the reference liquid version, but to facilitate and to ensure the consumption of an AAF, which can be problematic in infants and young children due to its taste and/or texture. In the present study, there was no reduction in consumption between

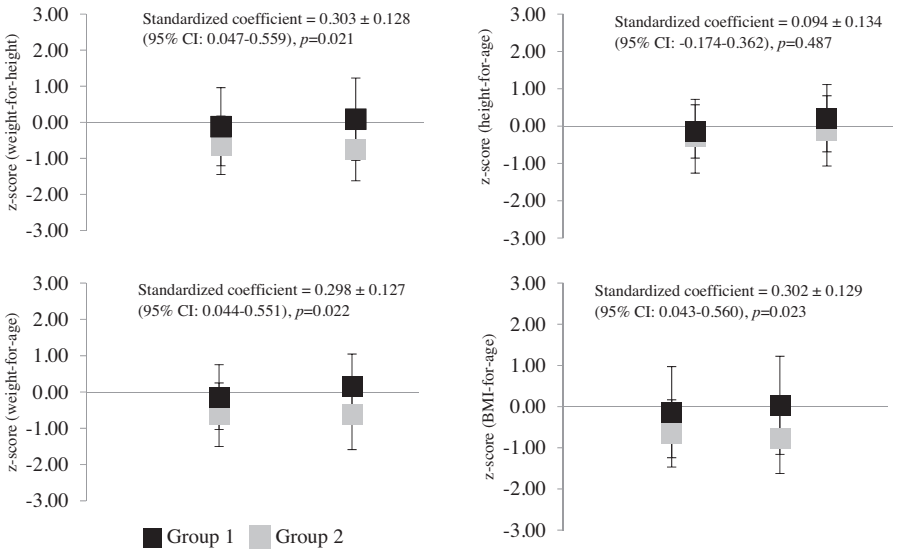
TABLE 1. Mean nutritional value for calcium, iron, vitamin D, protein, and energy intake (day 0–28) (PP set)

Parameter age	RDA*	Group 1	Group 2	$P^{\dagger}$
Calcium, mg/day				
Overall	500	437.0 (147.3)	315.0 (101.1)	0.012
<12 mo	500	530.0 (105.4)	396.0 (53.6)	0.006
>12 mo	500	314.0 (94.0)	234.0 (63.0)	ns
Iron, mg/day				
Overall	6–10	5.51 (2.221)	4.49 (1.819)	ns
<12 mo	6–10	7.09 (1.388)	6.08 (0.823)	ns
>12 mo	7	3.39 (0.862)	2.90 (0.787)	ns
Vitamin D, μg/day				
Overall	10–25	5.94 (2.509)	5.56 (2.076)	ns
<12 mo	20–25	7.73 (1.684)	7.33 (0.992)	ns
>12 mo	10	3.56 (0.71)	3.78 (1.028)	ns
Protein, g/kg body weight/day				
Overall	0.9–1.1	1.11 (0.279)	1.19 (0.281)	ns
<12 mo	1.1	1.21 (0.268)	1.32 (0.194)	ns
>12 mo	0.9–1.0	0.97 (0.253)	1.05 (0.298)	ns
Energy, kcal/day				
Overall	621-1219	457.08 (89.83)	434.78 (100.083)	ns
<12 mo	621–956	462.35 (91.337)	402.39 (54.551)	ns
>12 mo	956–1219	412.74 (81.037)	467.17 (126.898)	ns

Data (group 1 and group 2) are mean (SD).
ns = not significant; RDA = recommended daily allowance.
*RDA according to French standards (AFSSAPS/CNERMA/CNRS. Apports conseillés pour la population française. Tec & Doc, Paris, 3rd Edn, 2001).
$^{\dagger}P < 0.05$ was considered significant.

groups, indicating that the introduction of the spoon-fed yogurt-type formula did not adversely affect the amount of AAF consumed. In infants aged 6 to 12 months, the higher nutritional content of the test formula meant that for an equivalent overall consumption over the 28 days of the study, those who received the test formula (group 1) received a greater calcium intake than those fed the reference formula (group 2). The intake of calcium was statistically higher in group 1 than group 2 for the overall population and patients <12 months of age. No other statistically significant differences were observed for nutrients or energy. It is important to note that these data present the nutrient intake provided by the formulae alone, and therefore do not represent the total daily nutrient intake which was otherwise unaffected. Interestingly, there were significant differences in increases of some anthropometric data—z scores for weight-for-height, weight-for-age, and BMI-for-age were higher at day 28 for patients consuming Neocate with a yogurt-type texture. We can speculate that these differences in z score could be explained by the higher energy content of the Neocate with a yogurt-type texture compared to the liquid formulae, although no differences in energy intake and protein intake were observed between the 2 groups as changes in total intakes were not investigated. A further possible explanation could be that the consumption of Neocate with a yogurt-type texture improves the use and/or reduces the loss of nutrients caused by sustained allergic inflammation (19).

There was no difference in efficacy in terms of the incidence of CMA symptoms between the AAF administered with a yogurt-type texture for spoon-feeding compared to its usual administration as an oral liquid. The incidence of specific dermatological, gastrointestinal, and respiratory symptoms that are commonly associated with CMA was generally <50% at day 0, probably since an inclusion criterion required that all patients had been on an AAF diet for at least 1 month before enrolment. There was little change in



Data are Day 0 (left-hand side) and Day 28 (right-hand side) in each panel
Group 1=Reference+test formulae
Group 2=Reference formula only

FIGURE 3. Mean ± standard deviation (SD) z scores for weight-for-height, weight-for-age, height-for-age, body mass index (BMI)-for-age at enrollment (day 0) and at day 28 (PP set).

the incidence of symptoms in either group during the study, and no discernible difference between groups except for gastroesophageal reflux, which showed greater improvement for the test formula.

Both formulae were well tolerated, although the incidence of TEAEs was higher in group 1 than group 2. This is likely to be a reflection of the open-label study design, with parents of infants receiving the test formula being more attentive to any reaction of the infant, and is not considered to be of clinical importance.

A limitation of the study is that the number of enrolled patients (17 per group) was lower than the planned sample size (24 per group). This was due to the stringent criteria for inclusion into the study only of infants with true severe CMA and the attendant difficulties in patient recruitment. Even if the planned sample size had, however, been reached it is unlikely that statistical significance would have been achieved for the analysis of the primary efficacy criterion between groups due to the high *P* values obtained. Although some statistical differences were observed for the anthropometric data, it is not possible to draw robust conclusions regarding the clinical significance since the study duration was limited to 28 days.

Overall there was no difference in efficacy, formula consumption, and tolerability between the new spoon-fed yogurt-type AAF formula and the reference formula, whereas significantly higher calcium intake was achieved with the new formula.

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