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RESEARCH ARTICLE

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Tolerance and growth outcomes in children diagnosed with cow's milk protein allergy and prescribed an extensively hydrolyzed casein formula (Damira 2000©) in Spain: The DELISA study

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Abstract
Objective: This study assessed the tolerance of a commercial, extensively hydrolyzed casein formula (eHCF), in a cohort of children with cow's milk protein allergy (CMPA) as a primary outcome, as well as its effect on growth outcomes.
Methods: Observational retrospective study of CMPA patients taking eHCF for at least 4 months. Patients were followed for three visits.
Results: A total of 61 evaluable pediatric patients with CMPA were included in the study. The patients had a follow-up period of 8.4 months, with a mean age of 3.1 ± 2.5 months at the first hospital visit, and 11.5 ± 5.3 months at the second follow-up visit. At the first hospital visit, the weight, height, and body mass index (BMI) were recorded as 5.6 ± 1.4 kg, 59.3 ± 6.1 cm, and 15.6 ± 1.7, respectively, increasing to 9.2 ± 1.5 kg, 73.9 ± 6.5 cm, and 16.9 ± 1.4 at the second follow-up visit. The mean Z-scores for weight-for-age (WAZ), height-for-age (HAZ), BMI for age (BAZ), and weight-for-height (WHZ) were −0.36 ± 0.95, −0.26 ± 1.00, −0.29 ± 1.05, and

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−0.22 ± 1.1, respectively, at the first hospital visit, and 0.09 ± 0.79, 0.05 ± 1.03, 0.10 ± 0.87, and 0.13 ± 0.85 at the second follow-up visit. The eHCF was well tolerated by 100% of patients with no immediate allergic or intestinal reactions recorded during the follow-up visits.
Conclusions: The participating physicians rated the tolerance of the eHCF as good in 100% of the patients (95% CI: 94.1–100). Over a follow-up period of 8.4 months, pediatric patients with CMPA consuming the eHCF showed anthropometric Z-scores WAZ, HAZ, BAZ, and WHZ between −1 and 1, within a range close to the mean of a standard normal distribution.

Introduction

Cow's milk protein allergy (CMPA) is an immune-mediated reaction to proteins found in cow's milk and one of the most common and early causes of food allergy in infants.[1,2] The major milk allergens are casein (responsible for 39–54% of sensitizations) and whey α-lactalbumin and ß-lactoglobulin proteins (triggering 13–76% of reported sensitizations).[3,4] Most individuals with cow's milk allergy have sensitivity to both caseins and whey proteins.[1] CMPA is classified according to the body's immune response to the allergen, as immunoglobulin E (IgE)-mediated and non-IgE-mediated allergies. However, a mixed presentation of both immune responses can also occur.[5–7]

Cow's milk protein allergy incidence and prevalence estimates may vary due to factors such as misinterpreted milk reactions, diverse diagnostic criteria, geographic differences, dietary exposures, demographics, and its tendency to resolve naturally over time in most cases.[8,9] The prevalence of CMPA among infants in developed countries, based on studies conducted between 1967 and 2001, was reported to be approximately 2–3%.[10] Nwaru et al. performed a systematic review and meta-analysis of CMPA prevalence in European studies published between 2000 and 2012, reporting an overall lifetime prevalence of 6%.[11] The EuroPrevall study, a year later, used rigorous ascertainment, including double-blind placebo-controlled food challenge (DBPCFC) in 12,000 children and showed an overall CMPA incidence of 0.54% across Europe in the first 2 years of life, with most affected children having specific IgE antibodies to cow's milk.[12] In the Spanish population, the incidence of IgE-mediated CMPA during the first year of life is reported to be 0.36%.[2,13]

Cow's milk protein allergy manifests with cutaneous (70–75%), and less frequently, gastrointestinal (GI) (13–34%) and respiratory symptoms (1–8%). Up to one out of four infants presents with a combination of symptoms involving more than one organ or system.[7] Most children with IgE-associated CMPA react with cutaneous symptoms, whereas those with non-IgE-associated cow's milk proteins (CMP) have relatively more GI symptoms.[12] It can have an immediate onset, usually IgE-mediated, with symptoms occurring within minutes to 2 h after ingestion. In contrast, the slow-onset reaction is typically non-IgE-mediated, where symptoms may develop within hours or days, but rarely weeks, after ingestion.[5,7,14]

Cow's milk protein allergy is usually cured, and most children develop tolerance to CMP before the age of 3, usually earlier for non-IgE mediated forms.[15] Until tolerance is reached, the only therapeutic strategy to treat CMPA is a strict CMP elimination diet. Breastfeeding is the recommended feeding for infants, which means restricting CMP from the breastfeeding mother's diet. It emphasizes the importance of correct diagnosis of CMPA in infants, as misdiagnosis leads to unnecessary elimination in diets for both infants and breastfeeding mothers. However, when breastfeeding is not possible or not sufficient, nutritional management with an extensively or extremely hydrolyzed protein formula (eHF) of casein (eHCF) or whey proteins (eHWF) or rice hydrolysate should be the first choice according to the European and international guidelines.[2,7,16] The extensive hydrolysis process reduces the allergenicity of CMP, which, together with an appropriate infant formula reconstitution, allows matching the nutritional needs of the infant. Indeed, the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) and the European Society for Pediatric Allergology and Clinical Immunology (ESPACI) conditioned the use of infant hydrolyzed formulae to be supported by clinical trials confirming the tolerance of eHF by more than 90% of the infant population tested with a 95% confidence interval (CI); that is, at least 90% of infants with CMPA do no manifest any clinical allergy symptom under double-blind, placebo-controlled conditions.[17–19]

Replacement formula must be nutritionally adequate, meeting the requirements of Directive 1999/21/EC of March 25, 1999 on dietary foods for special medical purposes, Directive 2006/141/EC of December 22, 2006 on infant formulae and follow-on formulae and amending Directive 1999/21/EC, and Directive 2013/46/EU of August 28, 2013 amending Directive 2006/141/EC concerning protein requirements for infant formulae and follow-on formulae.[17,20,21] The studied eHCF has been produced in accordance with the European legislation on dietetic foods for special medical purposes. Its safety was first evaluated in 2009 by Ibero et al. in 67 children aged 1 month to 7 years, strictly selected by a positive CMP prick test and/or specific IgE test, with a positive milk provocation test.[22] In this study, the formula was tolerated by 66 of the 67 infants (98.5%), all of whom were negative for specific IgE antibodies to the hydrolysate. While the casein hydrolysate remains unchanged, the eHCF has undergone modifications since the last EU regulation in 2016, with its most recent reformulation occurring in December 2018. The addition of docosahexaenoic acid (DHA), less protein, and more vitamin D are among the formula changes.

The primary objective of the DELISA study was to assess the tolerance of a reformulated eHCF in a cohort of children with CMPA. As secondary objectives, the study sought to evaluate how the consumption of this reformulated eHCF affected growth outcomes in these children, by measuring weight, height, and the related Z-scores, weight-for-age (WAZ), height-for-age (HAZ), weight-for-height (WHZ), and body mass index (BMI) for age (BAZ).

Methods

Study design and setting

This was a national, multicenter, observational, retrospective study designed to assess the tolerance of an eHCF, currently on the market, in patients diagnosed with CMPA. The methodology was based on a retrospective chart review and collection of data already recorded in the medical records of all patients meeting the eligibility criteria, where available. Patients were followed retrospectively for a total of three visits (the first hospital visit and two follow-up visits). See Figure 1.

The study was conducted at eight national hospitals distributed throughout Spain, thus ensuring a representative sample (Table S1).

The study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice Guidelines, and applicable regulatory requirements. The study protocol was approved by the Independent Ethics Committee (IEC) of Fundación Jiménez Díaz, Madrid, Spain. The IEC approved the informed consent exemption for this study (NCT06273371).

Study population

Eligible patients were infants diagnosed with CMPA when they were less than 1 year old and had been taking eHCF for at least 4 months before the start of the study (start of data collection). This specific age range was selected because CMPA is most commonly diagnosed in infancy, and early intervention with eHCF is crucial for managing the allergy and supporting normal growth and development. The consumption of eHCF for a minimum of 4 months ensured that the study evaluated the long-term tolerance and effectiveness of the formula. The CMPA diagnosis had to be confirmed either through a double-blind placebo-controlled food challenge (DBPCFC) or was highly suspected based on specific suggestive symptoms. In addition, patients should have had information available on child growth (weight and length) and the following anthropometric indices at diagnosis and for at least 2 follow-up visits after the first hospital visit/4 months: Z-scores WAZ, HAZ, WHZ, and BAZ.

Premature children with a low birth weight (<2.5 kg), those diagnosed with a metabolic condition that impacts development and growth or with a congenital condition and/or with prior or current disease that in the opinion of the investigator could potentially interfere with the aim of the study, or those who used other infant formulae or breast milk in addition to the study product of interest during the retrospective study period were excluded from the study.

The case studies selected for this observational retrospective study were chosen based on their relevance to the primary objective of assessing the tolerance of an eHCF in children diagnosed with CMPA. The selection process involved a thorough review of medical records from eight hospitals across Spain according to the specific inclusion and exclusion criteria. The total observation period of the study, that is, the range of data collection time, ranged from January 2019 to May 2023. The methodology was based on a retrospective chart review and collection of data already recorded in the medical records of all patients who met the eligibility criteria, where available. As this is a retrospective non-interventional study, the prescription of Damira 2000, the nature and timing of visits and assessments, and the collection of data were carried out according to routine clinical practice at each site, regardless of whether the study was being done or not. To avoid selection biases, the patients included were selected consecutively from among those who met the eligibility criteria for participating in the study.

Study treatment

The studied formula is a 100% extensive casein hydrolysate obtained by enzymatic degradation and ultrafiltration, formulated to help reverse growth retardation because of CMPA, to be well tolerated, and to help improve symptoms. It is indicated for CMPA and lactose intolerance. Several brands of extensive casein hydrolysate formula can be found in the market, for example, Damira 2000© (Spain), Picot Pepti Junior Casein (France), Alula Gold EHF (South Africa),

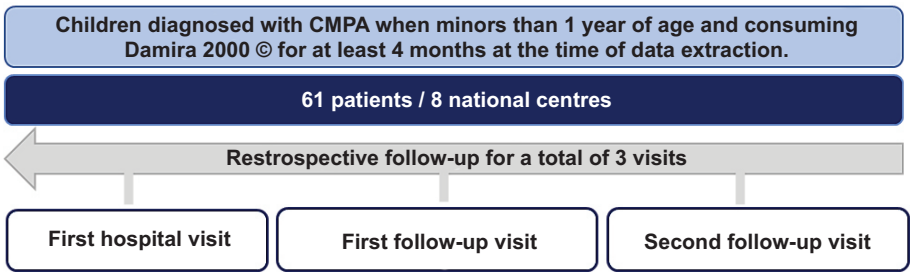

Figure 1 Study design.

Alula Allergy Extensive Hydrolyzed Formula (China), and so on. The present study has been performed in Spain with the Damira 2000© brand.

The prescription of eHCF to patients included in this retrospective chart review was unrelated to the study. The evaluated eHCF was prescribed to patients in the usual way, according to the terms of the market authorization and product label, irrespective of the conduct of this study. Complete independence between product prescription and study initiation was guaranteed by the retrospective design of the study.

Data collection and study outcomes

All study data were collected from the patient's medical history according to the standard clinical practice of the site for patient follow-up, performed through an electronic Case Report Form (eCRF). The collected data were submitted to the appropriate work procedures to comply with the FDA 21 CFR Part 11 regulation, which ensured that the data received via electronic transmission are as valid as the originals received on paper. The total observation period of the study, that is, the data collection time ranged from January 2019 to May 2023.

The primary objective was to evaluate the tolerance of the eHCF marketed in children with CMPA after the last reformulation. To this end, the good tolerance of the eHCF was evaluated by the number and percentage of patients with no (=0) immediate allergic reactions or intestinal reactions. The immediate reactions were defined as those allergic reactions occurring within 1 h after intake, while the intestinal reactions were defined as delayed reactions (developed after ≥2 h of consumption) involving the gastrointestinal (GI) tract. The doctor then registered the answer (Yes/No) to the following questions: (i) Does the doctor consider the tolerance of the eHCF to be good? and (ii) Have there been any allergic reactions after its consumption?

The secondary objective consisted of evaluating the effect of the eHCF on growth outcomes using weight, height, and the related Z-scores, WAZ, HAZ, WHZ, and BAZ, assessed at the first hospital visit and at each follow-up visit.[23]

Statistical analysis

The sample size was based on the number of patients who had to be included in the study to make it possible to obtain sufficient data to achieve the primary objective. The secondary objective was fulfilled as a result, based on the size determined by the primary objective of the study. Based on the article published by Ibero et al.,[22] in 67 children (1 month to 7 years) with CMPA, the formula was tolerated by 66 of the 67 patients analyzed (98.5%). Using a one-sided 95% CI, the initial sample size of 50 patients provided an estimation error of approximately 6% for the rate of tolerance. The study protocol included a predefined criterion: if the analysis of the first 50 children showed a tolerability of less than 98% (more than 1 child with allergic reactions), the sample size would be extended to 100 children to enhance the precision of the results. With the potential expanded sample size of 100 children, the maximum estimation error would decrease to 4.3%, allowing for more precise conclusions if needed. The Exact (Clopper–Pearson) method was employed for these statistical estimates, ensuring robust and reliable calculations throughout the study.

Statistical analysis was performed on the evaluable population, defined as all patients meeting all inclusion criteria and none of the exclusion criteria. Continuous variables were described by centralization and dispersion statistics: mean and standard deviation (SD). Categorical variables were described using absolute and relative frequencies. Percentages were calculated considering all responses and only valid responses (those with available data). For dependent samples, parametric (paired t-test) or nonparametric (Wilcoxon) statistical tests were used, depending on the sample distribution. For statistical analyses, two-sample t-tests were used with a significant level of 95% ($\alpha = 0.05$). Missing data were not imputed and were left as lost. Data were analyzed using SPSS v29.0 or later.

Concerning the study's endpoints, descriptive statistics were used to analyze tolerance to the eHCF, as the number and percentage of patients with no immediate allergic reactions or intestinal reactions. WAZ, HAZ, WHZ, and BAZ indices were calculated using the World Health Organization reference tables and scoring algorithms: https://www.who.int/tools/child-growth-standards/standards/weight-for-age. Descriptive statistics are presented for each visit and compared by paired t-test. A P-value below 0.05 was considered significant. The 95% confidence intervals (CIs) have been calculated (using the Clopper and Pearson method), when applicable, for the outcome variables associated with the main and secondary objectives.

Results

At the time of database lock on January 11, 2024, a total of 61 pediatric patients with CMPA were included in the study, and all were evaluable since no screening failures were registered. A total of 33 patients were male (54.1%) and had a mean (±SD) birth weight of 3.3 ± 0.4 kg. The patients had a follow-up period of 8.4 months, with a mean age of 3.1 ± 2.5 months at the first hospital visit (baseline), 6.5 ± 3.4 months at the first follow-up visit, and 11.5 ± 5.3 months at the second follow-up visit.

The eHCF was well tolerated by 100% (95% CI: 94.1–100) of patients with no immediate allergic or intestinal reactions registered by the doctor during the follow-up visits (Table 1). In all patients, participating physicians considered the tolerance of the eHCF to be good.

At the first hospital visit, weight, height, and BMI registered a mean of 5.6 ± 1.4 kg, 59.3 ± 6.1 cm, and 15.6 ± 1.7, increasing to 9.2 ± 1.5 kg, 73.9 ± 6.5 cm, and 16.9 ± 1.4, respectively, in the second follow-up visit (Figure 2). On average, head circumference increased by 4 cm at the first follow-up visit, from a mean ± SD of 38.0 ± 2.2 cm at baseline to 42.0 ± 2.8 cm. The growth continued, with a further increase of 2 cm observed at the second follow-up visit, where a mean head circumference of 44.2 ± 1.7 cm was registered for the participating infants (Figure 2).

Table 1 Tolerance of a commercially extensively hydrolyzed casein formula consumption.

	Follow-up 1 *n (%)*	Follow-up 2 *n (%)*	Throughout the study *n [% (95% CI)]*
Does the Doctor consider the tolerance of the eHCF to be good? (answer = Yes)	61 (100.0)	61 (100.0)	61 [100.0 (94.1-100.0)]
Have there been any allergic reactions after its consumption? (answer = No)	61 (100.0)	61 (100.0)	61 [100.0 (94.1-100.0)]

The good tolerance of the eHCF formula was evaluated by the Doctor through the number and percentage of patients with no (=0) immediate allergic reactions or intestinal reactions. The 95% CI has been calculated using the Clopper and Pearson method. CI: Confidence interval

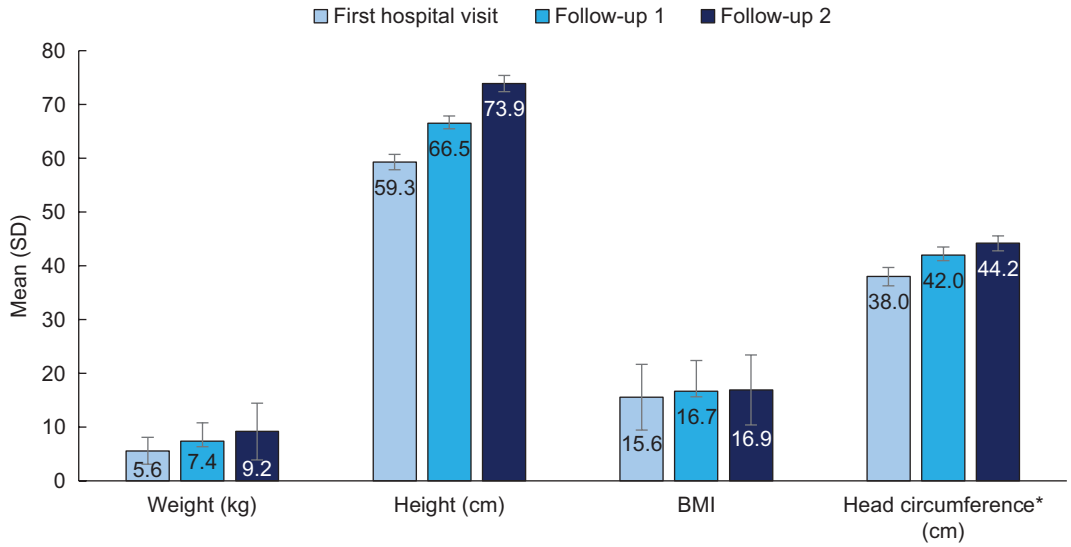

Figure 2 Data are shown as mean (SD) for 61 evaluable patients, except for *head circumference, with n = 27, n = 28, n = 26 for the first hospital visit, follow-ups 1 and 2, respectively. BMI: Body mass index; SD: Standard deviation The mean Z-scores WAZ, HAZ, BAZ, and WHZ were −0.36 ± 0.95, −0.26 ± 1.00, −0.29 ± 1.05, and −0.22 ± 1.1, respectively, at the first hospital visit; −0.15 ± 0.81, −0.09 ± 0.97, −0.14 ± 0.89, and −0.09 ± 0.91 at the first follow-up visit; and 0.09 ± 0.79, 0.05 ± 1.03, 0.10 ± 0.87, and 0.13 ± 0.85 at the second follow-up visit (Figure 3). Paired comparisons of the scores (WAZ, HAZ, WHZ, and BAZ) between the different visits were made two by two (Figure 3).

Discussion

This observational and retrospective study shows that pediatric patients diagnosed with CMPA before 1 year of age, and who had been taking an eHCF for at least 4 months at the time of chart review, tolerated the formula very well and none of them experienced allergic reactions. The tolerance of the eHCF was considered to be good for 100% of the patients (95% CI: 94.1-100).

The first-line treatment for food allergy disorders is avoidance of the suspected allergen. Concerning CMPA, the use of eHFs reduces allergenicity significantly when compared to other formulas of therapeutic diet[24,25] since the milk proteins are broken down into smaller peptides through extensive hydrolysis, reducing the number of conformational and sequential epitopes.[26,27] Numerous studies have demonstrated favorable tolerance and safety profiles for eHFs.[28,29] The results from the DELISA study provide additional support for using eHFs as the first choice in CMPA nutritional management.[3,26]

The patients had a mean age of 3.1 months at the first hospital visit, 6.5 months at the first follow-up visit, and 11.5 months at the second follow-up visit, meaning that the time of follow-up was about 8.5 months.

Although not statistically tested, the mean of weight, height, and BMI increased from the first hospital visit (5.6, 59.3, and 15.6, respectively) to the first (7.4, 66.5, 16.7) and the second follow-up visits (9.2, 73.9, 16.9). On average, head circumference increased by 4 cm at the first follow-up visit and by 2 cm at the second follow-up visit. Z-score results for all visits were between −1 and 1, within a range close to the mean of a standard normal distribution, with significant increases. The eHFs are elaborated to provide adequate nutrition for infants with CMPA, supporting normal growth and development. A study conducted in Thailand in 2021 followed 116 infants diagnosed with CMPA for up to 12 months on administered eHF, AAF, soy-based formula (SF), chicken-based formula, and breast milk.[30] Improvement in growth was significantly more pronounced in CMPA infants fed with eHF when compared to

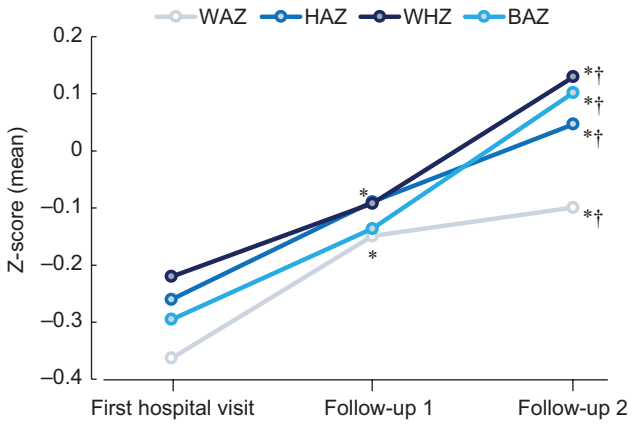

Figure 3 Growth outcomes in CMPA infants receiving eHCF. *Significant versus first hospital visit (P < 0.05); †Significant versus first follow-up visit (P < 0.05). Mean Z-scores calculated according to the World Health Organization (WHO) scoring algorithms. BAZ: Body mass index-for-age z-score; HAZ: Height-for-age z-score; WAZ: Weight-for-age z-score; WHZ: Weight-for-height z-score

other diets.[30] Another study in 2023 in 226 infants with CMPA at 35 pediatric gastroenterology and allergy centers across Turkey showed that the use of eHCF during the first 6 months of life was associated with a normal growth profile and improved WFA and WFL Z-scores.[27] Lindsey et al. evaluated 315 healthy infants at 21 sites in four countries, comparing eHF (n = 158) with a cow's milk control formula (n = 157), revealing that growth parameters, including absolute weight, length, and head circumference as well as z-scores, did not differ significantly between the two groups.[28] The results of growth assessment after eHCF consumption presented here confirm that infants fed with eHFs exhibit normal growth profiles, which is crucial for their overall health.[27,28,30]

This study suffered from the inherent limitations of observational and retrospective design, selection bias, and the availability of data. However, patients were consecutively recruited from among those who met the eligibility criteria, so the impact of selection bias was minimized. Furthermore, all patients included were analyzed, and all data except head circumference were available, which also minimized the information bias. The limited sample size also compromised the generalizability of the results; nonetheless, the selection of participating centers distributed around Spain ensured a representative sample. Another limitation of our study was that we did not use validated questionnaires or assess sleeping patterns, which would have provided additional valuable insights into the characteristics of the children. However, we chose to focus solely on allergic symptoms to ensure that the data collected were accurate and thoroughly completed by the physicians.

Conclusions

The DELISA study results showed that the studied eHCF formula was well tolerated by more than 90% of pediatric patients diagnosed with CMPA and below 1 year, who were included in this study. No patients experienced allergic reactions to the formula, and in all cases, participating physicians considered the tolerance of the eHCF to be good. In addition, over a follow-up period of 8.4 months, pediatric patients with CMPA taking the eHCF exhibited normal growth profiles and showed significant increases in the anthropometric Z-scores WAZ, HAZ, BAZ, and WHZ. These findings demonstrate that eHCF formulas are a safe option for infants with CMPA, supporting normal growth and development while preventing allergic reactions.

Supplementary Materials

Table S1 lists the participating investigators and study sites in the DELISA study.

Institutional Review Board Statement

This study is in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines and applicable regulatory requirements. The study protocol was approved by the Independent Ethics Committee (IEC) of Fundación Jiménez Díaz, Madrid, Spain.

Informed Consent Statement

The IEC approved the informed consent exemption for this study.

Data Availability Statement

The datasets generated and/or analyzed during this study are available from the corresponding author on reasonable request.

Acknowledgments

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Author's Contribution

Conceptualization: M.R, C.B., M.B., and J.E.; Methodology: M.R, C.B., M.B., and J.E.; Investigation: M.B., G.R.M, R.L., S.F.C., M.J.B.V., A.R.M., J.R.A., and R.G.D.C.M.; Writing—original draft preparation: M.B., M.R, C.B., and J.E.; Writing—review and editing: M.B., G.R.M., R.L., S.F.C., M.J.B.V., A.R.M., J.R.A., R.G.D.C.M., C.B., J.E., and M.B. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

Cecile Bonhomme is an employee of Lactalis Nutrition Santé. Javier Estrada and Marylise Beaucreux are

employees of Lactalis Nutrition Iberia. The other authors declare no conflicts of interest.

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Supplementary

Table S1 Participating investigators and study sites in the DELISA study.

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Dr. Alejandro Rodríguez Martínez	Hospital Universitario Virgen del Rocío, Sevilla
Dr. Joaquín Reyes Andrades	Instituto Hispalense de Pediatría, Sevilla
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