ISSN: 3067-2376
Research Article
Journal of Comparative Medicine Research Reviews and Reports

Improvement of Gastro-Intestinal Symptoms in Infants Consuming a Goat Milk-Based Formula: A Randomized Controlled Pilot Study

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Submitted: 11 June 2025 **Accepted:** 17 June 2025 **Published:** 01 July 2025

https://doi.org/10.63620/MK.JCMRRR.2025.

Citation: *Goossens, D., Knipping, K., Pellis, L., van der Zee, L., Soría López, M., & López-Escobar, A. (2025). Improvement of Gastro-Intestinal Symptoms in Infants Consuming a Goat Milk-Based Formula: A Randomized Controlled Pilot Study. J of Comp Med Res Rev Rep, 2(4), 01-08.*

Abstract

Introduction: *Many infants aged between 0-6 months experience mild gastro-intestinal (GI) symptoms. The main objective of this study was to explore if infants with mild symptoms have significantly less symptoms after goat milk-based formula (GMF) consumption compared to infants receiving standard treatment.*

Methods: *Formula-fed infants (1-3 months; n=18) were randomized to use GMF or to continue their current CMF with probiotic Lactobacillus reuteri drops (CMFp) for 28 days. Infants had an assessed cow's milk-related symptom score (CoMiSS®) between 6-12 at baseline, indicating mild symptoms. Endpoints included symptoms (CoMiSS®), parental stress (PSI-SF), quality of life of the parents (WHOQOL-BREF) and infant's weight and length.*

Results: *After 14 days of intervention, the median (25th and 75th percentile) CoMiSS® in the GMF group was significantly lower compared to the CMFp group (GMF: 5 (3.5-6.5), CMFp : 11 (5.0-11.0), p=0.047). After 28 days of intervention, the median CoMiSS® was still lower in the GMF group compared to the CMFp group (GMF: 3, CMFp: 6, p=0.302), mainly due to more firm stools (p=0.016). Stress and quality of life improved in the parents of the GMF group, but not in the CMFp group. All infants showed healthy growth and tolerated the formula well.*

Conclusion: *Infants with mild GI symptoms showed significantly less symptoms after 2 weeks of GMF use compared to CMFp, mainly due to a normalization of stool patterns. This pilot study suggests that infants with mild GI symptoms could benefit from GMF.*

Keywords: Gastrointestinal Symptoms, Goat Milk-based Formula, Cow's Milk-related Symptoms, Comiss.

Introduction

Exclusive breastfeeding for the first 6 months is the universally recommended nutrition for infants by the World Health Organization (WHO) [1]. In case (exclusively) breastfeeding is no longer possible, infant formulas are recommended. Most infant formulas currently on the market are based on cow's milk, but goat milk-based formulas (GMF) are a suitable alternative. Goat milk is considered a safe and suitable source of protein for in-

fant formula according to the European Food Safety Authority (EFSA) and Food and Drug Administration (FDA) [2, 3]. GMF has shown to provide adequate growth and is safe to use in infants [4, 5].

Over half of infants experience mild gastro-intestinal (GI) symptoms like spitting up, watery or hard stools, bloating and extensive unexplained crying in the first 6 months of life [6-8]. These symptoms usually appear around 15 days of life and naturally improve after 4 months of age. These mild GI symptoms can lead to a decreased quality of life (QoL) and stress in both infants and parents [6, 8]. This underlines the search for relief of the infant's symptoms.

Often the aetiology of these GI symptoms is not known, but these symptoms may be due to the immaturity of the digestive tract and immune system in early life. Many parents switch formula in their search for relief of their infant's symptoms. Infants with mild GI symptoms could benefit from an infant formula that is easy to digest. An in vitro model simulating infant conditions, showed that GMF has a more similar protein digestion rate to human milk, while the digestion rate of cow's milk-based formula (CMF) was significantly lower [9]. The easier digestibility of GMF may be due to differences in casein composition: goat milk proteins have a lower level of αS1-caseins and a higher level of β-caseins which could lead to looser curds of goat milk in the stomach [10, 11], making the proteins more accessible for digestive enzymes.

A case study in 23 infants reported that after 3 weeks of GMF use, softer stools were observed and crying had reduced from 3 hours per day to 1 hour per day [12]. In addition, parents reported improvements in their infant's GI and skin symptoms after 14 days GMF use as measured in cross-sectional studies [13, 14].

The main objective of this study was to explore whether infants with mild symptoms have significantly less (severe) symptoms after 14 days GMF use compared to infants using their standard CMF supplemented with probiotic Lactobacillus Reuteri drops (CMFp).

Methods

Study Design

This study was an open-label, prospective, randomized, controlled, pilot study, approved by the medical ethical committee of HM Hospitals (Madrid, Spain). Participants were recruited from May 2019 to April 2021 during standard check-ups.

Infants visited the hospital at baseline and at day 14 and 28 of intervention. During each visit, the CoMiSS® was assessed and weight and length of the infants was measured. Between visits, parents completed a diary at day 5, 9 and 28 of intervention to evaluate the volume of formula that has been consumed by their infant and the tolerability of the products. In the diaries parents also completed a parental stress (Parental Stress Index-Short Form, PSI-SF) and quality of life (World Health Organization Quality Of Life – short version, WHOQOL-BREF) questionnaire. All parents provided written, informed consent prior to the start of the study. The study was registered at www.clinicaltrials.gov (NCT06301139, first enrolment May 1, 2019).

Participants

Eligible participants were healthy full-term infants (gestational age between 37-42 weeks), aged 1-3 months with a birth weight between 2,500-4,500 grams. Infants were exclusively CMF fed prior to the start of the study and had a CoMiSS® of ≥ 6 and < 12 and had persistent mild symptoms for >7 days at baseline.

Exclusion criteria were a history of GI disorders, cow's or goat milk protein allergy, lactose intolerance, any congenital illness or malformation that may affect infant feeding or normal growth. Infants who participated in another clinical study or received supplemental feeding were excluded.

Allocation and Intervention Products

Infants enrolled in the GMF group received Kabrita® Gold stage I Infant Formula (Ausnutria B.V., The Netherlands) (Appendix 1). The control group (CMFp) continued the CMF of their parent's choice supplemented with probiotic Lactobacillus Reuteri Protectis DSM 17938 drops (BioGaia, Spain). This probiotic is administered by adding 5 drops to the CMF in the afternoon. During the intervention, consumption of foods other than the allocated formula and probiotic drops was not allowed. The GMF and probiotics were supplied free of charge. Allocation to the intervention group was based on block randomization with a 1:1 allocation ratio as determined by an independent statistician.

Measurements and Outcomes

Mild GI symptoms were assessed using the CoMiSS®, which was designed as an awareness tool for cow's milk-related symptoms including gastrointestinal, cutaneous and respiratory symptoms [15]. The total CoMiSS® consists of subscores on daily hours of crying, volume and frequency of regurgitation, stool consistency, presence of eczema and urticaria, and presence and severity of respiratory symptoms such as wheezing. The stool consistency is scored in the CoMiSS® by the Brussels Infants and Toddlers Stools (BITSS) [16]. The CoMiSS® has been validated and considered useful in clinical studies [15, 17, 18].

The parental quality of life was assessed with the WHO-QOL-BREF and stress levels with the PSI-SF in the diary at baseline, day 5, 9 and 28 by both the mother and father. WHO-QOL-BREF is a questionnaire consisting of 26 multiple choice questions in the domains physical health, psychological, social relationships, and environment, and has been validated [19, 20]. WHOQOL-BREF scores are transferred to 0-100 points interval with higher scores denoting higher quality of life. PSI-SF yields a total stress score based on 36 questions on 3 different scales: parental distress, parent-infant dysfunctional interaction, and difficult infant. Percentile PSI-SF scores range from 15-100% with higher scores reflecting more stress. The PSI-SF has been validated in Spanish parents [21].

Demographic and baseline characteristics were recorded during the baselines visit. Volume intake (ml/day) of GMF and CMFp were recorded in the diaries during intervention. Weight and length were measured by the investigator during the baseline, day 14 and day 28 visits. Infant weight was measured without clothing and diaper on a calibrated electronic scale to the nearest 10 g. Recumbent length was recorded using a calibrated length board to the nearest 0.1 cm. Corresponding z-scores for weight-for-age, length-for-age, weight-for-length were calculated using

the WHO Child Growth Standards [22]. Adverse events and medication use were recorded by the parents in the dairy and at each study visit.

Statistical Analyses

Differences between the GMF and CMFp group were analysed through an independent t-test for normally distributed variables, Wilcoxon-Mann-Whitney test for skewed variables or Fisher's exact test for categorical variables. Baseline characteristics of the participants are presented as mean (SD), as median (interquartile range (IQR)) or n (%) when appropriate. For all tests, a p-value of 0.05 was considered statistically significant. Statistical tests were performed using SAS 9.4 software. All analyses were based on the all-subjects treated group: all subjects who had been randomized and who consumed at least one bottle as based on the diary volume intake data.

Results

General Characteristics

Eighteen infants started consuming GMF or CMFp in this study, thirteen infants in the GMF group and five in the CMFp group. The mean age of the infants was 42.7 days with 8 girls and 10 boys included in this study. Two infants in the CMFp group switched after 14 days towards the GMF group because of unsatisfying results. Data from day 28 of these 2 infants were excluded from the statistical analyses. Baseline infant characteristics were comparable.

Table 1: Baseline characteristics in median (25th and 75th percentile) or n (%) of the GMF and CMFp group.

	GMF	CMFp
N	13	5
Sex (boy)	7 (53.8%)	3 (60.0%)
Ethnicity (Caucasian)	13 (100%)	5 (100%)
Age (days)	45 (32.0, 55.0)	31 (27.0, 32.0)
Breastfed prior to trial (yes)	7 (53.8%)	4 (80.0%)
Volume intake (ml)	325 (190.0, 510.0)	430 (250.0, 680.0)
CoMiSS®	8 (8.0, 9.0)	8 (8.0, 11.0)

GMF: Goat milk-based infant formula; CMFp: Cow's milk-based infant formula with probiotics; CoMiSS: Cow's Milk-related Symptom Score

At baseline, median total CoMiSS® was 8 for both the infants randomized to the GMF group and for the CMFp group. In the CMFp group, the infants continued to use the CMF of parent's choice supplemented with the probiotic Lactobacillus reuteri. One of the 5 infants enrolled in the CMFp group used a partially hydrolysed CMF. The other 4 infants in the CMFp group used a CMF with intact proteins.

CoMiSS®

There were no significant differences in CoMiSS® between the two groups at baseline (table 2). After 14 days of intervention, the median CoMiSS® was 5 (25th, 75th percentile: 3.0, 6.5) in the GMF group (n=13) and was significantly lower (p=0.047) compared to the CMFp group (n=5) with a median of 11 (5.0, 11.0).

Table 2: CoMiSS scores in median (25th and 75th percentile) at baseline, after 14 days and 28 days of the GMF and CMFp group.

	GMF	CMFp#	p value
Baseline	8 (8.0, 9.0)	8 (8.0, 11.0)	0.650
Total CoMiSS (0-33)	5 (4.0, 5.0)	4 (4.0, 4.0)	0.684
Crying (0-6)	4 (2.0, 4.0)	4 (4.0, 4.0)	0.623
Stools (0-6)			
Regurgitation (0-6)	1 (1.0, 2.0)	1 (1.0, 2.0)	1.000
Respiratory (0-3)	0 (0.0, 0.0)	0 (0.0, 0.0)	1.000
Skin – Urticaria (0-6)	0 (0.0, 0.0)	0 (0.0, 0.0)	1.000
Skin -head/neck/trunk, arms/hands/legs/feet (0-6)	0 (0.0, 0.0)	0 (0.0, 1.0)	0.127
Day 14			
Total CoMiSS (0-33)	5 (3.0, 6.5)	11 (5.0, 11.0)	0.047
Crying (0-6)	2 (1.0, 3.0)	4 (3.0, 4.0)	0.115
Stools (0-6)	1 (0.0, 2.0)	4 (4.0, 4.0)	0.016
Regurgitation (0-6)	1 (1.0, 2.0)	1 (0.0, 1.0)	0.293
Respiratory (0-3)	0 (0.0, 0.0)	0 (0.0, 0.0)	1.000
Skin – Urticaria (0-6)	0 (0.0, 0.0)	0 (0.0, 0.0)	1.000
Skin -head/neck/trunk, arms/hands/legs/feet (0-6)	0 (0.0, 0.0)	0 (0.0, 0.0)	0.558

Day 28			
Total CoMiSS (0-33)	3 (2.0, 5.0)	6 (3.0, 8.0)	0.302
Crying (0-6)	1 (1.0, 2.0)	2 (0.0, 3.0)	0.728
Stools (0-6)	0 (0.0, 2.0)	4 (2.0, 4.0)	0.098
Regurgitation (0-6)	1 (1.0, 2.0)	1 (0.0, 1.0)	0.293
Respiratory (0-3)	0 (0.0, 0.0)	0 (0.0, 0.0)	1.000
Skin – Urticaria (0-6)	0 (0.0, 0.0)	0 (0.0, 0.0)	1.000
Skin -head/neck/trunk, arms/ hands/legs/feet (0-6)	0 (0.0, 0.0)	0 (0.0, 0.0)	0.558

CMFP group consists of five infants at baseline and Day 14, and of 3 infants at day 28

GMF: Goat milk-based infant formula; CMFp: Cow's milk-based infant formula with probiotics; CoMiSS: Cow's Milk-related Symptom Score

After 28 days of intervention, the CoMiSS® further decreased in both groups, but was still lower in the GMF group (n=13, median 3 (2.0, 5.0)) compared to the CMFp group (n=3, median 6 (3.0, 8.0)), although no longer statistically significant (p=0.302).

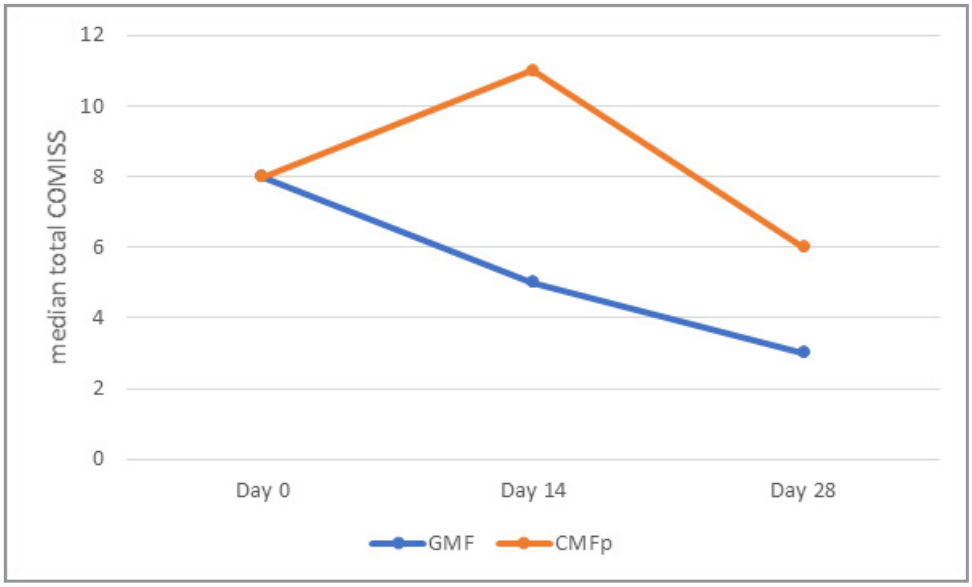

Figure 1: Median CoMiSS® at baseline and after 14 days and 28 days of intervention of infants using GMF and CMFp. * p<0.05; GMF: Goat milk-based infant formula; CMFp: Cow's milk-based infant formula with probiotics; CoMiSS: Cow's Milk-related Symptom Score

The CoMiSS® subscore for stools showed a significant difference at day 14 of intervention with the GMF group having the lowest score versus the CMFp group (GMF median 1.0 (0.0, 2.0) versus CMFp 4.0 (4.0, 4.0, p=0.016)). After 28 days of intervention, the median CoMiSS subscore for stools was still lower for the GMF group than the score in the CMFp group (GMF 0 (0.0, 2.0), CMFp 4 (2.0, 4.0)), but no longer significant (p=0.098). The median BITSS types of stool consistency decreased in the GMF group from type 5 (soft stools) towards type 3/4 (normal stools) after 28 days of intervention, but remained unaffected in the CMFp group: type 6 (liquid stools) at baseline versus type 5/6 (liquid/soft stools) after 28 days of intervention.

The other CoMiSS® subscores were not significantly different between groups during intervention. However, the CoMiSS® subscore for crying did decreased with 4 points in the GMF group compared to a decrease of 2 points in the CMFp group, parallel to the decrease in total CoMiSS® (table 2). The number of crying hours in the GMF infants decreased from 4-5 hrs per day at baseline (CoMiSS® crying score 5) towards 1-1.5 hours per day after 28 days intervention (CoMiSS® crying score 1). The number of crying hours in the CMFp infants decreased from 3-4 hrs per day at baseline (CoMiSS® crying score 4) towards 1.5-2 hours per day after 28 days intervention (CoMiSS® crying score 2).

Quality of Life and Parental Stress

In both mothers and fathers of infants allocated to GMF group, the median WHOQOL-BREF score improved at day 28 of intervention (mothers: baseline 53 (36.3, 66.1) towards 57 (48.4, 64.4) at day 28, fathers: baseline 58 (43.3, 72.2) towards 68 (59.1, 76.8) at day 28). The improvement in quality of life in both the mothers and fathers was mostly driven by an improvement in the subdomains 'social relationship', followed by 'physical health' and 'environment'. In contrast, the median WHOQOL-BREF in the CMFp group worsened at day 28 of intervention with 2

points for the mothers and with 5 points for the fathers. However, there were no statistically differences in the medians observed between the GMF and CMFp groups during intervention.

A similar improvement could be seen for stress as assessed with PSI-SF. The stress scores improved with 7 points for the mothers of the GMF group (baseline: 92 (65.0, 116.0), day 28: 85 (53.0, 94.0)) and with 12 points for the fathers (baseline: 76 (68.5, 99.0), day 28: 64 (50.0, 81.0)). In the CMFp group an increase in median PSI-SF was seen of 14 points for the mothers and of 2 points for the fathers indicating more stress. However, no statistically differences in PSI-SF scores were observed between the GMF and CMFp groups during intervention.

Safety and Tolerance Outcomes

The volume intake of GMF and CMFp were comparable during intervention. At day 28, a mean volume intake of 653.8 ml/day (SD 238.1) was consumed in the GMF group and a mean volume of 770.0 (SD 334.5) in the CMFp group. All infants individually showed appropriate growth with z-scores weight-for age, length-for-age and weight-for-length within -2SD and +2SD WHO standards. No differences in anthropometric measurements were observed between groups.

Table 3: z-score weight-for-age, length-for-age and weight-for-length in means (SD) of infants in the GMF and CMFp group at baseline and at day 14 and 28 of intervention.

	GMF boys	GMF girls	CMFp boys	CMFp girls
z-score weight-for-age				
baseline	-0.990 (0.716)	-1.088 (1.035)	-0.683 (0.569)	-1.135 (0.530)
day 14	-0.787 (0.707)	-0.972 (1.049)	-0.710 (0.391)	-0.575 (1.167)
day 28	-0.832 (0.883)	-0.803 (1.087)	-0.653 (0.521)	NA
z-score length-for-age				
baseline	-1.341 (1.084)	-1.020 (1.059)	-0.337 (0.781)	-1.020 (0.806)
day 14	-1.060 (1.024)	-0.494 (1.057)	-0.583 (0.548)	-0.385 (1.379)
day 28	-0.820 (1.176)	-0.440 (1.050)	-0.510 (0.704)	NA
z-score weight-for-length				
baseline	0.381 (0.507)	-0.360 (1.678)	-0.643 (2.057)	-0.465 (0.375)
day 14	0.360 (0.756)	-0.808 (1.071)	-0.217 (1.378)	-0.285 (0.078)
day 28	-0.100 (0.829)	-0.557 (0.832)	-0.277 (1.662)	NA

NA = there were no girls in the CMFP group after 28 days of intervention
GMF: Goat milk-based infant formula; CMFp: Cow's milk-based infant formula with probiotics

During the 28 days intervention, there were 13 adverse events recorded in the GMF group and 2 in the CMFp group. The higher number of adverse events in the GMF group can be explained by the higher number of infants in the GMF group compared to the number of infants in the CMFp group. Adverse events recorded were bronchitis, otitis, urinary tract infections, mycosis, vomiting and dermatitis. In the GMF group, 1 adverse events (otitis) was recorded as moderately severe. None of the adverse events were related to the formula used and no serious adverse events occurred.

Discussion

This randomized controlled pilot study demonstrated that infants with mild symptoms have significantly less symptoms after 14 days GMF use, compared to infants using CMF supplemented with probiotics (CMFp), mainly due to a normalizing stool pattern and reduced crying. The stool consistency in the GMF group changed from soft stools (type 5 on BITSS) towards normal stools (type 3/4) after 28 days of intervention, while the stool consistency in the CMFp group remained unaffected (liquid/soft, type 5/6) indicating that GMF normalizes the stool consistency. In addition, the CoMiSS® subscore for crying decreased with 4 points in the GMF group and with 2 points in the CMFp group indicating fewer crying hours per day. These findings can be clinically important since about half of the infants are having mild GI symptoms including excessive crying (21%), constipation (18%) and diarrhoea (4%) [7]. The effects of GMF were compared with the use of regular CMF supplemented with the probiotic Lactobacillus reuteri. In a systematic review, Lactobacillus reuteri was reported to reduce colic in breastfed infants, although the effects were not significant in formula fed infants [23]. The efficacy of the combination of GMF with a probiotic strain could be interesting to study. No effects on the CoMiSS® subscore for cutaneous and respiratory symptoms were seen in our study.

The lower CoMiSS® and the reduction of mild GI symptoms in the GMF group during intervention could be due to the different composition of goat milk proteins as compared to cow's milk proteins. The digestive system and the microbiota of infants undergoes a strong maturation during the first months of life and infants might benefit during their first year of life of an easily digestible formula. In vitro studies with infant settings showed that goat milk proteins are digested more efficiently than cow's milk protein [24-26]. The lower αS1-casein that is found in goat milk compared to cow's milk is potentially due to softer and looser curds which might reduce GI discomfort and improve stools [9, 11, 25, 27].

In addition, this study showed that parental stress and quality of life improved in both the mothers and fathers of the GMF group in parallel to the reduction of GI symptoms. GI symptoms in infants often lead to parental stress, sleepless nights and concerns [6, 8]. A reduction of stress and an improvement of quality of life are regarded very relevant for both parents of infants.

Previous studies have already established that growth in infants fed GMF is adequate and does not differ from infants consuming CMF, which was confirmed in this study [5, 28-30]. Remarkably, we found that on average the z-scores were negative, nevertheless, all z-scores were within 2 SD, indicating adequate and normal growth.

This study was conducted mainly during the COVID-19 pandemic, which resulted in a low enrolment rate over the pre-specified recruitment time. Consequently, the power of the study to detect differences between the GMF and CMFp groups was low, although significant differences in CoMiSS® could still be detected after 14 days of intervention. The open-label design of this study also merits attention. The study was not blinded, which might have resulted in bias from the physician and parents when answering questionnaires. Moreover, 5 infants in the CMFp group were randomized but dropped out of the study immediately after the randomization due to the open-label study design, which has led to an unequal distribution between the 2 groups. A double-blinded study with a higher power to confirm the conclusions found in this pilot study is warranted. Another limitation of this study is that the control group continued the CMF of their parents' choice. This resulted in variation in CMF compositions, even resulting in the inclusion of 1 infant using a formula with hydrolysed proteins. To make firm conclusions about the efficacy of GMF, a double-blind comparison versus CMF with identical composition except for the protein base is warranted. On the other hand, this study describes a comparison of GMF versus a standard treatment using different types of commercially available CMF supplemented with Lactobacillus reuteri, and generates in this way real-life evidence which could be regarded as strength of the study. Another strength of this study is that the primary outcome was measured with the CoMiSS® which is a validated tool. All CoMiSS® forms were recorded by 1 single physician for all infants at all visits to reduce interpersonal variations. Another strength of this study is that infants are all <4 months and consumed formula only and had no complementary feeding, which makes it more likely that the positive effects seen are due to the formula.

Conclusions

In conclusion, GI symptoms were significantly less in infants with mild symptoms after 14 days GMF use compared to the infants using CMF with supplemental probiotics, mainly due to the normalization of stool patterns and reduced crying hours. After 28 days of GMF use, parental stress and quality of life improved. This study gives a first indication that infants with mild GI symptoms could benefit from GMF. However, the present study was a pilot study and a well-powered, double-blinded study with a standardized CMF control product is recommended.

Declarations

Ethics Approval and Consent to Participate

The study was approved by the medical ethical committee of HM Hospitals (Madrid, Spain). All parents provided written, informed consent prior to the start of the study. Registration number at www.clinicaltrials.gov: NCT06301139

Consent for Publication

This publication does not contain any individual person's data in any form

Availability of Data and Materials

The datasets during and/or analysed during the current study available from the corresponding author on reasonable request.

Competing Interests

DG, KK, LP and LvdZ are employees of Ausnutria B.V.

Funding

The study was funded by Ausnutria B.V.

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Appendix 1: Composition of GMF

Nutrient	Content		
		per 100 kcal (418 kJ)	per 100 mL
Protein	total goat whey protein goat casein protein	2.5 g 1.6 g 0.93 g	1.7 g 1.1 g 0.6 g
Carbohydrate	total lactose	11.3 g 9.3 g	7.4 g 6.1 g
Fat	total saturated fat monounsaturated fat poly unsaturated fat high sn-2 palmitic vegetable oil linoleic acid α-linolenic acid AA DHA	5.1 g 1.9 g 1.8 g 0.96 g 0.79 g 880 mg 74 mg 31 mg 15 mg	3.4 g 1.3 g 1.2 g 0.65 g 0.54 g 590 mg 50 mg 9.7 mg 6.8 mg
Vitamins	vitamin A vitamin D3 vitamin E vitamin K1 vitamin C vitamin B1 (thiamin) vitamin B2 (riboflavin) vitamin B6 vitamin B12 niacin folic acid pantothenic acid biotin	90 IU/RE 1.6 µg 1.6 mg α-TE 7.9 µg 14.6 mg 94 µg 171 µg 72 µg 0.26 µg 913 µg 14.7 µg 556 µg 2.4 µg	61 IU/RE 1.1 µg 1.1 mg α-TE 5.4 µg 9.9 mg 64 µg 116 µg 49 µg 0.18 µg 621 µg 10 µg 378 µg 1.6 µg
Minerals	calcium phosphorus magnesium iron zinc manganese copper iodine sodium potassium chloride selenium fluoride	84 mg 54 mg 8.4 mg 0.90 mg 0.85 mg 11.9 µg 66 µg 12.5 µg 29 mg 103 mg 75 mg 2.6 µg ≤2.7µg	57 mg 37 mg 5.7 mg 0.61 mg 0.58 mg 8.1 µg 45 µg 8.5 µg 20 mg 70 mg 51 mg 1.8 µg ≤2.7µg
Others	Choline inositol taurine L-carnitine	17.6 mg 6.0 mg 9.1 mg 2.4 mg	12 mg 4.1 mg 6.2 mg 1.6 mg