Supplementary Materials (Otten et al. Nutrients 2023)

Table S1: Weight gain (g/day) between 30 days of age (V1) and 120 days of age (V4) – Sensitivity analysis including potential confounding factors

		n	LSM	SEM	95% CI (two-sided)	Two-sided superiority *p* value	97.5% CI (one-sided)	One-sided non-inferiority *p* value[a]
PPS	**eHF**	149	28.99	0.68	[27.29;30.68]			
	CF	148	28.79	0.69	[27.07;30.51]			
	eHF vs CF		0.20	0.48			[-0.75;+inf]	<0.0001
	Product					0.6784		
	Baseline weight					0.0007		
	Sex					0.1470		
	Birth weight					0.5449		
	Gestational age					0.0040		
	Age of mother (at infant birth)					0.0510		
	BMI of mother (at delivery)					0.0174		
	Educational level of mother					0.6572		
FAS	**eHF**	158	28.85	1.09	[26.37;31.33]			
	CF	155	28.74	1.09	[26.24;31.23]			
	eHF vs CF		0.11	0.49			[-0.85;+inf]	<0.0001
	Product					0.8170		
	Baseline weight					0.0015		
	Sex					0.0262		
	Birth weight					0.5287		
	Gestational age					0.0332		
	Age of mother (at infant birth)					0.2374		
	BMI of mother (at delivery)					0.1443		
	Educational level of mother					0.7183		

[a] non-inferiority margin: -3 g/day

BMI: body mass index (kg/m^2); CF: control formula; CI: confidence interval; eHF: infant formula manufactured from extensively hydrolysed whey protein; FAS: full analysis set; inf: infinity; LSM: least

square means; *n*: number of observations; PPS: per protocol set; SEM: standard error of mean

Table S2: Mean daily gain in weight, length and head circumference from 30 days of age (V1) (FAS), mean (SD)

	Visit	Age at visit (days)	eHF (*n* = 158)	CF (*n* = 157)[a]	BF (*n* = 41)[b]
Weight gain (g/day)	2	60	33.6 (9.1)	33.4 (9.5)	29.4 (4.8)
	3	90	31.5 (6.1)	31.0 (5.7)	30.1 (4.6)
	4	120	29.1 (4.9)	28.8 (4.4)	29.2 (4.1)
	5	180	23.2 (4.1)	22.7 (3.2)	23.1 (3.8)
Length gain (mm/day)	2	60	1.1 (0.5)	1.1 (0.5)	1.3 (0.6)
	3	90	1.1 (0.4)	1.1 (0.4)	1.2 (0.5)
	4	120	1.1 (0.3)	1.0 (0.3)	1.1 (0.4)
	5	180	0.9 (0.2)	0.9 (0.2)	0.9 (0.3)
Head circumference gain (mm/day)	2	60	0.6 (0.3)	0.6 (0.3)	0.7 (0.3)
	3	90	0.5 (0.2)	0.5 (0.2)	0.6 (0.2)
	4	120	0.5 (0.1)	0.5 (0.2)	0.5 (0.1)
	5	180	0.4 (0.1)	0.4 (0.1)	0.5 (0.1)

No statistically significant differences between CF and eHF were observed.

[a] Missing values in CF: weight gain: V2: *n* = 1; V3: *n* = 3; V4, V5: *n* = 2 length gain: V2: *n* = 1; V3: *n* = 2; V4, V5: *n* = 3; head circumference gain: V2: *n* = 1; V3, V4, V5: *n* = 3

[b] Missing values in BF: head circumference gain: V3: *n* = 1

BF: breastfed reference group; CF: control formula; eHF: infant formula manufactured from extensively hydrolysed whey protein; FAS: full analysis set; *n*: number of observations; SD: standard deviation; V: visit

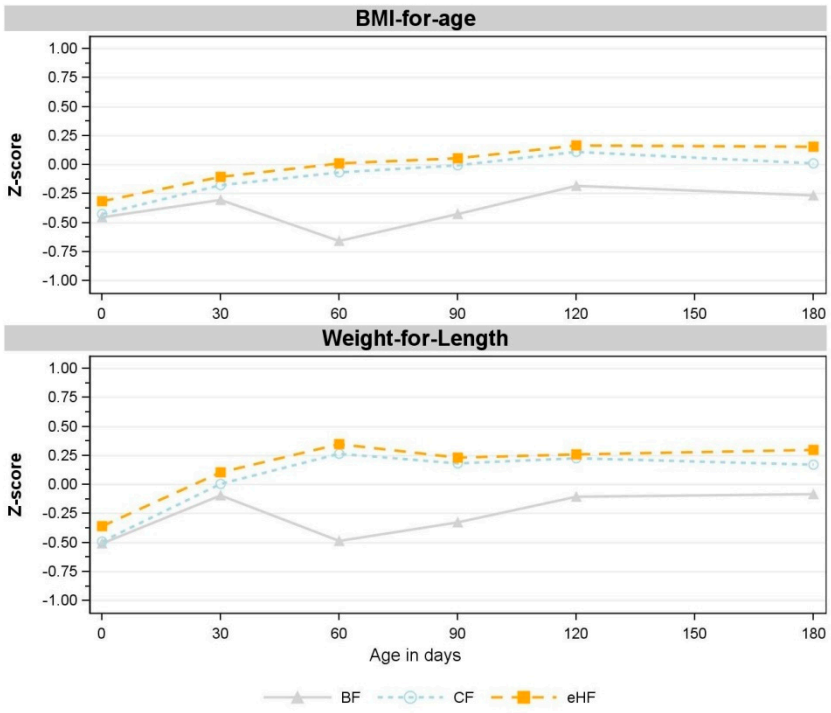

Figure S1*:* Observed mean z-scores for BMI-for-age and weight-for-length between birth and 180 days of age (V5) (FAS)

V1: 30 days; V2: 60 days; V3: 90 days; V4: 120 days; V5: 180 days

No statistically significant differences between CF and eHF were observed.

Missing values in CF: BMI-for-age: V1: *n* = 2; V3: *n* = 3; V4, V5: *n* = 2; weight-for-length: V1: *n* = 2; V3: *n* = 3, V4, V5: *n* = 2

Missing values in eHF: BMI-for-age: V4: *n* = 1; weight-for-length: V4: *n* = 1

BF: breastfed reference group; BMI: body mass index (kg/m^2); CF: control formula; eHF: formula manufactured from extensively hydrolysed whey protein; FAS: full analysis set; *n*: number of observations; V: visit

Table S3: Feedings characteristics (PPS), mean (SD)

	Visit	Age at visit (days)	eHF (*n* = 149)	CF (*n* = 148)	BF (*n* = 41)
Average number of feedings per day	1	30	7.1 (0.8)	7.0 (0.8)	7.4 (0.6)
	2	60	6.1 (0.5)	6.1 (0.5)	6.6 (0.5)
	3	90	5.8 (0.5)	5.7 (0.5)	5.8 (0.5)
	4	120	5.7 (0.6)	5.6 (0.6)	5.5 (0.5)
	5	180	4.7 (0.6)	4.6 (0.6)	4.5 (0.6)
Average amount of study product per day (mL/day)	1	30	741.9 (125.5)	745.6 (125.0)	-
	2	60	777.9 (90.2)	777.0 (91.3)	-
	3	90	813.1 (57.7)[a]	794.4 (62.0)	-
	4	120	852.7 (64.2)	844.2 (56.9)	-
	5	180	844.4 (110.4)	838.0 (112.2)	-
Average energy intake from study product (kcal/day)	1	30	489.7 (82.8)	492.1 (82.5)	-
	2	60	513.4 (59.5)	512.8 (60.2)	-
	3	90	536.7 (38.1)[a]	524.3 (40.9)	-
	4	120	562.8 (42.4)	557.2 (37.6)	-
	5	180	557.3 (72.9)	553.1 (74.1)	-

[a] CF vs. eHF $p = 0.0218$ for average amount of study product per day as well as for average energy intake from study product.

BF: breastfed reference group; CF: control formula; eHF: formula manufactured from extensively hydrolysed whey protein; *n*: number of observations; PPS: per protocol set; SD: standard deviation; V: visit

Table S4: Descriptive statistics of intervention-emergent adverse events by MedDRA coding (ITT)

	eHF (*n* = 160)		CF (*n* = 158)		BF (*n* = 41)	
	Infants *n* (%)	**Events *n***	**Infants *n* (%)**	**Events *n***	**Infants *n* (%)**	**Events *n***
All intervention-emergent adverse events	10 (6.3%)	14	6 (3.8%)	11	0 (0.0%)	0
System organ class (SOC)						
Gastrointestinal disorders	5 (3.1%)	5	3 (1.9%)	3	0 (0.0%)	0
General disorders and administration site conditions	1 (0.6%)	1	1 (0.6%)	2	0 (0.0%)	0
Infections and infestations	2 (1.3%)	2	2 (1.3%)	2	0 (0.0%)	0
Investigations	1 (0.6%)	1	0 (0.0%)	0	0 (0.0%)	0
Psychiatric disorders	2 (1.3%)	2	2 (1.3%)	2	0 (0.0%)	0
Respiratory, thoracic and mediastinal disorders	2 (1.3%)	2	0 (0.0%)	0	0 (0.0%)	0
Skin and subcutaneous tissue disorders	0 (0.0%)	0	1 (0.6%)	1	0 (0.0%)	0
Surgical and medical procedures	1 (0.6%)	1	1 (0.6%)	1	0 (0.0%)	0
Preferred term (PT)						
Abdominal pain	1 (0.6%)	1	1 (0.6%)	1	0 (0.0%)	0
Agitation	1 (0.6%)	1	2 (1.3%)	2	0 (0.0%)	0
Body temperature increased	1 (0.6%)	1	0 (0.0%)	0	0 (0.0%)	0
Bronchitis	1 (0.6%)	1	0 (0.0%)	0	0 (0.0%)	0
Constipation	2 (1.3%)	2	1 (0.6%)	1	0 (0.0%)	0
Crying	1 (0.6%)	1	1 (0.6%)	1	0 (0.0%)	0
Fungal infection	0 (0.0%)	0	1 (0.6%)	1	0 (0.0%)	0
Immunisation	1 (0.6%)	1	1 (0.6%)	1	0 (0.0%)	0
Pyrexia	0 (0.0%)	0	1 (0.6%)	1	0 (0.0%)	0
Rash	0 (0.0%)	0	1 (0.6%)	1	0 (0.0%)	0
Regurgitation	0 (0.0%)	0	1 (0.6%)	1	0 (0.0%)	0
Respiratory tract infection	1 (0.6%)	1	0 (0.0%)	0	0 (0.0%)	0
Restlessness	1 (0.6%)	1	0 (0.0%)	0	0 (0.0%)	0
Rhinitis	1 (0.6%)	1	1 (0.6%)	1	0 (0.0%)	0
Rhinorrhoea	1 (0.6%)	1	0 (0.0%)	0	0 (0.0%)	0
Vomiting	2 (1.3%)	2	0 (0.0%)	0	0 (0.0%)	0

When applying MedDRA coding, one AE can be allocated to multiple SOCs/PTs. Therefore, the total number of MedDRA-coded AEs exceeds the total number of recorded AEs.

AE: adverse event; BF: breastfed reference group; CF: control formula; eHF: infant formula manufactured from extensively hydrolysed whey protein; ITT: intention-to-treat population; MedDRA: Medical Dictionary for Regulatory Activities; *n*: number of observations/events; PT: preferred term; SOC: system organ class