SIMILAC® ALIMENTUM® COMPENDIUM OF STUDIES

Similac® ALIMENTUM®

Table of Contents

* Sponsored by Abbott.

Introduction

This compendium includes summaries of 6 key studies supporting the use of Similac® Alimentum® in infants and children. Similac Alimentum is a nutritionally complete, hypoallergenic, extensively hydrolyzed, casein-based formula for infants with cow's milk allergy and colic due to protein sensitivity.

Why is a hypoallergenic, extensively hydrolyzed, casein-based formula important?

Formulated with a predigested protein, this hypoallergenic, extensively hydrolyzed, casein-based formula virtually eliminates allergic reactions in most babies who are allergic to cow's milk protein.

Who needs an extensively hydrolyzed formula?

Extensively hydrolyzed protein-based formulas are most commonly indicated for the dietary management of infants and children who suffer from:

- Cow's milk allergy
- Sensitivity to intact protein

Similac Alimentum features:

- DHA & ARA to help support brain and eye development
- A unique blend of 2 carbohydrates using 2 absorptive pathways to help maximize absorption and minimize malabsorption risks
- Made with oils that have been shown to be well absorbed—approximately 33% of the fat blend as medium-chain tryglycerides (MCTs)
- 2'-FL HMO for immune support

Effectiveness of Casein Hydrolysate Feedings in Infants With Colic

Jakobsson I, Lothe L, Ley D, Borschel MW. Effectiveness of casein hydrolysate feedings in infants with colic. *Acta Paediatr.* 2000;89:18-21.

BACKGROUND

Colic has been reported in about 20% of infants, yet the causes of infantile colic are not fully understood. One etiology appears to be sensitivity to dietary proteins, and the symptom is crying.

OBJECTIVE

The aim of this study was to compare effectiveness of 2 extensively hydrolyzed, casein-based infant formulas for reducing colic symptoms.

METHODS

This study was a randomized, single-center study of infants with severe colic using a crossover design. Colic was defined as intermittent, unexplained, excessive crying many times a day for at least 4 days per week for ≥1 week, with each episode lasting 30 minutes to 2 hours and totaling 3 hours or more crying per day.

Infants were enrolled for the feeding trial from the Malmö Sweden General Hospital outpatient clinic and were randomized to 1 of 2 feeding sequences: (1) 7 days on casein hydrolysate formula 1, CH1 (Similac Alimentum, Abbott), then 7 days on casein hydrolysate formula 2, CH2 (Nutramigen, Mead Johnson Nutritionals) or (2) 7 days on CH2, then 7 days on CH1. Parents of enrolled infants recorded daily formula intake, stool patterns, crying time and intensity, and other colic-associated conditions (frequency of vomiting, disturbed sleep, and diaper rash). Behavior data were summarized as a percent of days the behavior was reported. Baseline crying and colicky symptoms were monitored for 2 days prior to the study start.

Following the crossover study, investigators performed randomly-ordered, double-blinded studies of infant challenges with bovine milk protein, whey protein, and placebo on days 15, 18, and 21. Positive response was defined as ≥1.5 hours/day of crying.

Study conducted with a previous formulation of Similac Alimentum without 2'-FL HMO, lutein or beta-carotene.

RESULTS

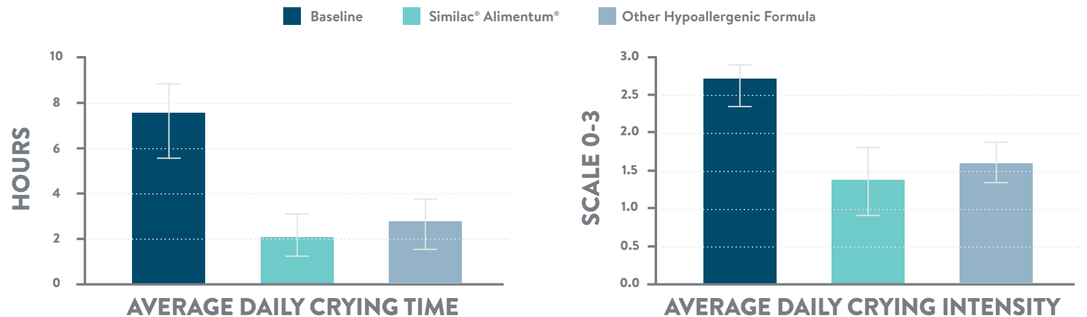
Enrolled infants (n=22) were 2 to 8 weeks of age. Of these, 10 were randomized to CH1/CH2, while 12 were assigned to CH2/CH1. In 15 of 22 infants, both CH1 and CH2 formulas were associated with significant and comparable reduction in crying intensity and duration, with 12 of 14 infants showing ≥ 30% reduction in crying. While stool consistency did not differ significantly between the 2 study periods, the incidence of liquid stools compared to baseline was only higher with feeding of CH2.

Of the 15 completers, 12 infants underwent challenge testing, 11/14 had a positive response to whey, 10/14 to milk protein, and 2/13 to placebo, confirming the population was experiencing protein sensitivity.

CONCLUSIONS

Findings showed that 2 casein-based, hydrolyzed protein feeding formulas were equally effective in managing colic symptoms associated with protein sensitivity. The observation that both formulas were similarly effective suggests that removal of intact milk proteins from the infant diet was the most likely reason for their effectiveness.

BEHAVIOR COMPARISONS FOR INFANTS WHO COMPLETED COLIC STUDY*,†



* Colic symptom reduction was evident in most infants within just 24 hours of initiating Similac Alimentum feeding. Based on a clinical study with Alimentum Ready to Feed without 2'-FL HMO, lutein and beta-carotene. A crossover clinical study of infants experiencing colic symptoms due to cow's milk protein sensitivity showed 5 of 6 infants initiated on Alimentum during the first week achieved a reduction in excessive crying. Data on File, Study AC84, August 2004. Abbott Nutrition, Columbus, Ohio.

† Caregivers and investigators judged the infants to display fewer colicky symptoms compared to baseline.

Study conducted with a previous formulation of Similac Alimentum without 2'-FL HMO, lutein or beta-carotene.

Growth of Healthy Term Infants Fed Ready-to-Feed and Powdered Forms of an Extensively Hydrolyzed Casein-Based Infant Formula: A Randomized, Blinded, Controlled Trial

Borschel MW, Baggs GE, Barrett-Reis B. Growth of healthy term infants fed ready-to-feed and powdered forms of an extensively hydrolyzed casein-based infant formula: a randomized, blinded, controlled trial. *Clin Pediatr*. 2014;53:585-592.

BACKGROUND

Infant formulas often differ in the sources and levels of protein, fat, carbohydrate, vitamins, and minerals. The formula form (ready-to-feed or powder), alterations in nutrients, changes in manufacturing processes and packaging can impact bioavailability of nutrients and may conceivably influence growth and tolerance of infants. Formulas with extensively hydrolyzed protein are susceptible to Maillard reaction because most of the protein is present as free amino acids and very short peptides.

OBJECTIVE

The purpose was to examine the growth and tolerance of healthy term infants fed a ready-to-feed (RTF) or powdered (PWD) formulation of an extensively hydrolyzed, casein-based formula to determine if the product form had any effect on growth and tolerance.

METHODS

This study was a masked, controlled, randomized, parallel trial to evaluate the growth of infants fed 2 different extensively hydrolyzed, casein-based infant formulas during the first 4 months of life. The study also assessed infant tolerance of the formulas. Healthy, full-term infants with a birth weight ≥2500 g were randomized between birth and 9 days of age; parents agreed to feed the assigned formula exclusively and ad libitum from enrollment up to 112 days infant age.

Both infant formulas provided levels of nutrients consistent with recommendations of the American Academy of Pediatrics and with US infant formula regulations.

NUTRITIONAL COMPOSITION OF STUDY FORMULAS

	Similac Alimentum RTF		Similac Alimentum PWD	
	Source	Content, g/L	Source	Content, g/L
Protein	100% extensively hydrolyzed casein tryptophan, cystine and tyrosine	18.8*	100% extensively hydrolyzed casein tryptophan, cystine and tyrosine	19.2
Carbohydrate	70% sucrose, 30% modified tapioca starch	70.4*	70% corn maltodextrin; 30% sucrose†	69.1
Fat	38% safflower oil; 33% MCT; 29% soy oil	38.1*	38% HO safflower oil; 33% MCT; 29% soy oil	37.6

* Average of 3 batches.
† Current ratio is 80% corn maltodextrin; 20% sucrose.
Abbreviation: HO, high oleic; MCT, medium-chain triglycerides.
Study conducted with a previous formulation of Similac Alimentum without 2'-FL HMO, lutein or beta-carotene.

The primary variable was weight gain from 14 days of age until 112 days of age and weight at enrollment, 14, 28, 56, 84 and 112 days of age. Length, length gains, head circumference (HC), and HC gains were also measured. Tolerance was evaluated by stool frequency, mean rank stool consistency (MRSC), using a 5-point scale where 1=watery, 2=loose/mushy, 3=soft, 4=formed, 5=hard, and the percent of feedings with spit-up and/or vomit, as reported by parents. Infants were monitored from the time of enrollment up to 112 days of age. Supportive variables included subject demographics.

Although parents were aware if their infant was receiving RTF or PWD, study personnel were not aware of feeding assignments. Safety determination was based on collecting adverse events (AEs) and serious adverse events (SAEs).

RESULTS

A total of 195 infants were enrolled and randomized with 137 completing (n=70 RTF; n=67 PWD). Between groups, there were no significant differences in the primary exit reason or in early exits due to intolerance. There were 187 AEs (97 RTF, 90 PWD) and 13 SAEs (6 RTF, 7 PWD) with no significant differences between groups.

Mean weight gain from days 14 to 112 were similar and not statistically different in the 2 groups (RTF 28.9 ± 0.7 g/day; PWD 28.4 ± 0.7 g/day). Likewise, there were no significant differences in lengths or head circumferences. In terms of tolerance, the percentage of feedings with spit-up and/or vomit did not differ significantly. Infants fed RTF passed more stools/day compared to the infants fed PWD and MRSC did not differ throughout the study.

CONCLUSIONS

When healthy term infants were fed either RTF or PWD versions of an extensively hydrolyzed, casein-based formula (Similac Alimentum), both formulas were safe, supported normal growth, and were well tolerated. Thus, any manufacturing or compositional differences had no adverse influences on nutrient bioavailability.

Safety of Casein Hydrolysate Formula in Children With Cow Milk Allergy

Sampson HA, Bernhisel-Broadbent J, Yang E, Scanion SM. Safety of casein hydrolysate formula in children with cow milk allergy. *J Pediatr.* 1991;118:520-525.

BACKGROUND

Children with cow milk allergy need to avoid cow milk proteins in their diets to avoid allergic responses. Common feeding strategies include soy formula or hypoallergenic, extensively hydrolyzed formulas.

OBJECTIVE

The purpose of this study was to confirm safety of feeding a new extensively hydrolyzed casein-based formula to children allergic to cow milk.

METHODS

As a first step, pre-clinical testing of the formula samples using polyacrylamide gel electrophoresis (PAGE) and enzyme-linked inhibition immunoassay (ELISA) was completed to ensure adequate hydrolysis of milk proteins prior to testing in milk-allergic children.

Twenty-five subjects with documented current CMA diagnosis (cow's milk allergy) participated (age range 8 months – 9½ years) and many were documented to have allergies to other foods. If current CMA needed to be established, an oral challenge to cow milk was conducted using Nutramigen (Mead Johnson Nutritionals, Evansville, IN) as the placebo before the test formula was challenged.

Of the 25 subjects, 4 had either a recent positive cow milk challenge or accidental exposure to cow milk. The remaining 21 subjects underwent double-blind, placebo-controlled food challenges to cow milk and Similac Alimentum on separate days. Challenges consisted of administering up to 10 g of dehydrated, defatted cow milk or 10 g of powdered Similac Alimentum in 100 mL of Nutramigen during a period of 60 to 90 minutes. Placebo challenges on each day consisted of administration of 100 mL of Nutramigen in a randomized manner. Each challenge was initiated with 5 mL of formula and formula quantities increased every 15 minutes until symptoms developed or the entire amount was consumed. If no reactions occurred on the day of the Similac Alimentum challenge, subjects were then fed 180 to 240 mL of Similac Alimentum under observation.

RESULTS

For the cow milk challenge, 19/21 reacted positively, displaying a variety of cutaneous, respiratory, and gastrointestinal symptoms within 45 to 90 minutes of challenge. These 19 subjects and the 4 subjects with recent positive challenges/accidental exposures all tolerated all placebo challenges. As with the placebo formula, all children (n=23) tolerated the blinded challenge to Similac Alimentum and all tolerated subsequent open feeding of Similac Alimentum without difficulty.

CONCLUSIONS

The results of this study documented that a sample of cow milk-allergic children were safely able to consume Similac Alimentum without allergic response.

Study conducted with a previous formulation of Similac Alimentum without 2'-FL HMO, lutein or beta-carotene.

Double-Blind, Placebo-Controlled, Food Challenges (DBPCFC) of a Strong-Tasting Food: Lessons Learned

Borschel MW, Burks AW. Double-blind, placebo-controlled, food challenges (DBPCFC) of a strong-tasting food: lessons learned. *Clinical and Translational Allergy*. 2014;4(Suppl 1):95.

BACKGROUND

Medical recommendations and regulatory guidelines dictate testing of formulas intended to be fed to infants and children with food allergies.

OBJECTIVE

The purpose of this study was to generate double-blind, placebo-controlled food challenge data on Similac Alimentum.

METHODS

Nine children (age range 1.1-4.7 years) with documented IgE-mediated cow's milk allergy participated. DBPCFC were performed over a 3-day period using procedures described by Sampson et al (*J Pediatr*;118:520). DBPCFC were conducted on each of the first 2 days. Day 3 was an open challenge of Similac Alimentum if subjects experienced no reaction to the blinded challenge of Similac Alimentum. Flavoring was optional and, if chosen, was used in all challenges.

RESULTS

Six subjects received a challenge to cow's milk with positive results. Three had a repeat reaction to cow's milk due to accidental exposure prior to entry so were not re-challenged. Eight subjects successfully completed the DBPCFC and open feeding with Similac Alimentum. One subject with a history of anaphylaxis to cow's milk reacted to both formulas (both included chocolate flavoring). Three months later, the subject was re-challenged with Similac Alimentum with strawberry syrup and reacted so was not challenged with Nutramigen (Mead Johnson Nutritionals, Evansville, IN). These challenges were considered "inconclusive" because it was impossible to determine if the subject reacted to the formula or the syrup(s).

CONCLUSIONS

The data from this study, combined with those from Sampson et al (1991), support current recommendations for hypoallergenicity labeling to document that with 95% confidence, Similac Alimentum was tolerated by at least 90% of the subjects documented to be allergic to cow's milk.

Study conducted with a previous formulation of Similac Alimentum without 2'-FL HMO, lutein or beta-carotene.

Growth, Tolerance, and Compliance of Infants Fed an Extensively Hydrolyzed Infant Formula with Added 2'-FL Fucosyllactose (2'-FL) Human Milk Oligosaccharide

Ramirez-Farias C, Baggs GE, Marriage BJ. Growth, tolerance, and compliance of infants fed an extensively hydrolyzed infant formula with added 2'-FL Fucosyllactose (2'-FL) human milk oligosaccharide. *Nutrients.* 2021 Jan 9;13(1):186.

BACKGROUND

Formulas with extensively hydrolyzed protein are often the first formula recommended by healthcare professionals for infants with suspected or confirmed cow's milk allergy who do not tolerate breast milk or who are not breastfed. Extensively hydrolyzed formulas (eHF) are also used for infants with persistent symptoms such as diarrhea, constipation, spit-up, vomiting, or fussiness.

OBJECTIVE

The purpose was to assess the growth, tolerance, compliance, and change in clinical symptoms in infants with suspected cow's milk allergy or persistent feeding intolerance symptoms when fed a casein-based eHF with added 2'-FL HMO.

METHODS

This was a non-randomized, single-group, multicenter study enrolling infants with suspected food protein allergy, persistent feeding intolerance symptoms, or other conditions where an eHF was deemed appropriate by a healthcare professional. Eligible infants consuming an eHF without 2'-FL were enrolled into a 60-day feeding trial and switched to an eHF with 2'-FL as sole-source nutrition.

The study formula was a clinically labelled, hypoallergenic, casein-based powdered eHF designed to provide 20 kcal per fl oz at standard dilution with 0.2 g/L of 2'-FL. (Similac® Alimentum®, Abbott Nutrition, Abbott Laboratories, Columbus, OH, USA).

Weight, length, and head circumference measurements were collected at study entrance, Visit 3 (30 ± 3 days), and Visit 4 (60 ± 5 days). Intake and stool records were completed by parents and an Infant Feeding and Stooling Pattern Questionnaire was completed at Visit 1 to assess the baseline status of infants. Daily intake and stool records were recorded up to Visit 2 (study day (SDAY) 7), and three consecutive days before Visit 3 (SDAY 30 ± 3) and Visit 4 (SDAY 60 ± 5) to assess tolerance and change in perceived clinical status after feeding the study formula.

The primary outcome was maintenance of weight-for-age *z* score. The World Health Organization growth standards were used as the basis for *z* score determinations. Secondary variables were mean rank stool consistency (MRSC) score on a 5-point scale (1=watery, 2=loose/mushy, 3=soft, 4=formed, 5=hard), predominant stool color, predominant stool consistency, average daily number of stools per day, percent of feedings with spit-up/vomit associated with feeding (within 1 hour), weight, interval weight gain per day, length, interval length gain per day, head circumference (HC), and interval HC gain per day. Supportive variables were average volume of study formula intake per day (mL/day), parental responses to the Infant Feeding and Stool Patterns Questionnaire, the Formula Satisfaction Questionnaire and Clinical Symptoms Questionnaire. Clinical symptoms reported by the parents were reviewed at enrollment, visit 2 (SDAY 7), and Visit 4 (SDAY60) by the investigators. Safety monitoring consisted of the collection of adverse events and serious adverse events during the study.

RESULTS

A total of 48 subjects were enrolled, but one subject did not receive study product, so 47 subjects comprised the intent-to-treat group. Thirty-six subjects were included in the protocol evaluable cohort.

Weight *z* scores of infants showed a statistically significant improvement from day 1 to SDAY 60 ($p=0.0078$). In addition, 78% (95% confidence interval: 61%, 0%) of the infants maintained their weight-for-age *z* scores.

Tolerance measures such as MRSC, stool color, average volume of formula intake, and percent of feedings associated with spit-up/vomit after 1 hour of feeding per day were comparable to other eHF feeding studies that did not contain 2'-FL.

Interestingly, parents reported improvement in symptoms in some infants that were already on an eHF formula (changes in symptoms are shown below). A limitation of this study is the length of time the infants were consuming an eHF without 2'-FL before starting the study formula.

CONCLUSIONS

The results of this study demonstrate that eHF formula with added 2'-FL was safe, well tolerated, and well accepted, enabling adequate volume to demonstrate a statistically significant improvement of weight-for-age *z* scores. In addition, after the 60-day feeding period, parents reported no change, improvement, or resolution of some persistent feeding intolerance symptoms.

CHANGE IN CLINICAL SYMPTOMS IN INFANTS AT 7 AND 60 DAYS AFTER SWITCHING TO eHF WITH 2'-FL

Clinical symptoms	Prior to Being Placed on a Hypoallergenic Extensively Hydrolyzed Formula (n)	At Study Initiation (n)	At Study Visit 2 (Day 7), n (% of Subjects With the Symptom at Entry)	At Study Visit 4 (Day 60), n (% of Subjects With the Symptom at Entry)
Diarrhea	9	2	1 (50%)–Same 1 (50%)–Resolved	2 (100%)–Better
Constipation	18	6	4 (67%)–Better 1 (17%)–Resolved 1 (17%)–Worse	1 (17%)–Same 3 (50%)–Better 2 (33%)–Resolved
Blood in stool	4	1	1 (100%)–Resolved	1 (100%)–Resolved
Vomiting	11	4	1 (25%)–Better 3 (75%)–Resolved	1 (25%)–Same 3 (75%)–Resolved
Spit-up/Gagging/Reflux	25	17	6 (35%)–Same 10 (59%)–Better 1 (6%)–Worse	5 (29%)–Same 10 (59%)–Better 2 (12%)–Resolved
Fussiness	24	10	5 (50%)–Same 2 (20%)–Better 2 (20%)–Resolved 1 (10%)–Worse	4 (40%)–Same 2 (20%)–Better 4 (40%)–Resolved
Rash or Eczema	9	7	2 (29%)–Same 4 (57%)–Better 1 (14%)–Resolved	2 (29%)–Same 3 (43%)–Better 2 (29%)–Resolved

A New Hydrolyzed Formula Is Well Tolerated in Infants With Suspected Food Protein Allergy or Intolerance

Borschel MW, Baggs GE. A new hydrolyzed formula is well tolerated in infants with suspected food protein allergy or intolerance. *The Open Nutrition Journal*. 2015;9:1-4.

BACKGROUND

Infants may experience gastrointestinal discomfort due to food allergies. Feeding a formula with extensively hydrolyzed protein may help ease symptoms for such infants.

OBJECTIVE

The aim of this observational study was to assess tolerance of an extensively hydrolyzed, casein-based infant formula by a population of infants with suspected food protein allergy or persistent feeding intolerance.

METHODS

This study was a prospective, non-random, single-group, multicenter design enrolling infants with suspected food protein allergy, persistent feeding intolerance, or with conditions for which an extensively hydrolyzed formula was deemed appropriate. Infants were enrolled into a 15-day feeding trial in which formula intake, stool patterns, weight, and length were measured. Infants were assessed at visit 1 (pre-study) and at visit 2 (on exit from the study). The primary outcome was maintenance of weight-for-age *z* scores during the study. The study also used questionnaires for parents to report on infant feeding and stooling patterns.

The study formula was a clinically labelled hypoallergenic, casein-based powder designed to provide 20 kcal/fluid ounce at standard dilution (Similac Alimentum, Abbott). The World Health Organization growth standards were used as a basis for *z*-score determinations. Parents ranked each infant stool according to the Mean Rank Stool Consistency (MRSC) score on a 5-point scale (1=watery, 2=loose/mushy, 3=soft, 4=formed, 5=hard).

RESULTS

A total of 25 infants enrolled in the study were 0 to 180 days old (mean age, 85± 8.9 days) and (a) were experiencing symptoms of feeding intolerance (eg, diarrhea, constipation, vomiting, or spit-up) and had at least one formula change or (b) were being fed another extensively hydrolyzed formula due to symptoms of suspected food protein allergy (milk and/or soy) or intolerance. At visit 1, 12 infants had symptoms of allergic colitis or food protein allergy/intolerance, 12 had persistent formula intolerance, and 11 had evidence of blood in stools, and 1 was recovering from necrotizing enterocolitis. With a mean weight-for-age *z* score of -0.62 ±0.19 at entry and -0.41 ± 0.16 at exit, the mean change in weight-for-age *z* score was +0.21 ± 0.10 (n=15). Daily stools averaged 1.8 ±0.4/day and were predominantly loose/mushy (43%) or soft (38%).

Of those parents who agreed most positively with feeding descriptions in questionnaires (always, frequently, some of the time), the most common changes from visit 1 to visit 2 are listed below.

CONCLUSIONS

Findings showed that the extensively hydrolyzed, casein-based study formula (Similac Alimentum) was well accepted and tolerated by infants who had suspected food protein allergy or persistent feeding intolerance. Babies consumed adequate formula volume and maintained weight-for-age *z* scores. Parents reported a high level of satisfaction with Similac Alimentum feeding.

PARENTS-REPORTED STATEMENT	VISIT 1 (%)	VISIT 2 (%)	CHANGE
My baby fussed or resisted the bottle while being fed the formula.	22	11	50% decrease
There were days my baby had too many bowel movements.	28	11	61% decrease
My baby cried or fussed before or during bowel movements.	56	34	39% decrease
My baby's stools were too hard.	36	0	100% decrease
My baby appeared constipated.	44	18	59% decrease

Study conducted with a previous formulation of Similac Alimentum without 2'-FL HMO, lutein or beta-carotene.

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Alphabetical by Author

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