



NEOCATE® SYNEO® INFANT RESEARCH HAS SHOWN:

CLINICAL TRIAL OUTCOMES

- TOLERANCE¹⁻⁴
- GROWTH¹⁻⁴
- MORE BALANCED GUT MICROBIOTA^{3-5*}

EXPLORATORY CLINICAL TRIAL FINDINGS

- FEWER REPORTED INCIDENCES OF INFECTIONS^{2,4†}
- REDUCED USE OF ANTIBIOTICS^{2†}
- REDUCED USE OF DERMATOLOGICAL MEDICATIONS^{4§}

Exploratory findings do not intend to offer final and conclusive results. Further research is needed to confirm the findings.



Gut dysbiosis^{II} has been shown in infants with food allergies⁶⁻⁸

Gut dysbiosis has been linked to:

- Immune-related diseases such as⁹⁻¹²:
 - > Atopic dermatitis
 - > Asthma
- Health problems later in life¹³⁻¹⁸

Neocate[®] Syneo[®] is the only amino acid-based formula clinically shown to target gut dysbiosis in infants with food allergies³⁻⁵



- Supports normal growth and development¹⁻⁴
- Effectively resolves food allergy symptoms²
- Helps balance the gut microbiota to be closer to that of healthy, breastfed infants^{3,5*}



Nutricia North America supports the use of breast milk wherever possible. Neocate[®] is a family of hypoallergenic, amino acid-based medical foods for use under medical supervision. Neocate Syneo Infant is indicated for the dietary management of cow milk allergy, multiple food allergies and related gastrointestinal and allergic conditions, including food protein-induced enterocolitis syndrome, eosinophilic esophagitis and gastroesophageal reflux.

*Infants after 8 weeks of management with standard amino acid-based formula (control) or amino acid-based formula with pre- and probiotics (test) compared to age-matched, healthy, breastfed infants. At 8 weeks, levels of both bifidobacteria and *Eubacterium rectale + Clostridium coccoides* group were measured as a percentage of total fecal bacteria. Test group median levels were different than control group ($p < 0.001$), and were closer to breastfed infant levels vs. control group. At 12 and 26 weeks test group mean levels continued to differ when compared to the control group (all $p \leq 0.001$), with most subjects still on assigned formula, in line with study design.

† One trial investigating 110 subjects found fewer reported incidences of overall infections, as a result of the safety evaluation, in the test group when compared to the control group ($p = 0.008$). A second trial investigating 71 subjects showed fewer reported incidences of ear infections, as a result of safety evaluation, in the test group when compared to the control group ($p = 0.011$).

‡ One trial investigating 110 subjects found a reduction in use of 'antibacterials for systemic use' (i.e. antibiotics), as a result of the safety evaluation, in the test group when compared to the control group ($p = 0.049$). Specifically amoxicillin was less often prescribed ($p = 0.004$).

§ One trial investigating 71 subjects observed a reduction in use of dermatologicals ($p = 0.019$) such as 'emollients and protectives' ($p = 0.023$), as a result of the safety evaluation, when comparing the test group to control group.

II Gut dysbiosis is an imbalance in the typical gut microbiota composition compared to healthy individuals¹⁹

References:

1. Harvey, et al. *Pediatr Res.* 2014;75:343-51. 2. Burks, et al. *Pediatr Allergy Immunol.* 2015;26:316-22. 3. Candy, et al. *Pediatr Res.* 2018;83:677-86. 4. Fox, et al. *Clin Transl Allergy.* 2019;9:5. 5. Wopereis, et al. *Clin Transl Allergy.* 2019;9:27. 6. Berni Canani, et al. *ISME J.* 2015. 7. Ling, et al. *Appl Environ Microbiol.* 2014;80:2546-54. 8. Thompson-Chagoyan, et al. *Pediatr Allergy Immunol.* 2010;21:e394-400. 9. Abrahamsson, et al. *J Allergy Clin Immunol.* 2012;129:434-40. 10. Forno, et al. *Clin Mol Allergy.* 2008;6:11. 11. Fujimura, et al. *Nat Med.* 2016;22:1187-91. 12. Arrieta, et al. *Sci Transl Med.* 2015;7:307ra152. 13. Kalliomaki, et al. *Am J Clin Nutr.* 2008;87:534-8. 14. Savage, et al. *Allergy.* 2018;73:145-52. 15. Rodriguez, et al. *Microb Ecol Health Dis.* 2015;26:26050. 16. West, et al. *Clin Exp Allergy.* 2015;45:43-53. 17. Koleva, et al. *Nutrients.* 2015;7:2237-60. 18. Walker. *Pediatr Res.* 2017;82:387-95. 19. Petersen, et al. *Cell Microbiol.* 2014;16:1024-33.



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Tolerance, Growth, and Gut Microbiota Trials:

- Harvey, et al. *Pediatr Res.* 2014;75:343-51.
- Burks, et al. *Pediatr Allergy Immunol.* 2015;26:316-22.
- ASSIGN Trial Publications:
 - Candy, et al. *Pediatr Res.* 2018;83:677-86.
 - Fox, et al. *Clin Transl Allergy.* 2019;9:5.
 - Wopereis, et al. *Clin Transl Allergy.* 2019;9:27.

Harvey BM, Langford JE, Harthoorn LF, et al. Effects on growth and tolerance and hypoallergenicity of an amino acid–based formula with synbiotics. *Pediatr Res.* 2014;75:343-51.

Background:

This study was designed to examine the effects of an amino acid-based formula (AAF) with an added synbiotic blend on growth as well as tolerance in a group of healthy infants.

Methods:

In a prospective, randomized, double-blind controlled study, healthy, full-term infants (n = 115) received either an AAF with an added synbiotic blend or an AAF that was already commercially available. Subjects received formula for 16 weeks. Primary outcome measures were growth, assessed by weight, length, and head circumference. Secondary outcome measures included gastrointestinal symptoms and stool characteristics. Also recorded were dietary intake, clinical laboratory results, and clinical examinations.

Results:

There were comparable results between groups in the measured parameters of growth. Similar results between groups were also seen for tolerance. There were minimal differences seen between groups in stool characteristics and gastrointestinal symptoms through the course of the study.

Conclusion:

This study showed that an AAF with an added synbiotic blend supports normal growth of healthy, full-term infants when fed as the sole source of nutrition. This study also demonstrates the safety and tolerance of an AAF with an added synbiotic blend with healthy, full-term infants. management of cow milk allergy, multiple food allergies and related GI and allergic conditions, including food protein-induced enterocolitis syndrome, eosinophilic esophagitis and gastroesophageal reflux.

Neocate® Syneo® Infant and Neocate® Infant DHA/ARA were both demonstrated to support normal growth.

Neocate Syneo Infant is a nutritionally complete, amino acid-based formula with prebiotics and probiotics (synbiotics) that is backed by this clinical trial in healthy infants to support normal growth and development, and to be safe and well tolerated.

Adapted from publicly available abstract - Full text available at <http://www.nature.com/pr/journal/v75/n2/full/pr2013211a.html>

Neocate® Syneo® is a hypoallergenic, amino acid-based medical food for use under medical supervision. Neocate Syneo Infant is indicated for the dietary management of cow milk allergy, multiple food allergies and related GI and allergic conditions, including food protein-induced enterocolitis syndrome, eosinophilic esophagitis and gastroesophageal reflux.

Burks AW, Harthoorn LF, van Ampting MTJ, et al. Synbiotics-supplemented amino acid-based formula supports adequate growth in cow's milk allergic infants. *Pediatr Allergy Immunol.* 2015;26:316-22.

Background:

Cow milk allergy (CMA) places children at risk for insufficient nutrient intake and poor growth. Because of this, the dietary management of CMA in children necessitates a diet that excludes allergens, while also promoting normal growth and development. This study set out to evaluate the growth of infants with CMA consuming a new amino acid-based infant formula (AAF) with an added synbiotic blend (prebiotics and probiotics). Safety was also evaluated.

Methods:

This prospective, double-blind controlled study involved full-term infants aged 0-8 months diagnosed with CMA. The infants were randomized to receive either a control AAF (Neocate Infant with DHA and ARA; n = 56) or a test AAF with synbiotics (Neocate + oligosaccharide blend + probiotic *Bifidobacterium breve* M-16V; n = 54). The study duration was 16 weeks and the primary outcome, growth, was assessed using weight, length and head circumference. Secondary outcome measures were parameters that assessed allergic signs and symptoms as well as stool characteristics.

Results:

At inclusion, infants were 4.5 ± 2.4 months of age. Results showed that both groups, infants receiving the AAF or the AAF with synbiotics, achieved adequate and similar growth during this study. Based on WHO 2006 growth charts, there were no significant differences (90% CI) between groups in Z-scores (test/control) after 16 weeks: weight ($p = 0.32$), length ($p = 0.21$) and head circumference ($p = 0.40$). There were also no significant differences between the two groups in weight-for-age or length-for-age Z-scores. In addition, both formulas were well tolerated and both reduced symptoms of CMA, with no difference in numbers of adverse events between the two groups.

Conclusion:

This study is the first to demonstrate that an AAF with an added synbiotic blend of specific components, suitable for infants with CMA, promotes normal growth, as well as growth in infants with CMA similar to a reference AAF. Neocate with synbiotics and Neocate Infant DHA/ARA were both demonstrated to support normal growth and resolve food allergy symptoms in infants with IgE- and/or non-IgE-mediated CMA.

This large clinical trial studying CMA infants supports that:

- Both Neocate® Syneo® Infant and Neocate® Infant DHA/ARA support normal growth and development of CMA infants.
- Neocate Syneo Infant is as safe and well tolerated as Neocate Infant DHA/ARA
- Neocate Syneo Infant resolves food allergy symptoms as effectively as Neocate Infant DHA/ARA

Adapted from publicly available abstract - Full text available at <http://onlinelibrary.wiley.com/doi/10.1111/pai.12390/full>
Neocate® Syneo® is a hypoallergenic, amino acid-based medical food for use under medical supervision. Neocate Syneo Infant is indicated for the dietary management of cow milk allergy, multiple food allergies and related GI and allergic conditions, including food protein-induced enterocolitis syndrome, eosinophilic esophagitis and gastroesophageal reflux.

Candy DCA, Van Ampting MTJ, Oude Nijhuis MM, et al. A synbiotic-containing amino acid-based formula improves gut microbiota in non-IgE-mediated allergic infants. *Pediatr Res.* 2018;83:677-86.

The ASSIGN Trial

Background:

Research has shown that infants and children with cow milk allergy have an imbalanced gut microbiota associated with their allergic condition. Prebiotics and probiotics (synbiotics) can modify gut microbiota and have potential in allergy management when combined with amino acid-based formula (AAF) for infants with cow milk allergy (CMA).

Methods:

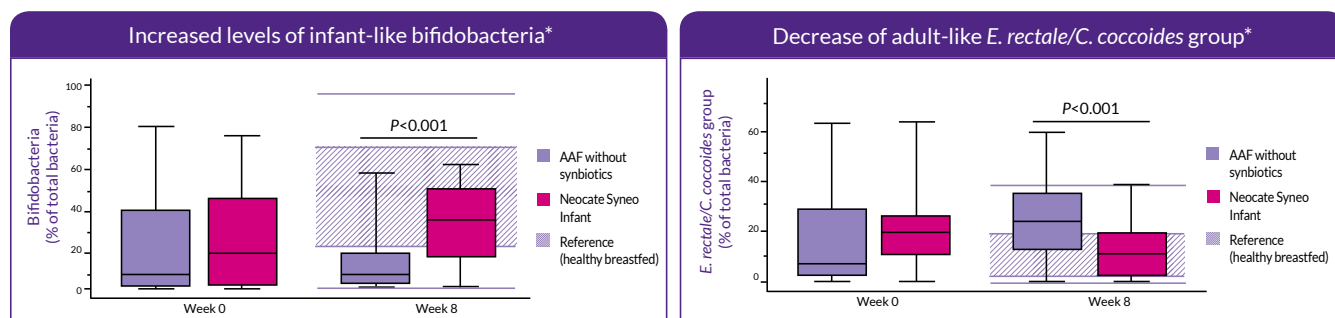
This multicenter, double-blind, randomized, controlled trial investigated the effects of an AAF containing a synbiotic blend on percentages of bifidobacteria and *Eubacterium rectale/Clostridium coccoides* group (ER/CC) in feces from infants with suspected non-IgE-mediated CMA. Feces from age-matched healthy, breastfed infants were used as reference (healthy breastfed reference (HBR)) for primary outcomes. The CMA subjects were randomized and received test or control formula for 8 weeks. Test formula was a hypoallergenic, nutritionally complete AAF containing a prebiotic blend of fructooligosaccharides and the probiotic strain *Bifidobacterium breve* M-16V. Control formula was AAF without synbiotics.

Results:

A total of 35 (test) and 36 (control) subjects were randomized; HBR included 51 infants. At week 8, the median percentage of bifidobacteria was higher in the test group than in the control group (35.4% vs. 9.7%, respectively; $P < 0.001$), whereas ER/CC was lower (9.5% vs. 24.2%, respectively; $P < 0.001$). HBR levels of bifidobacteria and ER/CC were 55% and 6.5%, respectively.

Conclusion:

AAF containing specific synbiotics, which results in levels of bifidobacteria and ER/CC approximating levels in the HBR group, improves the fecal microbiota of infants with suspected non-IgE-mediated CMA.



Neocate® Syneo® Infant is an amino acid-based formula with prebiotics and probiotics (synbiotics) that has been clinically shown to help address the hidden, underlying gut dysbiosis in infants with CMA by bringing the gut microbiota closer to that of healthy, breastfed infants.

Adapted from the publicly available full text article - <https://www.nature.com/articles/pr2017270>; <https://creativecommons.org/licenses/by/4.0/>
ASSIGN = Amino acid-based formula with Synbiotics – Study in Infants with Gastrointestinal Non-IgE-mediated cow's milk allergy

*The grey shaded area represents the sample 25th to 75th percentile of the reference group (healthy subjects) and the grey horizontal lines represent the minimum and maximum values of this reference group. The bottom and top edges of the box are located at the sample 25th and 75th percentiles. The center horizontal line is drawn at the 50th percentile (median). The whiskers of the box plots show the minimum and maximum values.

Nutricia North America supports the use of breast milk wherever possible. Neocate® Syneo® is a hypoallergenic, amino acid-based medical food for use under medical supervision. Neocate® Syneo® Infant is indicated for the dietary management of cow milk allergy, multiple food allergies and related GI and allergic conditions, including food protein-induced enterocolitis syndrome, eosinophilic esophagitis and gastroesophageal reflux.

Fox AT, Wopereis H, Van Ampting MTJ, et al. A specific synbiotic-containing amino acid-based formula in dietary management of cow milk allergy: a randomized controlled trial. Clin Transl Allergy. 2019;9:5.

The ASSIGN Trial

Background:

Here we report follow-up data from a multicenter, double-blind, randomized, controlled trial, which investigated fecal microbiota changes with a new amino acid-based formula (AAF) including synbiotics in infants with non-IgE-mediated cow milk allergy (CMA).

Methods:

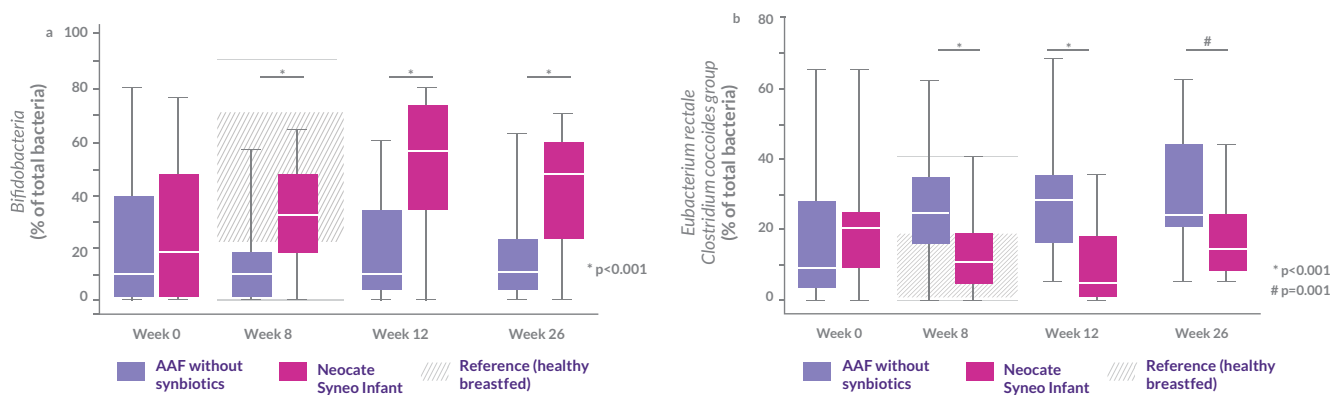
Subjects were randomized to receive test product (AAF including fructooligosaccharides and *Bifidobacterium breve* M-16V) or control product (AAF) for 8 weeks, after which infants could continue study product until 26 weeks. Fecal percentages of bifidobacteria and *Eubacterium rectale*/*Clostridium coccoides* group (ER/CC) were assessed at 0, 8, 12, and 26 weeks. Additional endpoints included stool markers of gut immune status, clinical symptoms, and safety assessments including adverse events and medication use.

Results:

The trial included 35 test subjects, 36 controls, and 51 in the healthy reference group. Study product was continued by 86% and 92% of test and control subjects between week 8–12, and by 71% and 80%, respectively until week 26. At week 26, median percentages of bifidobacteria were significantly higher in test than control [47.0% vs. 11.8% ($p<0.001$)], whereas percentages of ER/CC were significantly lower [(13.7% vs. 23.6% ($p=0.003$)). Safety parameters were similar between groups. Interestingly, use of dermatological medication and reported ear infections were lower in test versus control, $p=0.019$ and 0.011, respectively[†]. Baseline clinical symptoms and stool markers were mild (but persistent) and low, respectively. Symptoms reduced towards lowest score in both groups.

Conclusion:

Beneficial effects of this AAF including specific synbiotics on microbiota composition were observed over 26 weeks, and shown suitable for dietary management of infants with non-IgE-mediated CMA.



Neocate® Syneo® Infant has been clinically shown to help address the hidden, underlying gut dysbiosis in infants with CMA with a consistent effect seen in increasing infant-like bifidobacteria and decreasing the adult-like *E. rectale*/*C. coccoides* group through 26 weeks (6 months).

Adapted from the publicly available full text article - <https://ctajournal.biomedcentral.com/articles/10.1186/s13601-019-0241-3>; <https://creativecommons.org/licenses/by/4.0/>

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[†]Exploratory findings do not intend to offer final and conclusive results. Further research is needed to confirm the findings.

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Wopereis H, van Ampting MTJ, Cetinyurek-Yavuz A, et al. A specific synbiotic-containing amino acid-based formula restores gut microbiota in non-IgE-mediated cow milk allergic infants: a randomized controlled trial. Clin Transl Allergy. 2019;9:27.

The ASSIGN Trial

Background:

Altered gut microbiota is implicated in cow milk allergy (CMA) and differs markedly from healthy, breastfed infants. Infants who suffer from severe CMA often rely on cow milk protein avoidance and, when breastfeeding is not possible, on specialized infant formulas such as amino acid-based formulas (AAF). Herein, we report the effects of an AAF including specific synbiotics on oral and gastrointestinal microbiota of infants with non-IgE-mediated CMA with reference to healthy, breastfed infants.

Methods:

In this prospective, randomized, double-blind controlled trial, infants with suspected non-IgE-mediated CMA received test or control formula. Test formula was AAF with synbiotics (prebiotic fructooligosaccharides and probiotic *Bifidobacterium breve* M-16V). Control formula was AAF without synbiotics. Healthy, breastfed infants were used as a separate reference group (HBR). Bacterial compositions of fecal and salivary samples were analyzed by 16S rRNA-gene sequencing. Fecal analysis was complemented with the analysis of pH, short chain fatty acids (SCFAs) and lactic acids.

Results:

The trial included 35 test subjects, 36 controls, and 51 HBR. The 16S rRNA-gene sequencing revealed moderate effects of test formula on oral microbiota. In contrast, the gut microbiota was substantially affected across time comparing test with control. In both groups bacterial diversity increased over time but was characterized by a more gradual increment in test compared to control. Compositionally this reflected an enhancement of *Bifidobacterium* spp. and *Veillonella* spp. in the test group. In contrast, the control-fed infants showed increased abundance of adult-like species, mainly within the *Lachnospiraceae* family, as well as within the *Ruminococcus* and *Alistipes* genus. The effects on *Bifidobacterium* spp. and *Lachnospiraceae* spp. were previously confirmed through enumeration by fluorescent in situ hybridization and were shown for test to approximate the proportions observed in the HBR. Additionally, microbial activity was affected as evidenced by an increase of L-lactate, a decrease of valerate, and reduced concentrations of branched-chain SCFAs in test versus control.

Conclusions:

The AAF including specific synbiotics effectively modulates the gut microbiota and its metabolic activity in non-IgE-mediated CMA infants bringing it closer to a healthy, breastfed profile.

Neocate® Syneo® Infant positively changed the gut microbiota composition and its metabolic activity in infants with cow milk allergy bringing it closer to a healthy, breastfed profile.

Adapted from the publicly available full text article -<https://ctajournal.biomedcentral.com/articles/10.1186/s13601-019-0267-6>; <https://creativecommons.org/licenses/by/4.0/>

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