

# DIETARY MANAGEMENT OF COW'S MILK ALLERGY (CMA) CLINICAL BENEFITS OF SYNBIOTICS

CMA is common in infants and children, presenting with a range of symptoms affecting the gastrointestinal (GI) tract, skin and respiratory tract<sup>1-3</sup>. The gut microbiota plays a pivotal role in the development of the immune system. However, research has shown that infants with CMA have an altered gut microbiome compared with healthy breastfed infants. In addition, infants with CMA also face an increased susceptibility to infections compared with infants and children without CMA<sup>4</sup>. The impact of CMA goes beyond the clinical symptoms, impacting families and the wider healthcare system.

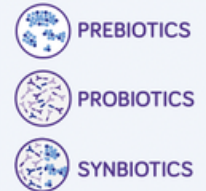


Breastmilk composition contains a wide range of important bioactive compounds which promote a healthy gut microbiota and immune system development<sup>5</sup>. Breastfeeding should be encouraged, however recognising that this is not always feasible for allergic infants, there has been a drive to develop hypoallergenic formulas with properties that mimic some of the bioactive compounds present in breastmilk.

Synbiotics are a combination of prebiotics (substrates that are selectively utilised by host microorganisms conferring a health benefit<sup>6</sup>) and probiotics (live microorganisms which when administered in adequate amounts confer a health benefit on the host<sup>7</sup>)<sup>8</sup>.

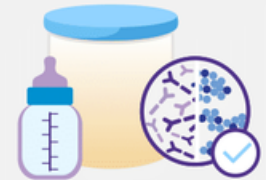
New innovations have allowed formula advancements with the inclusion of synbiotics. Pepti Syneo extensively hydrolysed formula (eHF) and Neocate Syneo amino acid based formula (AAF) contain a unique synbiotic blend of both prebiotics and probiotics, specifically selected for infants with CMA.

Studies have shown that hypoallergenic formulas with synbiotics support the gut microbiota in infants with CMA, prompting favourable shifts in gut microbial composition that are more reflective of the gut microbiota of healthy breastfed infants. Evidence consistently shows positive effects of synbiotics on immune-related outcomes<sup>9-13</sup>.



## CLINICAL STUDIES

To date, several studies have been conducted in hypoallergenic infant formulas with synbiotics including both Pepti Syneo (eHF)<sup>10,14,15</sup> and Neocate Syneo (AAF)<sup>9-14,16</sup>. Results have consistently demonstrated that these formulas are well tolerated, have a good safety profile, and support normal growth. Exploratory outcome data\* from these studies have reported additional interesting and clinically relevant findings.



### Medication use

- Reduced need for medication for functional GI disorders<sup>11</sup>
- Lower percentage of infants required antibiotics<sup>9,11</sup>
- Lower use of dermatological medication<sup>12</sup>
- Reduction of asthma medication at one year follow up<sup>14</sup>



### Dermatological symptoms

- Demonstrated greater improvement of atopic dermatitis<sup>\*\*10</sup>



### Infections

- Fewer infections<sup>11</sup> and GI infections<sup>13</sup>
- Fewer ear infections<sup>12</sup>



### Respiratory

- Lower prevalence of asthma-like symptoms at one year follow-up<sup>14</sup>



### GI

- Improved stool consistency and colour, closer to those of healthy breastfed infants<sup>16</sup>
- Reduction in constipation and dry stools<sup>10</sup>



### Hospitalizations

- Fewer hospitalizations due to infections<sup>13</sup>



■ = eHF related research  
■ = AAF related research

\* based on evaluation of adverse events and safety parameters in studies in infants with CMA receiving an hypoallergenic formula with synbiotics in comparison with hypoallergenic formula without synbiotics.  
\*\* in the subgroup of infants with IgE-associated atopic dermatitis.

## REAL WORLD EVIDENCE (RWE) STUDIES

Randomised controlled trials (RCTs) and RWE studies are often considered complementary<sup>17,18</sup>. To date, RWE studies in CMA infants given eHF or AAF with a synbiotic blend have shown consistent results with published RCTs.



### Hubbard et al. (2022)<sup>19</sup>

#### Single-arm, prospective study of CMA infants receiving eHF with synbiotics

- Improvements in severity of abdominal pain, burping, flatulence, constipation
- Improvements in atopic symptoms including rhinitis and itchy eyes
- Reduction in hospital visits and medications in the six months follow-up
- Improvements in caregiver reported quality of life

### Sorensen et al. (2021)<sup>20</sup>

#### Retrospective matched cohort comparing case records of CMA infants managed with AAF with synbiotics or AAF without synbiotics, found AAF with synbiotics to be associated with

- Lower rate of healthcare contacts
- Lower rates of infections and medication prescriptions
- Fewer GI, skin and/or respiratory symptoms
- Potential healthcare cost-savings

## SYSTEMATIC REVIEW

### Sorensen et al. (2021)<sup>21</sup>

#### Meta-analysis of four RCTs of CMA infants receiving AAF with synbiotics compared to AAF without synbiotics

- Significantly fewer infections
- Lower overall medication use
- Fewer hospital admissions

## PEPTI SYNEO (EHF) AND NEOCATE SYNEO (AAF)

Pepti Syneo (eHF) and Neocate Syneo (AAF) contain both the probiotic (*Bifidobacterium breve M-16V*) that is free from the main food allergens, and prebiotics (eHF: short chain GOS/long chain FOS; AAF: short chain FOS/long chain FOS, ratio 9:1) that mimic the diversity, quantity and functionality of oligosaccharides in human milk and have a bifidogenic effect.

These key components modulate the gut microbiota of CMA infants to improve the compositional profile closer to that of a healthy breastfed infant. This is important to support immune system development and therefore long term health.

### Pepti Syneo (eHF)

Pepti Syneo is an extensively hydrolysed formula for the dietary management of mild-moderate CMA.

Beyond clinical improvements and symptom relief in CMA infants<sup>10,14,19</sup> Pepti Syneo has been shown to:

- Be safe and well tolerated<sup>22</sup>
- Promote normal growth and development<sup>15</sup>
- Rebalance the gut microbiota by increasing levels of bifidobacteria<sup>10</sup>
- Reduce asthma-like symptoms at one year follow-up<sup>14</sup>
- Be the most palatable eHF by HCPs and parents in the UK<sup>23,24</sup>



### Neocate Syneo (AAF)

Neocate Syneo is an amino acid based formula for the dietary management of severe or complex CMA. Studies have consistently shown clinical improvements and symptom relief in CMA infants with Neocate Syneo<sup>12,20,21</sup>. Neocate Syneo has also been shown to:

- Be safe and well tolerated<sup>16</sup>
- Promote normal growth and development<sup>11</sup>
- Rebalance the gut microbiota of CMA infants closer to that of healthy breastfed infants<sup>9,11-13</sup>
- Result in fewer infections<sup>11-13,20,21</sup>
- Result in lower medication use<sup>9,11,12,20,21</sup>
- Result in lower hospital admissions<sup>13,20,21</sup>



**IMPORTANT NOTICE:** Pepti Syneo and Neocate Syneo are food for special medical purposes and should only be used under medical supervision, after full consideration of feeding options available including breastfeeding.

### REFERENCES

1. Pensabene L, Salvatore S, D'Auria E, Parisi F, Concolino D, Borrelli O, et al. Cow's Milk Protein Allergy in Infancy: A Risk Factor for Functional Gastrointestinal Disorders in Children? *Nutrients*. 2018;10(11).
2. Weimer DS, Demory Beckler M. Underlying Immune Mechanisms Involved in Cow's Milk-Induced Hypersensitivity Reactions Manifesting as Atopic Dermatitis. *Cureus*. 2022;14(8):e27604.
3. Perdikj Q, van Splunter M, Savelkoul HFJ, Brugman S, van Neerven RJJ. Cow's Milk and Immune Function in the Respiratory Tract: Potential Mechanisms. *Front Immunol*. 2018;9:143.
4. Sorensen K, Meyer R, Grimshaw KE, Cawood AL, Acosta-Mena D, Stratton RJ. The clinical burden of cow's milk allergy in early childhood: A retrospective cohort study. *Immun Inflamm Dis*. 2022;10(3):e572.
5. Carr LE, Virmani MD, Rosa F, Munblit D, Matazel KS, Elolimy AA, et al. Role of Human Milk Bioactives on Infants' Gut and Immune Health. *Front Immunol*. 2021;12:604080.
6. Gibson GR, Hutkins R, Sanders ME, Prescott SL, Reimer RA, Salminen SJ, et al. Expert consensus document: The International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of prebiotics. *Nature Reviews Gastroenterology & Hepatology*. 2017;14(8):491-502.
7. Hill C, Guarner F, Reid G, Gibson GR, Merenstein DJ, Pot B, et al. Expert consensus document: The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. *Nat Rev Gastroenterol Hepatol*. 2014;11(8):506-14.
8. Swanson KS, Gibson GR, Hutkins R, Reimer RA, Reid G, Verbeke K, et al. The International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of synbiotics. *Nat Rev Gastroenterol Hepatol*. 2020;17(11):687-701.
9. Candy DCA, Van Ampting MTJ, Oude Nijhuis MM, Wopereis H, Butt AM, Peroni DG, et al. A synbiotic-containing amino-acid-based formula improves gut microbiota in non-IgE-mediated allergic infants. *Pediatr Res*. 2018;83(3):677-86.
10. van der Aa LB, Heymans HS, van Aalderen WM, Sillevis Smitt JH, Knol J, Ben Amor K, et al. Effect of a new synbiotic mixture on atopic dermatitis in infants: a randomized-controlled trial. *Clin Exp Allergy*. 2010;40(5):795-804.
11. Burks AW, Harthoorn LF, Van Ampting MT, Oude Nijhuis MM, Langford JE, Wopereis H, et al. Synbiotics-supplemented amino acid-based formula supports adequate growth in cow's milk allergic infants. *Pediatr Allergy Immunol*. 2015;26(4):316-22.
12. Fox AT, Wopereis H, Van Ampting MTJ, Oude Nijhuis MM, Butt AM, Peroni DG, et al. A specific synbiotic-containing amino acid-based formula in dietary management of cow's milk allergy: a randomized controlled trial. *Clin Transl Allergy*. 2019;9:5.
13. Chatchatee P, Nowak-Wegrzyn A, Lange L, Benjaponpitak S, Chong KW, Sangsupawanich P, et al. Tolerance development in cow's milk-allergic infants receiving amino acid-based formula: A randomized controlled trial. *J Allergy Clin Immunol*. 2022;149(2):650-8.e5.
14. van der Aa LB, van Aalderen WM, Heymans HS, Henk Sillevis Smitt J, Nauta AJ, Knippels LM, et al. Synbiotics prevent asthma-like symptoms in infants with atopic dermatitis. *Allergy*. 2011;66(2):170-7.
15. Abrahamse-Berkeveld M, Alles M, Franke-Beckmann E, Helm K, Knecht R, Köllges R, et al. Infant formula containing galacto- and fructo-oligosaccharides and *Bifidobacterium breve M-16V* supports adequate growth and tolerance in healthy infants in a randomised, controlled, double-blind, prospective, multicentre study. *J Nutr Sci*. 2016;5:e42.
16. Harvey BM, Langford JE, Harthoorn LF, Gillman SA, Green TD, Schwartz RH, et al. Effects on growth and tolerance and hypoallergenicity of an amino acid-based formula with synbiotics. *Pediatr Res*. 2014;75(2):343-51.
17. Eichler HG, Pignatti F, Schwarzer-Daum B, Hidalgo-Simon A, Eichler I, Arlett P, et al. Randomized Controlled Trials Versus Real World Evidence: Neither Magic Nor Myth. *Clin Pharmacol Ther*. 2021;109(5):1212-8.
18. National Institute for Health and Care Excellence (NICE). Introduction to real-world evidence in NICE decision making. 2022. Available from <https://www.nice.org.uk/corporate/ecd9/chapter/introduction-to-real-world-evidence-in-nice-decision-making>
19. Hubbard GP, Atwal K, Graham L, Narayanan S, Cooke L, Casewell C, et al. Synbiotic containing extensively hydrolyzed formula improves gastrointestinal and atopic symptom severity, growth, caregiver quality of life, and hospital-related healthcare use in infants with cow's milk allergy. *Immun Inflamm Dis*. 2022;10(6):e636.
20. Sorensen K, Cawood AL, Gibson GR, Cooke LH, Stratton RJ. Amino Acid Formula Containing Synbiotics in Infants with Cow's Milk Protein Allergy: A Systematic Review and Meta-Analysis. *Nutrients*. 2021;13(3).
21. Sorensen K, Cawood AL, Cooke LH, Acosta-Mena D, Stratton RJ. The Use of an Amino Acid Formula Containing Synbiotics in Infants with Cow's Milk Protein Allergy-Effect on Clinical Outcomes. *Nutrients*. 2021;13(7).
22. Giampietro PG, Kjellman NI, Oldaeus G, Wouters-Wesseling W, Businco L. Hypoallergenicity of an extensively hydrolyzed whey formula. *Pediatr Allergy Immunol*. 2001;12(2):83-6.
23. Maslin K, Fox AT, Chambault M, Meyer R. Palatability of hypoallergenic formulas for cow's milk allergy and healthcare professional recommendation. *Pediatr Allergy Immunol*. 2018;29(8):857-62.
24. Data on file, updated independent taste panel report, Campden BRI, October 2020.