

## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form ([see an example](#)) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below. Some articles will have been accepted based in part or entirely on reviews undertaken for other BMJ Group journals. These will be reproduced where possible.

### ARTICLE DETAILS

|                            |  |
|----------------------------|--|
| <b>TITLE (PROVISIONAL)</b> | Extensively hydrolyzed casein formula supplemented with <i>Lactobacillus rhamnosus</i> GG maintains hypoallergenic status: Randomized double-blind, placebo-controlled crossover trial |
| <b>AUTHORS</b>             | Antonella Muraro, Maarten O Hoekstra, Yolanda Meijer, Carlos H Lifschitz, Jennifer LWampler, Cheryl L Harris and and Deolinda MF Scalabrin   |

### VERSION 1 - REVIEW

|                        |   |
|------------------------|---|
| <b>REVIEWER</b>        | Roberto Berni Canani, MD, PhD<br>Food Allergy Unit<br>Department of Pediatrics<br>European Laboratory for the Investigation of Food Induced Diseases<br>University Federico II<br>Naples Italy.<br><br>I've no conflict of interest with this study |
| <b>REVIEW RETURNED</b> | 25/11/2011  |

|                         |  |
|-------------------------|--|
| <b>GENERAL COMMENTS</b> | Overall interesting paper proposed by an experienced group in the field of food allergy. The paper is well written and the procedures are adequate to confirm the safety of this new diethotherapeutic option for children affected by cow's milk allergy.<br>The Introduction section seems redundant in part, I suggest to delate lines from 6 to 11 and from 13 to 30.<br>Some coorections should be removed from the text.<br>The quality of the figures should be improved. |
|-------------------------|--|

|                        |  |
|------------------------|--|
| <b>REVIEWER</b>        | Dr. Samuli Rautava, MD, PhD<br>Pediatrician<br>Turku University Hospital<br>Turku, Finland |
| <b>REVIEW RETURNED</b> | 11/12/2011   |

|                         |  |
|-------------------------|--|
| <b>GENERAL COMMENTS</b> | The study is rigorously conducted and the report well-written. LGG has been used extensively but the hypoallergenicity of EHF containing LGG has to my knowledge never been directly addressed. This report provides formal evidence for hypoallergenicity of EHF+LGG in infants and children with CMA. The results of the study are in line with previous experience and therefore hardly novel. Still, unambiguos data on the matter is welcome and the report deserves in my opinion to be published. |
|-------------------------|--|

|                 |             |
|-----------------|-------------|
| <b>REVIEWER</b> | Sig Johnsen |
|-----------------|-------------|

|                        |                      |
|------------------------|----------------------|
|                        | University of Surrey |
| <b>REVIEW RETURNED</b> | 22/12/2011           |

|                                  |  |
|----------------------------------|--|
| <b>THE STUDY</b>                 | <p>A cross-over design is appropriate (as has been used). However one might doubt that an interval between treatments (washout period) of 120 minutes is long enough adequately to reduce carry-over effects of one treatment to the next.</p> <p>It is difficult to follow the line of reasoning due to excessive use of acronyms</p> <p>The authors are frank that the conclusions are to some extent widely known already</p> |
| <b>RESULTS &amp; CONCLUSIONS</b> | The following leads me to question this: if my reading of the document is correct, 29 of the enrolled 31 participants experienced no adverse reactions, either with the active treatment or with the control.  |
| <b>REPORTING &amp; ETHICS</b>    | By the authors' own admission: this is virtually a redundant publication.  |
| <b>GENERAL COMMENTS</b>          | I am tending to suggest 'Major Revision' – paying particular attention to clarity of presentation.   |

#### VERSION 1 – AUTHOR RESPONSE

Reviewer: Dr. Samuli Rautava, MD, PhD  
 Pediatrician  
 Turku University Hospital  
 Turku, Finland

The study is rigorously conducted and the report well-written. LGG has been used extensively but the hypoallergenicity of EHF containing LGG has to my knowledge never been directly addressed. This report provides formal evidence for hypoallergenicity of EHF+LGG in infants and children with CMA. The results of the study are in line with previous experience and therefore hardly novel. Still, unambiguous data on the matter is welcome and the report deserves in my opinion to be published.

Reviewer: Sig Johnsen  
 University of Surrey, Surrey Clinical Research Centre

A cross-over design is appropriate (as has been used). However one might doubt that an interval between treatments (washout period) of 120 minutes is long enough adequately to reduce carry-over effects of one treatment to the next.

**Such a design, observing the same time intervals between the administrations of the treatments is well-described [1, 2] and has been validated in previous studies.[3-5] According to the guidelines, a minimum interval of 120 minutes between the two treatments was observed in the current study; however, that interval was increased based on the history of the allergic reactions for each individual.[2] Moreover, none of the participants in our study had a positive reaction to any of the treatments; therefore we had no inconclusive or doubtful challenge results for any participants.**

It is difficult to follow the line of reasoning due to excessive use of acronyms

We would prefer to continue using CMA for “cow’s milk allergy”, EH for “extensively hydrolyzed”, LGG for “Lactobacillus rhamnosus GG” as these are commonly used abbreviations for these terms, as well as “EHF” and “EHF-LGG” for the study group names, for ease of reference to the two study groups.

However, all instances of “CM” in the context of cow’s milk formula (CMF) and cow’s milk protein (CMP) have now been spelled out for ease of reading within the manuscript’s text. These changes are tracked in the revised manuscript.

The authors are frank that the conclusions are to some extent widely known already

The following leads me to question this: if my reading of the document is correct, 29 of the enrolled 31 participants experienced no adverse reactions, either with the active treatment or with the control.

**As stated in Results section of the ABSTRACT, none of the 31 participants experienced an adverse reaction with the active treatment or the control.**

**As stated in the Sample Size Determination section of the METHODS, our calculations prior to the study showed that we needed to study at least 29 participants and have none classified as positive in the DBPFC to allow the conclusion that the study provided 95% confidence that at least 90% of children with confirmed CMA who ingest the tested formula would have no reaction.**

**Therefore, although all 31 participants were classified as negative in the challenges, we had also focused on presenting the fact that at least 29 were classified as negative, in order to establish hypoallergenicity.**

By the authors’ own admission: this is virtually a redundant publication.

I am tending to suggest ‘Major Revision’ – paying particular attention to clarity of presentation.

## REFERENCES

1. Bock SA, Sampson HA, Atkins FM, Zeiger RS, Lehrer S, Sachs M, et al. Double-blind, placebo-controlled food challenge (DBPCFC) as an office procedure: a manual. *J Allergy Clin Immunol* 1988;82:986-97.
2. Bindsvlev-Jensen C, Ballmer-Weber BK, Bengtsson U, Blanco C, Ebner C, Hourihane J, et al. Standardization of food challenges in patients with immediate reactions to foods--position paper from the European Academy of Allergology and Clinical Immunology. *Allergy* 2004;59:690-7.
3. Sampson HA. Role of immediate food hypersensitivity in the pathogenesis of atopic dermatitis. *J Allergy Clin Immunol* 1983;71:473-80.
4. Sampson HA, Bernhisel-Broadbent J, Yang E, Scanlon SM. Safety of casein hydrolysate formula in children with cow milk allergy. *J Pediatr* 1991;118:520-5.
5. Burks W, Jones SM, Berseth CL, Harris C, Sampson HA, Scalabrin DM. Hypoallergenicity and effects on growth and tolerance of a new amino acid-based formula with docosahexaenoic acid and arachidonic acid. *J Pediatr* 2008;153:266-71.