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PEER-REVIEW REPORT

Name of journal: World Journal of Clinical Cases

Manuscript NO: 46867

Title: Hypoallergenicity of a thickened hydrolyzed formula in children with cow's milk allergy

Reviewer's code: 03334447

Reviewer's country: Netherlands

Science editor: Ying Dou

Reviewer accepted review: 2019-03-06 09:40

Reviewer performed review: 2019-03-13 11:37

Review time: 7 Days and 1 Hour

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	[ ] Accept (High priority)	Peer-Review:
[ ] Grade B: Very good	[Y] Grade B: Minor language polishing	[ ] Accept (General priority)	[Y] Anonymous
[ ] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] Minor revision	[ ] Onymous
[Y] Grade D: Fair	[ ] Grade D: Rejection	[Y] Major revision	Peer-reviewer's expertise on the topic of the manuscript:
[ ] Grade E: Do not publish		[ ] Rejection	[Y] Advanced
			[ ] General
			[ ] No expertise
			Conflicts-of-Interest:
			[ ] Yes
			[Y] No

SPECIFIC COMMENTS TO AUTHORS

Overall, this study is of interest but not unique in its way and it seems another hydrolysed formula that needs to be investigated before it can enter the market. Although I discovered that this thickened eHF formula is already in markets like France

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and Italy. This makes the relevance of this study questionable when the formula investigated here can be prescribed already. The design for hypoallergenicity testing as described in this manuscript is right and sufficiently explained. However, there are 2 big flaws in this study: - there is a complete lack of any sample size or power calculation for the 2nd phase of this study, namely the growth and efficacy/clinical benefit part. Therefore it gives the impression that the study is not sufficiently powered to investigate growth and to find any clinical benefit. Growth was measured in this small set of infants (L179-182), but only over 90 days / 3 months, while a proper growth study should be done over a larger group of infants (mostly >100 infants) with a solid power calculation (e.g. to be sufficiently powered to detect a possible growth difference) and preferably over a longer time period (e.g. at least 4 months / 16-17 weeks). - the homogeneity and allergic severity of this patient population is questionable since many infants at baseline had not very high symptom scores (a low CoMiSS at baseline rather points to a very mild allergy type (L263-264)) and the recruitment seemed biased to a specific subgroup not representing the full spectrum of CMA infants if those who had a previous reaction to an eHF, which was specified by the authors as 'a history of non-improvement of allergic symptoms when previously fed an eHF', were excluded (L120-121). Some patients had acute reaction or a clear SPT or IgE level, but many of them had also only a delayed reaction (maybe non-IgE-mediated?) (L236-248). The overall conclusion is that this manuscript is confusing about what the study is aimed for, it reports hypoallergenicity as primary outcome, but it also concludes about growth and efficacy regarding GI symptoms, whereas it's not properly designed to examine this. Some statements and conclusions really need to be toned down or even removed. Some further questions and suggestions: -At the end of the Introduction (L95-100) there are 2 objectives described, whereas the primary aim is hypoallergenicity and that should be clear. The clinical study design is not powered (at least there no mentioning of any

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sample size or power calculation) to study GI events like regurgitations. Mentioning this as a 2nd objective causes confusion. -In the methods, was there any rule set for compliance or drop out? For example, if the infants consumed less than 75% of their daily energy requirement, these infants should have been out of the analysis as this can influence significantly tolerance, growth and safety parameters! There is also no mentioning of complementary feeding practice for the 2nd part of the study. With an average age of 8 months, I may assume some might have been on weaning foods. -L110-112: is the amount of fiber (0.5g/110ml) also included in the carbohydrate level (6.9g/100ml)? -L114: 'compliant with EU legislation' needs a reference. -L118: better to call it 'exclusion criteria' instead of 'non-inclusion criteria'. -In the methods section, the authors don't mention the use of anti-histamines before the challenge as exclusion criteria. It should be specified whether this protocol / guideline was followed or not as anti-histamine use before challenge will influence the challenge outcome. -L258: it's better to say 'not related to either one of the study products' instead of 'not caused by' -L269-271: there were only few regurgitations at baseline, so again I'm wondering if this patient population was the right one to study potential anti-regurgitation benefits of this thickened eHF. -L273-275: was crying significantly lower at the end of the study, i.e. from 6 patients to 1 patient, but there is no p-value shown. -L282-286: the limitation of this paragraph is that there isn't a control, so no comparison can be made between the TeHF and the control AAF! -L287-291: again the relevance of these data is questionable since the study wasn't powered to test for differences in growth parameters. Only 29 infants are simply not enough to draw any conclusion about growth and the length of the study seems to short to detect any difference in growth. -L292-296: the paragraph about satisfaction by parents and clinician is very subjective. Suggestion to make it more factual and measurable. Again, a shortcoming is the lack of the control product or a comparison to it. -The discussion section is not very objective, e.g. almost everything in

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favour of the investigated TeHF, and the authors should reconsider some statements that were made. E.g. L312-313 'whatever CMA type…', 'whatever age…' isn't very factual, but very subjective interpretation, better to rephrase. -Conclusion on appropriate growth at L314-315 and L376-378 can, again, not be made based on the above comments of lack of power calculation and the limited study length. -L333-334: I cannot agree with the explanation that it was difficult to capture late reactions, there is good methodology – also published in other allergy studies - through standardized questionnaires and phone calls to follow these patient up accurately after a hospital visit or challenge. -The Discussion section should also discuss the patient population, especially why the symptoms (CoMiSS and regurgitation) were already low at baseline. Again, was it the right study population? -L385-387: it is questionable if the regurgitations were managed by the thickened feature of the TeHF or whether this symptom is primary to CMA and if CMA is properly managed by an hypoallergenic formula like an eHF, this symptom resolves already irrespective of having a thickener. The difficulty in this study is that there wasn't a control formula in the second phase, otherwise the authors could have addressed this. Figure 3: it is not clear why P-values are given in comparison to baseline assuming that an infant is normally growing and the NS (non significance) doesn't mean anything as the study was not sufficiently powered to detect any smallest difference between formulas.

INITIAL REVIEW OF THE MANUSCRIPT

Google Search:

[ ] The same title

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[ ] Plagiarism

[Y] No

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PEER-REVIEW REPORT

Name of journal: World Journal of Clinical Cases

Manuscript NO: 46867

Title: Hypoallergenicity of a thickened hydrolyzed formula in children with cow's milk allergy

Reviewer's code: 03337020

Reviewer's country: Poland

Science editor: Ying Dou

Reviewer accepted review: 2019-03-31 16:38

Reviewer performed review: 2019-04-03 15:26

Review time: 2 Days and 22 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection	Peer-Review: [Y] Anonymous [ ] Onymous Peer-reviewer's expertise on the topic of the manuscript: [Y] Advanced [ ] General [ ] No expertise Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

This is an appropriate study to validate the hypoallergencicity claim for this infant formula

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[Y] No