

In order to reply at best to the reviewer's comments, they have been numbered.

Reviewer #1

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

We thank the reviewer #1 for this nice comment.

Reviewer #2

We thank the reviewer for this detailed review.

1. *Overall, this study is of interest but not unique in its way and it seems another hydrolyzed 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 and Italy. This makes the relevance of this study questionable when the formula investigated here can be prescribed already.*

The formula tested in this study is a new formula that is not yet marketed. In the Abstract, it is indicated in the Aim part (L50), "To assess the hypoallergenicity of a **new** thickened extensively hydrolyzed casein-based formula (TeHCF) in children with cow's milk allergy (CMA)". Likewise, at the end of the Introduction, the objective is described as follows (L107-110), "The **primary** objective of this study was therefore to evaluate the hypoallergenicity of a **new** thickened extensively hydrolyzed casein-based formula (TeHCF) in children with CMA proven by a DBPCFC".

In France and Italy (and in other European markets), a thickened eHF is indeed currently marketed under Novalac brand and can be already prescribed (on the French market, the same eHF with no thickener is also marketed under Novalac brand). The difference between the formula tested in this study and the thickened formula currently on the market mainly lies in the presence of a new thickener, a mix of fibres based on pectin and locust bean gum. Given the presence of the new thickener, it was decided to evaluate the hypoallergenicity of this new formula.

To make clearer the difference between the new tested formula and the thickened formula currently on the market:

- ✓ the Abstract has been modified as follows (L50): Children diagnosed with CMA through a double-blind placebo-controlled food challenge (DBPCFC) were randomly administered increased doses of a placebo formula or the TeHCF (Allernova, **new thickener including fibres** (Novalac)) under double-blind conditions and medical surveillance on two separate days.
- ✓ the Methods part has been modified as follows (L121-127): Once reconstituted, the tested study formula (Allernova, **new thickener** (Novalac, United Pharmaceuticals, Paris, France)) [...] The **new** thickener was a patented mix of fibres, including pectin and locust bean gum.

*The design for hypoallergenicity testing as described in this manuscript is right and sufficiently explained. However, there are 2 big flaws in this study:*

- 2. 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).*

As required by the ICH guidelines (STATISTICAL PRINCIPLES FOR CLINICAL TRIALS), the sample size was calculated on the primary objective. As the assessments of growth parameters and CMA symptoms during the second study phase were secondary objectives, they were not taken into account in the sample size calculation. We agree that our study is most probably not sufficiently powered to show a difference in growth or CMA symptoms versus a control group.

However, as recalled in the Discussion, an increasing amount of data on the growth of children with food allergies, particularly CMA, is accumulating, so we considered as worthy to document the growth and the CMA symptoms of children exclusively formula-fed the TeHCF during 3 months and not only during 7 days after the food challenge. Sicherer et al., 2001 did that also: they determined the hypoallergenicity and efficacy of an amino acid-based formula (AAF) for children with CMA and multiple food allergies. Hypoallergenicity was determined by performing blinded oral food challenges in 31 children with CMA and in 18 of them, growth and tolerance were evaluated during a subsequent 4-month feeding with the AAF, with no control group included.

Concerning the study length, we considered that 3 months was an appropriate duration to document the growth of children exclusively formula-fed the TeHCF, as pointed out by a recent EFSA report (EFSA, 2017) on the preparation and presentation of an application for authorisation of an infant and/or follow-on formula manufactured from protein hydrolysates.

To take into account this comment, the following modifications were made:

- in the Abstract, L72-75 “The new TeHCF meets the hypoallergenicity criteria according to the American Academy of Pediatrics standards, **confirming that the tested TeHCF is adapted to the dietary management of children with CMA.** Moreover, growth was adequate **in the included population.**
- in the Core tip paragraph, L84: “The subsequent 3-month open exclusive feeding with the tested formula showed that the formula was still well tolerated

by the 29 children with CMA included, their growth was adequate, and parents and the investigator were very satisfied with the effect of the formula.”

- in the Discussion, L423-426: “Growth parameters of the children fed the TeHCF were within normal range throughout the 3-month period, indicating that this hypoallergenic formula is safe and ensures an adequate growth of children with CMA.”

#### References:

Sicherer SH, Noone SA, Koerner CB, Christie L, Burks AW, Sampson HA. Hypoallergenicity and efficacy of an amino acid-based formula in children with cow’s milk and multiple food hypersensitivities. *J Pediatr* 2001;**138**:688–93 [PMID: 11343044 DOI: 10.1067/mpd.2001.113007]

EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2017. Scientific and technical guidance for the preparation and presentation of an application for authorisation of an infant and/or follow-on formula manufactured from protein hydrolysates. *EFSA Journal* 2017;15(5):4779.

3. *the homogeneity and allergic severity of this patient population is questionable since:*
  - 3.1 *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))*

Indeed, the CoMiSS at baseline in this patient population was low, on average 1.4 (2.0). As the primary aim of the present study was the evaluation of the hypoallergenicity of the tested formula, children were asymptomatic for at least two weeks upon inclusion as recommended by guidelines on food challenge procedures (Sampson et al., 2012; Nowak-Wegrzyn et al., 2009). These references have been added in the Methods part, L132 as follows: Infants [...] iii) successfully fed an elimination diet for at least 2 weeks **as recommended by guidelines on food challenge procedures**<sup>[2,3]</sup>.

Children then underwent the DBPCFC with an at least one-week interval between each food challenge day to allow potential symptoms to resolve. Between each food challenge day and until the start of the exclusive formula-feeding with the TeHCF (i.e. at Baseline – D0 visit), the child was fed the formula that was successfully consumed before study inclusion (as indicated L167-168). The CoMiSS<sup>TM</sup> was thus very low at baseline.

To obtain a value of CoMiSS<sup>TM</sup> reflecting the allergic severity of the patient population, the CoMiSS<sup>TM</sup> should have been measured when cow’s milk proteins were still part of their diet. However, at that time, children did not comply with our inclusion criteria “successfully fed an elimination diet for at least 2 weeks”.

The Discussion has been changed to better explain why the CoMiSS<sup>TM</sup> was very low at baseline, as follows (L405-407): In the present study, children were asymptomatic for at least two weeks upon inclusion and then underwent the DBPCFC with an at least one-week interval between each food challenge day to allow potential symptoms to resolve. **Between each food challenge day and until the start of the exclusive formula-feeding with the TeHCF (i.e. at Baseline – D0 visit), the child was fed the**

**formula that was successfully consumed before study inclusion;** thus, the CoMiSS™ was very low at baseline.

### References:

Nowak-Wegrzyn A, Assa'ad AH, Bahna SL, Bock SA, Sicherer SH, Teuber SS, Adverse Reactions to Food Committee of American Academy of Allergy, Asthma & Immunology. Work Group report: oral food challenge testing. J Allergy Clin Immunol 2009;123:S365-383 [PMID: 19500710 DOI: 10.1016/j.jaci.2009.03.042]

Sampson HA, Gerth van Wijk R, Bindslev-Jensen C, Sicherer S, Teuber SS, Burks AW, Dubois AEJ, Beyer K, Eigenmann PA, Spergel JM, Werfel T, Chinchilli VM. Standardizing double-blind, placebo-controlled oral food challenges: American Academy of Allergy, Asthma & Immunology-European Academy of Allergy and Clinical Immunology PRACTALL consensus report. J Allergy Clin Immunol 2012;130:1260-74 [PMID: 23195525 DOI: 10.1016/j.jaci.2012.10.017]

*3.2 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).*

Here, patients whose symptoms did not improve when previously fed an eHF were not included. In the manuscript, the term eHF corresponds to special infant formulas whose protein fraction comprises extensively hydrolyzed cow's milk proteins (L102-103). According to paediatrician guidelines (Luyt et al., 2014; Koletzko et al., 2012; Fiocchi et al., 2010; AAP, 2000), it is recommended that any infant whose CMA symptoms persist when fed an eHF should be fed an amino-acids based formula (AAF). It is strongly advised that patients with a past reaction to an eHF shouldn't be fed an eHF, they were therefore excluded from this study.

The Methods part was modified as follows to make it clearer (L132-137): The main exclusion criteria [...] a history of a lack of improvement of allergic symptoms when previously fed an eHF **since for these children an AAF is recommended**<sup>[4-7]</sup>

### References:

American Academy of Pediatrics. Committee on Nutrition. Hypoallergenic infant formulas. Pediatrics 2000;106:346-9 [PMID: 10920165]

Fiocchi A, Brozek J, Schünemann H, Bahna SL, von Berg A, Beyer K, Bozzola M, Bradsher J, Compalati E, Ebisawa M, Guzmán MA, Li H, Heine RG, Keith P, Lack G, Landi M, Martelli A, Rancé F, Sampson H, Stein A, Terracciano L, Vieths S, World Allergy Organization (WAO) Special Committee on Food Allergy. World Allergy Organization (WAO) Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA) Guidelines. Pediatr Allergy Immunol 2010;21 Suppl 21:1-125 [PMID: 20618740 DOI: 10.1111/j.1399-3038.2010.01068.x]

Koletzko S, Niggemann B, Arato A, Dias JA, Heuschkel R, Husby S, Mearin ML, Papadopoulou A, Ruemmele FM, Staiano A, Schäppi MG, Vandenplas Y, European Society of Pediatric Gastroenterology, Hepatology, and Nutrition. Diagnostic approach and management of cow's-milk protein allergy in

infants and children: ESPGHAN GI Committee practical guidelines. J Pediatr Gastroenterol Nutr 2012;55:221–9 [PMID: 22569527 DOI: 10.1097/MPG.0b013e31825c9482]

Luyt D, Ball H, Makwana N, Green MR, Bravin K, Nasser SM, Clark AT, Standards of Care Committee (SOCC) of the British Society for Allergy and Clinical Immunology (BSACI). BSACI guideline for the diagnosis and management of cow's milk allergy. Clin Exp Allergy 2014;44:642–72 [PMID: 24588904 DOI: 10.1111/cea.12302]

*3.3 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).*

We agree with this observation. However, whatever the mechanism underlying food allergy, many data from the literature support the view that traditional tests (blood sIgE, SPT) for detecting food allergy have not a high sensitivity or specificity (too many false negative subjects). Even if two main different mechanisms are involved into the food allergy mechanism, both types are responsive to antigen exclusion from the diet. In addition, all subjects included in our study had a CMA proven by a DBPCFC, the gold standard diagnosis, as required by the American Academy of Pediatrics to evaluate the hypoallergenicity of a formula.

*4. 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.*

We revised the manuscript according to this general comment, please see more specifically the answers to the comments 2, 5, 15, 18 and 21.

*Some further questions and suggestions:*

*5. 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 is no mentioning of any sample size or power calculation) to study GI events like regurgitations. Mentioning this as a 2nd objective causes confusion.*

We understand that the description of the background for formula thickening, at the end of the Introduction, might indeed have caused confusion with the description of the primary objective.

Therefore, to avoid any misunderstanding, we moved what concerns the background for formula thickening from the Introduction to the Discussion.

The end of the Introduction is now: "The American Academy of Pediatrics established criteria to determine the hypoallergenicity of any formula intended for children with

CMA<sup>[7]</sup>. The **primary** objective of this study was therefore to evaluate the hypoallergenicity of a new thickened extensively hydrolyzed casein-based formula (TeHCF) in children with CMA proven by a DBPCFC.”

The Discussion is now:

- L428-431, “The **aim of the eHCF thickening is the management of the concomitant presence of CMA and regurgitations occurring when gastro-oesophageal reflux (GER) is present**<sup>[8]</sup> in some infants.
- L441-446 “CMA is often difficult to separate from functional gastro-intestinal disorder (FGID) in these patients when they present adverse GI reactions to cow’s milk for several reasons: **regurgitation is the most common FGID observed in the first year of life**<sup>[9,10]</sup> [...]”

6.

*6.1 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!*

During the second study phase, the compliance was evaluated by the investigator at each visit by asking parents if the child accepted the formula’s taste, if he/she had stopped the exclusive formula-feeding with the TeHCF or if he/she had taken another formula and what was the average volume of TeHCF taken by the child over the last 3 days (parents had to report for each feeding, the volume prepared and the volume left over, in their diaries over the 3 days before each visit). Based on this questioning, the investigator could decide to end the child’s study participation in case of poor compliance, or definitive interruption of the TeHCF feeding.

The Methods part was modified accordingly by adding the following sentences, L196-201: “The compliance was evaluated by the investigator at each visit by asking parents if the child accepted the formula’s taste, if he/she had stopped the exclusive formula-feeding with the TeHCF or if he/she had taken another formula and what was the average volume of TeHCF taken by the child over the last 3 days. In case of poor compliance to feeding recommendation, or definitive interruption of the TeHCF feeding, the investigator could decide to end the child’s study participation.”

In this study, the investigator did not require the end of child’s study participation for any of the patients, all children continued to be exclusively formula-fed with the tested formula for the 3 months of the second study phase. This was added in the Results part, L292-294: “All patients were fed the TeHCF for the open 3-month period and none dropped out of the study due to intolerance to the formula, **poor compliance to feeding recommendation or definitive interruption of the TeHCF feeding**”.

The objective of the second study phase was mainly to evaluate the tolerance of the TeHCF when taken as any other substitution formula by an infant with CMA in the “real life”, as part of a cow’s milk protein elimination diet. As the daily formula volume consumed by a child varies according to the child’s age but also from one child to another at the same age, no minimum volume of TeHCF to take each day could be set for the second study phase. The only recommendation was to completely replace the formula previously used with the TeHCF.

It has been made clearer L177-181: “If the TeHCF was tolerated during the DBPCFC and the CMA was confirmed, the child continued the study and started the open exclusive formula-feeding with the TeHCF **at D0 visit (also named Baseline visit, Figure 1) that consisted of a total replacement of the substitution formula used before D0 visit by the TeHCF.**”

*6.2 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.*

Indeed, 62.1% (18/29) of children were on weaning foods at inclusion. For the second part of the study, the only recommended feeding practice was that the child continues his/her usual cow’s milk proteins elimination diet. Indeed, as the primary outcome was evaluated during the first study phase, it was not necessary to ask parents to delay the introduction of the food allergens at the end of the study. It was up to the investigator to advise parents on how and when introduce food allergens according to the child’s feeding, allergic and personal history.

The following sentence has therefore been added L180-181: “In addition, the child continued his usual CMP elimination diet.”

*7. L110-112: is the amount of fiber (0.5g/100ml) also included in the carbohydrate level (6.9g/100ml)?*

According to the rules for the nutrition declaration set in the European Regulation 1169/2011 on the provision of food information to consumers, the amount of fibre is not included in the carbohydrate level.

*8. L114: ‘compliant with EU legislation’ needs a reference.*

The tested formula was compliant with the Commission Directive 1999/21/EC on dietary foods for special medical purposes in force at the start of the study. This reference has been added.

9. L118: better to call it 'exclusion criteria' instead of 'non-inclusion criteria'.

The term "non-inclusion criteria" has been replaced by "exclusion criteria".

10. 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.

Parents of infants taking antihistamine were advised to withhold these medications before the first challenge and for the whole first study part. Before each food challenge, the investigator had to check if the patient had stopped all medications including anti-histamines that could have interfered with the assessment of symptoms during food challenge.

The sentence on lines 147-149 has been modified as follows: "Before each FC day at the hospital, the investigator ensured that the child did not present any clinical abnormalities and had stopped all medications **including antihistamines** that could have interfered with the administration of the challenge."

11. L258: it's better to say 'not related to either one of the study products' instead of 'not caused by'

The sentence (L290-291) has been rephrased as follows: The investigator did not consider any of these changes as allergic reactions **related to** the TeHCF or placebo formula.

12. 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.

As previously explained (see the answer to the comment 5), the primary objective of this study was the evaluation of the hypoallergenicity of the TeHCF, and not its effect on regurgitations. It has been cleared by moving what concerns the background for formula thickening from the Introduction to the Discussion.

13. 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.

Here, the p-value was not indicated and the word "significantly" was not used because the evolution of this parameter was not statistically significant but *tended to be* statistically significant (p=0.06). To prevent any misunderstanding for the reader, the p-value was added (L309), as follows: Additionally, 20.7% (6/29) of patients cried for



more than 1.5 hours daily at baseline; after 7 days of TeHCF feeding, only 3.4% (1/29) of patients cried for more than 1.5 hours per day, **this change tended to be statistically significant (p=0.06).**

*14. 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!*

In the paragraph L282-286, we did not find where we made a comparison between the TeHCF and the control AAF. Indeed, this paragraph relates to results collected during the second study phase when children were fed the TeHCF as exclusive formula, so no comparison between the TeHCF and the control AAF was made.

*15. 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 too short to detect any difference in growth.*

As previously explained in the answer to the comment 2, we agree on the fact that the study wasn't powered to test for differences in growth parameters: the primary objective was the evaluation of the hypoallergenicity of the formula and not to show a difference in growth parameters with a control group of children fed a control formula.

However, we consider that the growth data collected during the 3 months of the second study phase should be given to the reader because they have been obtained in children who are most likely to benefit from these formulas, children aged 0-36 months, and they were obtained in children who were fed the TeHCF as it would be used in the real life. This paragraph corresponds to a description of collected results.

*16. 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.*

We absolutely agree on the fact that satisfaction is a very subjective measure, and that a control group during the second study phase would have clearly allowed us to know if the new TeHCF induced more satisfaction by the clinician and/or parents or not compared to a control formula.

In the Discussion, L371-373, the following sentence has been added: "The TeHCF could have been compared to a control formula, especially for the evaluation of the satisfaction of the formula effect by clinician and parents."

17. *The discussion section is not very objective, e.g. almost everything in 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.*

We agree on the fact that the age range of included children was not so large compared to other studies that assessed the hypoallergenicity of a formula (for example, Nowak et al., 2015 included children aged between 2 months and 12 years); conversely, we included the patient population the most likely to benefit from this type of formula, i.e. children aged 0-36 months. We have therefore deleted the lines L352-354, and changed the lines L347-348 to note this point, as follows: “Based on the findings of the present study, the new TeHCF tested in children with a proven CMA **and which correspond to the patient population the most likely to benefit from this type of formula, i.e. children aged 0-36 months**, meets the criteria of hypoallergenicity according to the AAP<sup>[8]</sup>.”

#### Reference:

Nowak-Węgrzyn A, Czerkies LA, Collins B, Saavedra JM. Evaluation of hypoallergenicity of a new, amino acid-based formula. Clin Pediatr (Phila) 2015;54:264-72 [PMID: 25395609 DOI: 10.1177/0009922814557785]

18. *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.*

L423-424 correspond to a description of the obtained results. Following the comment 2, L424-425 have been modified.

19. 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 patients up accurately after a hospital visit or challenge.*

We totally agree on the fact that similar methodologies than the one followed in our study, i.e. questionnaires and phone calls (replaced in our study by a visit with a clinical examination), have already been used before to capture late reactions after a food challenge. For example, when looking at the most recent studies that evaluated the hypoallergenicity of a formula, in Nowak-Węgrzyn et al. 2015, parents were asked to record, among others, the daily stool frequency and consistency, the frequency of spit-up and/or vomiting, any symptoms of potential allergic aetiology during the open challenge of one week after the food challenge. However, the fact remains that even if these tools are used, they will always rely on parents' report of observed signs and symptoms of the patient that may, for some of them, include a part of subjectivity. We therefore thought that it was important to remind it as a limit of the trial.

The sentence, L380, has therefore been modified as follows: “Moreover, children were clinically re-examined by the investigator and parents were required to accurately register the occurrence of any delayed reactions in diaries, **as already performed before**<sup>[11,12]</sup> to enable their objective evaluation by the investigator at follow-up visit.”

Reference:

Nowak-Węgrzyn A, Czerkies LA, Collins B, Saavedra JM. Evaluation of hypoallergenicity of a new, amino acid-based formula. Clin Pediatr (Phila) 2015;54:264–72 [PMID: 25395609 DOI: 10.1177/0009922814557785]

*20. 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?*

We reaffirm here that, according to us, it was the right study population to evaluate the hypoallergenicity of the TeHCF, the primary objective of the study, as already clarified in the answer to the comment 5.

The reasons why the CoMiSS™ value was low at baseline have been explained in the answer to the comment 3.1. The Discussion has been modified accordingly.

Concerning regurgitations, the same reasoning as the one for CoMiSS™ applies: given the primary objective of the study, the evaluation of the hypoallergenicity of the formula, allergic symptoms of children had to be low upon inclusion. It was therefore not planned in the present study to assess the effects of the thickening properties of the tested formula on the included population. However, it can be the objective of a future study, as explained in the Discussion, L434-444.

To take into account the comment, this sentence has been modified as follows: “Therefore, the new TeHCF deserves further investigation **in a patient population whose allergic symptoms are still present because the CMP have not yet been eliminated from their diet, on the contrary to children included in the present study which had to be successfully fed an elimination diet before inclusion so that their allergic symptoms were well improved. The effect of the TeHCF on gastro-intestinal symptoms in children presenting at enrolment symptoms suggesting a CMA, including severe regurgitations, should be compared to a control formula.**”

*21. 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.*

As previously explained (see the answers to the comments 5 and 20), the primary objective of this study was the evaluation of the hypoallergenicity of the TeHCF, and not its effect on regurgitations. To clarify this point, some modifications have been made as indicated on page 1 of this letter. In addition, we totally agree that the design of our study did not allow us to attribute the effect observed on regurgitations more to the presence of the thickener than to the cow's milk elimination diet.

In the present study, the main difficulty to evaluate the anti-regurgitation properties of the TeHCF is that allergic symptoms, including regurgitations, had at inclusion to have almost disappeared or to be well improved because of the study primary objective. So, even if a control group had been included in the second study part, it would have been impossible to compare the effect of that control formula to the TeHCF on regurgitations. To do so, it is necessary to conduct another study with a patient population whose allergic symptoms are well present at inclusion and which still has not eliminated cow's milk proteins from the diet, as explained in the answer to the comment 20.

*22. 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.*

As did Sicherer et al., 2001, we considered as valuable to know if growth parameters increased or not after 3 months of open feeding, even if the population was small, that's why statistical tests were performed between data obtained at each visit and baseline (start of the exclusive formula-feeding with the TeHCF).

#### Reference:

Sicherer SH, Noone SA, Koerner CB, Christie L, Burks AW, Sampson HA. Hypoallergenicity and efficacy of an amino acid-based formula in children with cow's milk and multiple food hypersensitivities. *J Pediatr* 2001;**138**:688-93 [PMID: 11343044 DOI: 10.1067/mpd.2001.113007]