Author's response to reviews

Title: Randomized double-blind placebo-controlled trial of sublingual immunotherapy in children with house dust mite allergy in primary care: study design and recruitment

Authors:

Cindy M.A. de Bot (c.debot@erasmusmc.nl)
Heleen Moed (h.moed@erasmusmc.nl)
Marjolein Y Berger (m.berger@erasmusmc.nl)
Esther Röder (e.roder@erasmusmc.nl)
Hans de Groot (h.degroot@erasmusmc.nl)
Johan C de Jongste (j.c.dejongste@erasmusmc.nl)
Roy Gerth van Wijk (r.gerthvanwijk@erasmusmc.nl)
Johannes C van der Wouden (j.vanderwouden@erasmusmc.nl)

Version: 2 Date: 11 September 2008

Author's response to reviews: see over
Date: September 11th 2008
Subject: Resubmission manuscript MS: 2623587981961243
Randomized double-blind placebo-controlled trial of sublingual immunotherapy in children with house dust mite allergy in primary care: study design and recruitment

Dear Editor,

Many thanks for reviewing our paper, to the reviewer for his constructive comments and for the opportunity provided to revise our paper. We have studied the issues raised by the reviewer thoroughly and addressed them in the revised manuscript which you will find attached to this mail. All modifications are listed and have been incorporated in the manuscript. We believe our paper has improved in reaction to the detailed comments, and hope that the manuscript is acceptable in its revised form.

On behalf of all authors,
Sincerely yours,

Cindy de Bot
Erasmus MC Rotterdam
The Netherlands
1. The analysis section gives the impression that the nasal score between groups at two years are being compared but by including the baseline nasal symptom score as a covariate it is the absolute change in nasal score between groups that is being compared. This is the correct analysis for change from baseline data, percentage change is not, but the authors need to make this clear.

We agree that the text may be interpreted incorrectly, and now explicitly refer to the Data analysis section.

2. The sample size calculation is based on a 30% reduction in baseline score. But this study is looking to find a difference in absolute change in nasal score from baseline. As this is used in the analysis it should also be used for the sample size calculation. The authors must state the clinically important difference in change from baseline nasal score and its standard deviation and the significance level and power for their sample size calculation. For example assuming that the change is 30% of 4.5 (the nasal score at the last week screening visit with a standard deviation of 2.6) this gives delta of approximately 0.5 which from gives a sample size of 105 at 5% significance and 95% power.

As we don’t like the idea of changing sample size calculations post hoc, we have added the proposed sentence as an alternative approach.

3. The subgroup analyses stratified by disease severity will presumably be underpowered because of the smaller sample size. The stratification also needs clarification as the criteria used and the number of strata are unspecified.

The proposed subgroup analyses should be considered exploratory, and not as hypothesis testing. Because of the smaller group sizes the chance of a type-II error is indeed elevated. We plan to dichotomize both characteristics (age and baseline nasal symptom score) at their median value.
4. Can the authors state if more than one child was recruited from the same family? There is an implicit assumption that each observation is independent but this would be violated if more than one child came from the same family.

*Indeed, 18 families provided more than one child. It concerns 39 children. We will test whether ‘family’ contributes significantly to the model (p < 0.20). If this is the case, we will add this factor as a random effect. We added this sentence to the analysis paragraph.*

Discretionary Revisions (which the author can choose to ignore)

5. Is the formal comparisons in Table 5 really necessary? The large sample size means that the 95% Confidence Interval is +/- 1.25%. Is a difference this small of any clinical significance at screening?

*We agree that the differences for age and gender are not impressive. We studied if age and gender groups are adequately represented in our study, as it might affect the generalizability of the results of the trial.*

6. In England and Wales children assent but their parents/guardian consent. Can this be clarified and can consent/assent be included in the flow diagram?

*There is no distinction made between assent and consent in the Netherlands. Under the age of twelve years written informed consent was obtained from the parents/guardians of the eligible child, but (of course) also the child had to agree to participate. At the age of 12 to 17 years written informed consent was obtained from both the child and its parents/guardians. Here the child assents and consents. We included this issue in the flow diagram.*