

Clarification of epicutaneous immunotherapy trial phase 3 results and methods for qualitative survey design



We are writing in regard to an article by Greenhawt et al¹ who report results from a qualitative study intended to “better understand what caregivers value in a therapy and assess their underlying goals in seeking such therapy.” We have concerns regarding the report’s content in terms of the assessment of the trial to which the authors refer and the survey methodology.

In the Introduction, the authors discuss developing therapies for peanut allergy, including peanut oral immunotherapy (OIT) and epicutaneous immunotherapy (EPIT). The authors state “moderate success” for the 2 therapies despite different populations, adverse event rates, and numbers needed to treat. The authors further report “favorable phase II and III data” for the 2 therapies, indicating “strong therapeutic promise for either methodology.” They continue with “in a pivotal 12-month phase III trial, 35.3% of patients wearing a 250mcg peanut EPIT patch daily achieved their primary endpoint (either a 300mg single dose peanut tolerance if entry challenge threshold was ≤10mg or a 1000mg single dose if the entry challenge threshold was >10mg) vs. 13.6% of placebo patients, with only a 1.1% rate of treatment related drop-out and a very low rate of treatment related adverse events.” The primary end point in the EPIT phase 3 trial (Efficacy and Safety of Viaskin Peanut in Children With Immunoglobulin E (IgE)-Mediated Peanut Allergy [PEPITES]) was not met, as noted in the DBV Technologies October 20, 2017 press release.² The primary end point, which evaluated the 95% confidence interval for the difference in response rates between the active and placebo arms, did not reach the 15% lower bound of the confidence interval that was mandated by the Food and Drug Administration as a minimal bar of clinical significance. It is unclear how this conclusion was reached, because only limited data are available from the phase 3 trial and have not been published.

Importantly, the quoted definition of the primary end point of PEPITES also was erroneous. As stated on www.clinicaltrials.gov, the primary end point was the initial eliciting dose (ED) of less than or equal to 10 mg and the ED was at least 300 mg of peanut protein at the post-treatment double-blinded, placebo-controlled food challenge, or the initial ED was more than 10 mg of peanut protein and the ED was at least 1,000 mg of peanut protein at the post-treatment double-blinded, placebo-controlled food challenge.³ Greenhawt et al¹ state that the primary end point was a 300- or 1,000-mg single-dose peanut tolerance. This statement is incorrect; in food allergy clinical trials, the tolerated dose is *not the same* as the dose that elicits a reaction (ie, the ED or reactive dose). The tolerated dose (or the single highest tolerated dose) is the highest dose given during a food challenge that elicits no symptoms or symptoms that are not clearly indicative of an allergic reaction. Conversely, the ED (or reactive dose) is the dose given during a food challenge that induces the onset of unequivocal allergic symptoms: it is a dose that is *not* tolerated. It is essential that the vernacular used to describe food allergy immunotherapy trial results is accurate, so as not to mislead caregivers and patients about research findings. We refer readers to a food allergy lexicon on the American College of Allergy, Asthma and Immunology Learning Connection website (<https://education.aaaai.org/content/foodallergy>)⁴ and a recent presentation by

Chippis et al⁵ at the European Academy of Allergy and Clinical Immunology Congress.

From an epidemiologic perspective, the survey is subject to several limitations. First, data from a small qualitative survey of a limited sample of patients and their families (N=22) undermine the validity and generalizability of the findings. Selection bias was present in many forms in the study sample, including an imbalance in the number of subjects surveyed, with an over-representation of patients from the EPIT trials (n = 15) vs only 6 participants from the OIT trial. Differences between subjects selected for the survey and those not included were not provided. Further, the report lacks an exhibit displaying differences in baseline characteristics between the included EPIT and OIT groups. Of additional concern is the fact that subjects who were interviewed for the survey were included after the decision to enroll in a given study (OIT or EPIT); these patients should have been interviewed before deciding on the particular course of treatment.

Second, response bias also was present, because the participants in the survey were likely suggestible. Specifically, their feelings about what the therapy might do and what their appropriate expectations should be might have been heavily influenced by how the site framed the experimental treatment during prescreening, the consenting process, and the study. Study participants are frequently motivated to show investigators that they are attentive and good participants—ultimately reporting what investigators want to hear. The article states that the interviews were “semi-structured,” yet, unfortunately, no details regarding the specific questions posed to subjects were provided.

Third, the authors state “recruitment continued until thematic saturation was met.” However, no explanation on how thematic saturation was reached and why not enough patients in the OIT group were recruited to balance the survey was provided. Thus, the themes that emerged were largely dominated by the EPIT group simply because that group was twice the size of the OIT group. The concept of “saturation” is prone to practical weaknesses, because data can never be truly saturated⁶ and prospective estimation of the number needed for saturation cannot be readily identified.^{7,8}

We believe that clarification of the phase 3 results from the EPIT trial, which did not meet its primary end point, is essential to communicate to readers. Because qualitative research provides valuable exploratory research, we trust that our comments will aid in the design of future qualitative studies to better understand patient perspectives.

References

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Authors’ response



We read with interest these 2 separate correspondences, both authored by employees of Aimmune Therapeutics.^{1,2} We certainly appreciate their interest in our qualitative research study about motivations for seeking peanut allergy therapy.³ With the potential approval of 2 drugs to help treat peanut allergy in the next year, this is a timely topic. Both queries highlight alleged problems regarding our methods and conclusion and voice rather fervent, somewhat misplaced, comments and inappropriate posturing regarding Aimmune’s interpretation of DBV’s topline data for their phase 3 trial.⁴ These pieces also read as a curious disapproval of this work based on their perception that our findings are biased toward a particular product. It should have been obvious that the brief description of both trials was simply background context; otherwise, that section of our article has no pertinence to our project. We discuss only the study participant—described motivations for seeking therapy, ascertained through our qualitative interviews, and do not make any conclusions or speculations about how these may fit a particular product. Thus, any associations or judgments made about the quotes and themes presented and how these may relate to particular products are Aimmune’s alone not ours. This is quite clear given we made no such statements or judgments in our article.

There is some difficulty in understanding precisely the point these correspondences are trying to make. A common theme of both is a distracting and entirely nonsequitur argument about the product phase 3 trial and results, which are immaterial to our study aim and methods. Their strong criticism of the trial outcomes of a perceived rival developing their own product is unwarranted in this forum, particularly given that our study explored motivations for seeking therapy not satisfaction with phase 3 trials results. Therefore, we leave it to the reader to decide what the outcome of our conclusions may or

may not imply regarding a specific product. Each reader can weigh the issues that Aimmune raises in light of forthcoming published phase 3 trial data for both products. The correspondence authors accurately identify a typographical error in our introduction, which was detected in the early-view manuscript version beneath the clearly identified watermark of uncorrected proof before the galley proof was available to us and then corrected.

It is difficult to address the specific methodologic criticisms waged, given that they are steeped in significant misunderstanding of qualitative research and methods and how this differs from quantitative or market research. This is not the forum to discuss such differences, and we included references for the sound qualitative methods we followed in our article.^{5,6} I will briefly address 2 points raised. First, qualitative sampling does not aim for balance or stratifications customary in quantitative research. Instead, is based on the concept of purposeful sampling to achieve maximal variation regarding the experience being elicited, which continues not until some specific number of participants is reached but rather until thematic saturation is met (ie, when no new information is being obtained through the interviews).^{5,6} This is an iterative and fluid process, which to an inexperienced reader may feel more subjective and potentially biased compared with quantitative studies. However, when well-established qualitative methods are followed, as was done in our study, research into understanding questions related to experience and motivations can be explored.

Second, as we have noted, this study had nothing to do with the study participant’s actual trial enrollment status. Our aims and hypothesis were not to perform comparative analysis of our findings among products or enrollees of different trials. Such a study would be quantitative not qualitative. Our focus was to understand the deeper themes, goals, and motivations of parents to consider seeking any peanut allergy treatment for their child. Despite Aimmune’s concerns of the constituency of our sample, we found there was uniformity in the motivations and concerns expressed about therapy from caregivers of children enrolled in both trials that undermines the notion that such responses could be stratified by the participant’s specific trial enrollment. As well, our purpose was not to ascertain caregiver alignment of their goals with the actual trial results (again, better answered with a quantitative study design). That said, Aimmune’s concern raised here is surprising given that the goal of both of the phase 3 peanut allergy treatment trials were identical—desensitization to a small amount of peanut protein, albeit achieved through different mechanisms and with end points defined differently—by an eliciting dose that provokes objective symptoms in one trial and by the highest dose tolerated with no more than mild symptoms (but not the highest dose at which the patient was completely asymptomatic) in the other.^{4,7} The suggestions that our research participants were “likely suggestable,” were motivated to show us they were

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Disclaimer: Drs Sicherer and DunnGalvin were authors on the original article and were aware of the correspondences but were uninvolved in the formulation and content of this response and have given us written permission to not include them.

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