acknowledgements

This work was partly funded by the National Research University Project, Office of Higher Education Commission (NRU59-003-HR), the Center of Excellence on Medical Biotechnology (CEMB), ST Postgraduate Education and Research Development Office (PERDO), SB-60-003-03, Chulalongkorn Academic Advancement (2nd Century Project-CUAASC), and a 90th Anniversary of Chulalongkorn University Scholarship.

Conflict of Interest

AFS is inventor on a patent application with regard to the VLP-display technology (WO2016112921 A1) licensed to AdaptVac. A.F.S. is currently partially employed in AdaptVac. The remaining authors declare that they have no conflicts of interest.

Author Contributions

AJ and AFS designed the study. SJ produced all the SpyTagged-pDp1, untagged VLPs, SpyCatcher-VLP, and performed the experiments on immunogenicity and allergenicity. AJ provided supervision and analyzed the data. AJ, AFS, and SJ drafted the manuscript. All authors contributed to and approved the final version of the manuscript.

Sirikarn Jitthamstaporn1
Adam F. Sander2
Alain Jacquet1

1Center of Excellence in Vaccine Research and Development, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand
2Centre for Medical Parasitology, Department of Immunology

Supporting Information

Additional supporting information may be found in the online version of the article at the publisher’s website.

DOI: 10.1111/all.15130

No apparent impact of incremental dosing on eliciting dose at double-blind, placebo-controlled peanut challenge

To the Editor,

Oral food challenges (OFC) are the gold standard diagnostic for food allergy, but not without limitation. Administering incremental doses every 15-30min differs from a real-world exposure where ingestion occurs at a single episode. Blumchen et al. reported a median time to objective symptoms of 55min (range 5-210min)1; if
doses are given every 15 min, this could significantly overestimate the reaction threshold.\(^1,2\) This could also occur due to incremental dosing causing transient desensitization.\(^3\) With OFC increasingly used to determine starting doses for oral immunotherapy and guide dietary avoidance,\(^4\) we assessed how clinical thresholds and symptoms of OFC compare to an ingestion more representative of real-world consumption.

Seventeen peanut-allergic adults (median age 24 years, range 18–40) underwent initial double-blind, placebo-controlled food challenge (DBPCFC) to peanut, as part of a clinical trial (TRACE Peanut study; ClinicalTrials.gov Identifier: NCT02665793). Detailed methods are described elsewhere.\(^5\) Doses were given every 30 minutes (using a water-continuous dessert matrix) according to the following schedule: 3 μg, 30 μg, 300 μg, 3 mg, 30 mg, 100 mg, 300 mg and 1000 mg of peanut protein (or placebo), until stopping criteria (adapted from PRACTALL consensus criteria) were met.\(^5\) Participants returned for two further DBPCFC, at 8–12 week intervals later. The first was an ‘abbreviated’ DBPCFC using the same matrix, with the first active dose equivalent to the maximum tolerated dose at baseline DBPCFC (see Figure 1 and Table S1); this was done as a safety measure. Subjects allocated (by computer randomization) to placebo: had two initial placebo doses, prior to active doses (Figure 1). The third DBPCFC used the same abbreviated protocol, but with the appropriate dose given as peanut butter (Kraft Foods) mixed into a soya-based spread (Wowbutter) and eaten as a small 3 cm sandwich (Kingsmill 50/50 bread). For all challenges, the dosing interval was 30 minutes, although this could be doubled if symptoms were progressing. Triangle testing demonstrated the suitability of Wowbutter for blinding, and prior tolerance to this was demonstrated in all participants. The study was approved by the NHS Human Research Authority (reference 15/LO/0286), and written informed consent from all participants.

At baseline DBPCFC, the median cumulative eliciting dose (cumED) was 133 mg (IQR 83.3–433.3 mg) peanut protein; 2/17 patients had anaphylaxis (WAO 2020 criteria). Median cumED at abbreviated challenge was 133 mg (IQR 33.3–433.3 mg) (Figure 2A). The shift in cumED was not significant (p=0.10, Wilcoxon sign-rank test), and there were no major differences in clinical symptoms observed (Fig S1), with 4/17 having anaphylaxis. Fourteen subjects underwent the third DBPCFC using peanut butter sandwiches (one had too low a cumED for the appropriate dose to be accurately measured, and two declined). Median cumED at this challenge was 433 mg (IQR 33.3–1433.3 mg), representing a non-significant half-log increase in cumED (p>0.05; Figure 2B); 2/14 had anaphylaxis.

In a systematic review and meta-analysis of peanut-DBPCFC, 69% of peanut-allergic individuals show a shift in cumED over time; in 56%, this is limited to a half-log difference, equivalent to 1 dosing interval with a PRACTALL-based semi-log dosing regimen.\(^6\) Indeed, Dua et al reported a fall of around 0.5-log (equivalent to 1 dosing increment) at subsequent OFC in these same participants.\(^5\) Therefore, the non-significant shift in cumED with an abbreviated challenge protocol is entirely consistent with the inherent ‘noise’ in determining cumED at OFC. We undertook a post hoc power calculation; our sample size would have been sufficient to detect a 1-log difference in cumED with at least 90% power, that is greater than that due to the inherent intraindividual variability.

In summary, we did not find a significant difference in either cumED or symptoms following DBPCFC with a 30-minutely incremental dosing protocol, compared to an abbreviated challenge which is more representative of a normal consumption episode. In addition, there was no significant difference in cumED between baseline DBPCFC and a more ‘real-world’ exposure to peanut butter in a sandwich. Therefore, using threshold data from OFC (with 30-minute dosing intervals) is a valid approach to individual allergen risk management. Importantly, the impact of cofactors was minimized due to the nature of the study design. In reality, thresholds will vary due to cofactors among other reasons,\(^6\) so appropriate caution should be exercised in extrapolating challenge thresholds into clinical advice at an individual patient level.

**KEYWORDS**

allergy, eliciting dose, food challenge, lowest observed adverse effect level, peanut

**FUNDING INFORMATION**

This research was funded through the European Union’s Seventh Framework Program for research, technological development and demonstration (iFAAM (Integrated Approaches to Food Allergen and Allergy Risk Management), grant agreement no. 312147) and a
UK Medical Research Council Clinician Scientist award to PJT (reference MR/K010468/1). Clinical challenges in the TRACE Peanut study were funded by the UK Food Standards Agency, and the NIHR Biomedical Research Centre based at Imperial College Healthcare NHS Trust and Imperial College London. The views expressed in this article are those of the author(s) and do not necessarily reflect those of the NHS, NIHR or the Department of Health.

ACKNOWLEDGEMENTS
We thank our study participants, who were recruited through the TRACE Peanut study (funded by the UK Food Standards Agency); we are grateful to the study investigators (Chief investigator A Clark) and the Food Standards Agency for their support; and to the members of our Data Safety Monitoring Board: Professor Stephen Till, Dr Hazel Gowland and Dr Mich Erlewyn-Lajeunesse. We are grateful to Emily Wilson, Louise Cross and staff at the Respiratory Clinical Research Facility at the Royal Brompton Hospital for their clinical support.

CONFLICT OF INTEREST
All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare grants from UK Medical Research Council, NIHR/Imperial BRC and UK Food Standards Agency for the submitted work. MRG is now employed by Laboratorios Leti, this occurred following data lock and completion of study analyses. SRD reports grants from the Immune Tolerance Network, National Institute of Allergy and Infectious Diseases, ALK-Abelló, Regeneron, and Biotech Tools outside the submitted work; personal fees from Anergis, Circassia, Biomay, Merck, Allergy Therapeutics, Med Update GmbH and Food Standards Agency. RJB reports personal fees from Prota Therapeutics, DBV Technologies, Cochrane Collaboration, John Wiley & Sons on behalf of Clinical and Experimental Allergy, personal fees from giving expert testimony, outside the submitted work. ENCM reports grants from the UK Biological and Biotechnological Sciences Research Council, DBV Technologies, Reacta Biotech, the Medical Research Council, the European Union, and the UK Food Standards Agency and has patents pending to Reacta Biotech Ltd (PCT/GB2016/051637 and PCT/GB2016/053829). PJT reports grants from UK Food Standards Agency, JM Charitable Foundation and End Allergies Together, outside the submitted work; personal fees from UK Food Standards Agency, DBV Technologies, Aimmune Therapeutics, Allergenis and ILSI Europe outside the submitted work. All other authors declare no competing interests.

Olaya Álvarez García1,2
Joan Bartra1,3
Monica Ruiz-García1
Isabel J. Skypala1,4
Stephen R. Durham1,4
Robert J. Boyle1
E.N. Clare Mills5
Paul J. Turner1

1National Heart & Lung Institute, Imperial College London, London, UK
2Complexo Hospitalario Universitario de Ferrol, A Coruña, Spain
3Hospital Clinic de Barcelona, Barcelona, Spain
4Royal Brompton and Harefield Hospitals NHS Foundation Trust, London, UK
5Division of Infection, Immunity & Respiratory Medicine, Manchester Institute of Biotechnology, University of Manchester, Manchester, UK

Correspondence
Paul Turner, National Heart & Lung Institute, Imperial College London, Norfolk Place, London, W2 1PG, UK.
Email: p.turner@imperial.ac.uk

ORCID
Joan Bartra https://orcid.org/0000-0001-7767-4730
Stephen R. Durham https://orcid.org/0000-0001-5264-6207
Paul J. Turner https://orcid.org/0000-0001-9862-5161
To the Editor,

Chronic rhinosinusitis (CRS) with nasal polyps (CRSwNP) is a primary, diffuse CRS-phenotype, in the Western world having a type-2 (T2) endotype predominance. With 85% of CRS-patients belonging to the working-age population, it constitutes a vast economic burden to society. Productivity losses from absenteeism and presenteeism are the major cost expense, followed by healthcare consumption. Despite optimal care, a subpopulation of CRSwNP-patients remains insufficiently controlled. Biologicals targeting T2-pathway components have recently been registered for severe, uncontrolled CRSwNP. This new and promising treatment modality has been implemented in the integrated CRS care pathways, alongside (updated) assessment criteria for current clinical CRS-control and response to biologicals of CRSwNP. Dupilumab, blocking IL-4 and IL-13 by targeting IL-4Ra, is registered for CRSwNP via the registration trials LIBERTY NP SINUS (LNPS)-24 and LNPS-52. Recent systematic review and appraisal further concluded dupilumab efficacious, although cost-effectiveness remains undissolved and insufficient data heretofore impedes head-on comparison to other agents. We report our provisional findings from a real-life, prospective observational cohort, aimed to evaluate the therapeutic efficacy of add-on dupilumab as the primary biological therapy in an adult CRSwNP-population (≥18y) in our tertiary referral center, and to verify the EPOS2020 biologicals indication criteria. Eligible patients from this cohort with ≥12w follow-up, until and including May 2021, were included in this study. Dupilumab was auto-administered subcutaneously, 300mg 1x/2 weeks (Q2W). Stepwise interdose interval prolongation (SIIP) by 2w ensued in those with moderate to excellent response, with minimal 24w-interim periods, thus proceeding the successfully explored SIIP in LNPS-52 (officially off-label dosing interval; full methodology in Supplements). Mean scores of all primary outcomes improved significantly from baseline (n=131) to the 24w (n=98) and 48w (n=26) timepoints: SinoNasal Outcome Test-22 (SNOT-22, 0 – 110) improved from 52.4 (s.d.: 19.6) to 18.5 (12.9) and 16.8 (12.4), respectively; bilateral Nasal Polyp Score (NPS, 0 – 8) improved from 5.4 (2.0) to 1.6 (1.7) and 1.0 (1.7); Sniffin’ Sticks-12 identification test (SSIT-12; 0 – 6 anosmia, 7 – 10 hyposmia, 11 – 12 normosmia) improved from 3.6 (2.1) to 7.3 (2.8) and 8.3 (3.2); if applicable, asthma control test (ACT, 5 – 25) improved from 17.8 (4.6), to 21.8 (3.4) and 23.5 (1.9), increasing the rate of well-controlled asthma from 45.6% at baseline to 76.8% and 94.1%, respectively (Table 1 & Figure 1a-d). At baseline, CRS was controlled in 0%, partly controlled in 4.2%, and uncontrolled in 95.8%. At 24w and 48w, respectively, 75.7% and 93.8% were partly controlled, and 24.3% and 6.2% were uncontrolled; “controlled CRS” was unachievable with biologicals considered rescue treatment (Table 1 & Table S1). Rescue treatment otherwise was applied in two cases (oral corticosteroids and no antibiotics). Four patients ceased treatment, due to non-responsiveness (1); subjective insufficient control (1); persistent hypereosinophilia (1); and possible treatment emergent