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REVIEW ARTICLE

GA²LEN ANACARE consensus statement: Potential of omalizumab in food allergy management

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Abstract

Immunoglobulin E (IgE)-mediated food allergies are the most common type of food allergy, often causing rapid symptoms after exposure to allergens posing a serious health risk and a high impact on patient's and caregiver's quality of life. Omalizumab, a humanized anti-IgE monoclonal antibody, reduces allergic reactions by binding to circulating IgE. Omalizumab has been successfully used in allergic asthma, chronic rhinosinusitis with nasal polyps, and chronic urticaria, and was recently approved for treating IgE-mediated food allergies by the US Food and Drug Administration (FDA). This GA²LEN ANACARE Consensus Statement presents our position on the use of omalizumab for treating IgE-mediated food allergies, based on a systematic review

and meta-analysis, experience with use for other conditions, and expert consensus achieved via an eDelphi process. Following publication of the recent OUtMATCH study (stage 1) results and subsequent FDA approval, we propose that there is now sufficient evidence to recommend omalizumab as the only drug currently available that can mechanistically reduce IgE-mediated food allergic reactions. We acknowledge that the evidence does not reach the highest level of evidence which would be needed for a guideline recommendation.

KEYWORDS
anaphylaxis, desensitization, food allergy, immunoglobulin E, omalizumab

1 | INTRODUCTION

GA^{2}LEN, the Global Allergy and Asthma Excellence Network, was created in 2004 as the European Union network of excellence in collaboration with EAACI (European Academy of Allergy and Clinical Immunology). Currently, it is the largest and most active worldwide multidisciplinary network of clinical and research centers in allergy and asthma. An important GA^{2}LEN activity is knowledge-exchange to progress novel and emerging approaches to treat severely affected patients. Here, the GA^{2}LEN ANACARE centers of reference and excellence for anaphylaxis and food allergy outline our consensus statement on the use of omalizumab for treating IgE-mediated food allergy, acknowledging its existing licenses for other allergic diseases and its recent approval for IgE-mediated food allergy by the US Food & Drug Administration (FDA). We summarize our current position on the use of this biologics, and outline current evidence gaps which preclude a more comprehensive set recommendations.

2 | CHALLENGES OF FOOD ALLERGY

The number of people diagnosed with an immediate-type IgE-mediated food allergy is increasing. The prevalence and types of food allergies vary globally, but up to 6% of children and 3% of adults may be affected by allergies to cow's milk, hen's egg, peanuts, sesame, wheat, and other foods, which has consequences on those providing safe food options for them.[1] While most reactions are not life-threatening, severe anaphylaxis reactions do occur, which can be fatal. Our current inability to identify those at greatest risk of more severe reactions means that people with food allergy are often managed as being at equal risk of fatal reactions, causing unnecessary anxiety and excessive dietary restriction.

Until recently, the mainstay of management was to avoid the trigger food allergens and prescribe adrenaline (epinephrine) auto-injectors for use in the event of an allergic reaction. However, this is not always easy in day-to-day life. It can be difficult to avoid "hidden" foods and there is always a danger of cross contamination. Adults and children with food allergies can become fearful of having a reaction, which can affect their nutrition, health, and mental wellbeing.[2] The aim of GA^{2}LEN is to investigate and offer the best treatment options available. In our understanding, simple avoidance measures are not in line with the World Health Organization (WHO) standards, which state that everyone deserves the highest level of health.

Food allergies have been shown to significantly affect the quality of life in patients of all ages, and the mental wellbeing of the whole family.[3–5] Management involving avoidance of allergen(s) by eating a very restricted diet can adversely impact health and nutrition such as creating gut inflammation and barrier dysfunction.[6,7] Fear of a potential reaction when in social situations, particularly those that involve food, may lead individuals and their families to greatly restrict their, or their child's social lives.[6,8]

By definition, IgE-mediated allergy requires the presence of a specific antigen as well as a specific IgE antibody recognizing this antigen. Therefore, reducing serum IgE offers another approach (alongside allergen avoidance) to reduce the risk of an acute allergic reaction. In this position paper, we assess evidence relating to the use of omalizumab for specific patient subgroups that have a difficulty avoiding their food allergen, for example, people with multiple food allergies, those who have a very low reaction threshold and may therefore be prone to react to low-level allergen contamination, as well as higher risk patients such as those living in remote areas without access to emergency care. We also explore the use of omalizumab as an adjunct therapy in patients who fail to achieve successful desensitization with food allergy immunotherapy due to frequent adverse events.

3 | BACKGROUND INFORMATION ON OMALIZUMAB

In IgE-mediated food allergy, mediators such as histamine and leukotrienes are released from mast cells, which in turn cause clinical symptoms. Omalizumab (Xolair) is a commercially available humanized anti-IgE monoclonal antibody that interferes with the body's immune system to reduce people's sensitivity to allergens. It was first approved by the FDA for moderate-severe asthma in 2003; subsequently, the approved indications have broadened and now include childhood asthma, chronic rhinosinusitis with nasal polyps, chronic

urticaria and – since February 2024 – for IgE-mediated food allergy in certain adults and children aged one year or older.[9]

Due to its anti-IgE mechanism of action, it helps to reduce immune responses in people with IgE-mediated food allergies. Omalizumab binds to circulating IgE, reducing IgE receptor expression and decreasing mediator release from mast cells and basophils. In food allergy, omalizumab may also exert its protective effect through the formation of allergen-specific circulating IgE-IgG complexes, which compete with cell-bound IgE for epitopes on allergen surface, thus disrupting IgE receptor aggregation.[10–12] Since omalizumab is a nonspecific anti-IgE antibody and inhibiting IgE is the basic principle of treating a type I allergic reaction, this medicine is not restricted to specific allergens and may be effective for people with multiple food allergies, commonly found in clinical practice. The principle of IgE-mediated allergic reactions is conserved in evolution and is independent of age, gender, and race.

Treatment dose remains a matter of debate. In a cohort of 181 food-allergic patients treated with omalizumab, its efficacy was shown to correlate with its dosage per weight but not with its dosage per total IgE and body weight.[12] For asthma, the omalizumab dosage is determined according to the IgE levels and body weight, and in urticaria a flat rate of 300 mg omalizumab is used but up dosing may be required in patients with higher BMI.[13] In an ongoing large DBPC study on the use of omalizumab for treatment of food allergy, the dose is based only on body weight (16 mg/kg and 8 mg/kg),[14] and in the recently completed clinical trials, the same treatment dosage was used as in the asthma treatment protocol.[14–16] The recent approval for omalizumab in IgE-mediated food allergy uses the same dose recommendations as for asthma,[10] that is, based on serum total IgE levels and body weight, as this is the approach used in the OUtMATCH study.[9]

4 | METHODS USED TO DEVELOP THIS POSITION STATEMENT

GA^{2}LEN considered the role of omalizumab as part of a comprehensive management plan for people with one or more food allergies. We developed our position based on available evidence and expert opinion.

We drew on a systematic review and meta-analysis of research on omalizumab alone or used in conjunction with oral immunotherapy.[17] The review protocol is registered in the International Prospective Register of Systematic Reviews (PROSPERO; number: CRD42021245895). We replicated this analysis using the same search terms to confirm results, since the initial work was industry sponsored. In summary, the reviewers searched seven databases for published and unpublished randomized controlled trials (RCTs), controlled clinical trials and observational studies available as of November 2020. They found 36 relevant studies with a total of 953 children and adults. There were 9 RCTs, 19 controlled clinical trials and 8 observational studies. The purpose of this position paper is not to summarize the systematic review,[17] but to present some of the key findings as evidence to support our position.

We formed an Expert Group made up of 40 experts from 16 countries. We used an eDelphi process to consider the evidence about the safety and effectiveness of omalizumab in food allergy as well as to discuss the current clinical practice in the different centers. The Expert Group considered the findings from the systematic review,[17] as well as studies published since which include Stage 1 from the OUtMATCH study,[16,18] as well as other relevant RCTs, as described in detail below. The main statements of this paper were voted on in the eDelphi, and a 70% consensus was considered as the agreement threshold. The questions were formulated and voted on during ANACARE general assembly meetings in the first half of 2023, and the 4-point Likert scale for response options (strongly agree, agree, disagree, strongly disagree) was applied. Two rounds of eDelphi were conducted. In the final round, out of the 51 experts who were invited to participate in the questionnaire, 38 responded, giving a response rate of 74.5%. The results of the eDelphi questionnaire were pooled into two groups (agree and disagree) and are presented in Figure 1A–F, all having responses above 70%.

5 | CURRENT LEVEL OF EVIDENCE FOR USE OF OMALIZUMAB IN FOOD ALLERGY

5.1 | Omalizumab as monotherapy

The systematic review included 12 studies about using omalizumab as monotherapy to treat people with food allergy.[15,16,19–29] Overall, omalizumab increased thresholds for allergen reactivity, improved their quality of life, and was not associated with many adverse effects. People allergic to multiple foods or to peanuts were usually at least 2–3 times more able to tolerate these foods compared to the baseline threshold after a course of omalizumab that was administered every 2–4 weeks, for 24 weeks. Studies have reported enhanced tolerance to peanut of 500–6500 mg.[20,21,29] The findings were more heterogeneous for people allergic to milk or hen's eggs. The phase III OUtMATCH study results indicated that a 16-week omalizumab treatment was superior to placebo in increasing the reaction threshold for peanut and other common food allergens in individuals with multiple food allergies.[16] A limitation of the OUtMATCH study is that the primary outcome was the proportion of participants able to tolerate ≥600 mg of peanut protein without experiencing dose-limiting symptoms at double-blind food challenge, rather than a change in reaction threshold, which is a more relevant patient outcome. The Expert group also noted the findings from the TOFAC study of 20 children, which reported a significant increase in threshold following 3 months of omalizumab.[15]

The Expert Group considered that while previous studies were small and therefore at greater risk of bias, the OUtMATCH study addressed this limitation. Furthermore, given the consistency of the OUtMATCH results with previous studies, the Expert Group concluded that there is now sufficient evidence to recommend omalizumab as monotherapy for use in selected patients with IgE-mediated food allergy (Figure 1A). A notable limitation of using

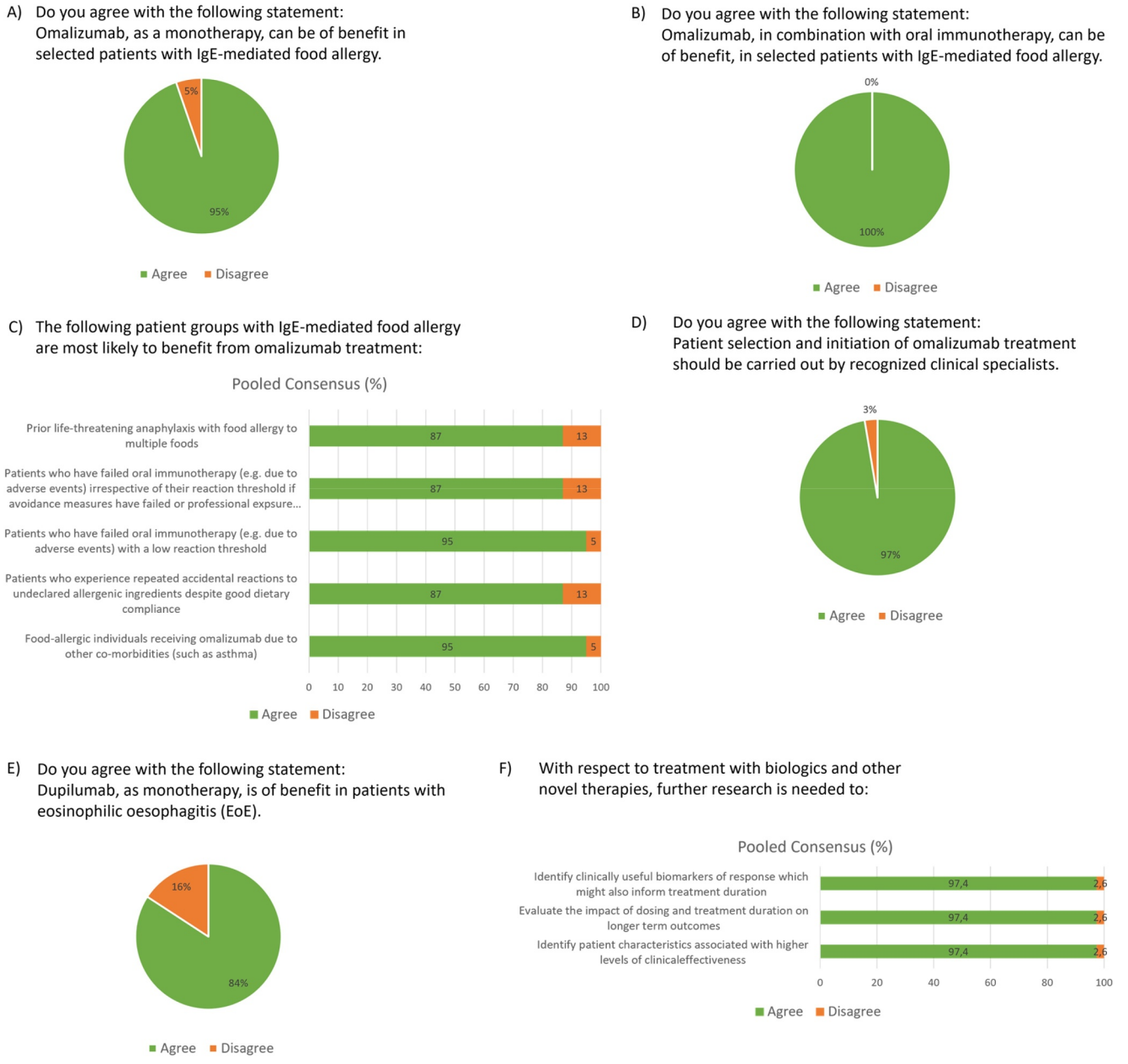

FIGURE 1 Pooled eDelphi study second round results on the ANACARE expert opinion statements about the use of omalizumab and other biologics for food allergies and eosinophilic esophagitis.

omalizumab as monotherapy is that long treatment durations may be required, which are costly and may be inconvenient for patients. Using the safe symptom-free interval induced by this therapy to induce specific tolerance by oral immunotherapy against the relevant food allergens is therefore likely to be a more cost-effective use.

5.2 | Omalizumab in combination with oral immunotherapy (OIT)

Food allergen immunotherapy has recently become available to treat people, especially children, with peanut allergy in many countries worldwide, including the USA and countries in. It has been used in clinical studies for people with other food allergies, mainly milk and egg.[30]

Allergen immunotherapy (AIT) is often associated with adverse effects because people cannot always tolerate the rising doses of the elicit food. Some studies found that 1 in 10 people suffered systemic reactions, especially during the escalation phase.[31] To address this important issue, recent findings on co-administration of adjuvants with peanut OIT demonstrated the potential in reducing adverse events, increasing the body's ability to develop sustained unresponsiveness and the long-term efficacy of AIT.[32–34] This means that immunotherapy must be provided in specialized centers with

appropriate medical supervision. The observed adverse effects are one of the barriers why specific immunotherapy has not been fully established for treating food allergies to date.

The systematic review included 22 studies of omalizumab used in combination with oral immunotherapy.[34–55] The reviewers concluded that adding omalizumab to the treatment regimen may help people tolerate oral immunotherapy better and have fewer reactions.

The potential advantages of using omalizumab with oral immunotherapy are:

- increased safety and efficacy of oral immunotherapy
- better tolerability of the allergen at higher doses
- reduced duration of the escalation phase of oral immunotherapy
- improvement of asthma, which may be a co-morbidity and is a recognized co-factor in severity of food allergy reaction.

Based on the available data, the ANACARE experts are of the opinion that Omalizumab, in combination with oral immunotherapy, can be of benefit in selected patients with IgE-mediated food allergy (Figure 1B). High quality evidence from large RCTs is currently lacking; however, the Expert Group noted the results from at least 2 large RCTs are expected soon: Stage 2 of OUtMATCH[19] and the BOOM study, a double-blind RCT comparing omalizumab to placebo as an adjunct to oral immunotherapy in subjects aged 6–25 years with multiple food allergy.[14] More robust research is needed to explore the benefit effect size of omalizumab and whether it differs among people with various food allergies. The most effective dosing schedule and duration of treatment also need to be explored further.

5.3 | Safety profile

The safety and efficacy of omalizumab have been reviewed for other diseases. Godse et al. 2015 reviewed reports of studies involving chronic urticaria patients in which most often no or very mild adverse effects were observed.[56] The safety in pediatric asthmatic patients was reviewed by Chipps et al. 2017, which resulted in an overall support of the current guidelines that recommend omalizumab as an add-on treatment in children with uncontrolled persistent allergic asthma.[57] Omalizumab has been shown to be safe for use in other diseases and may be beneficial to specific food allergic patient subgroups. The use of omalizumab allows flexibility in the treatment of food allergy in which the drug can be tested for a limited period.

6 | POSITION STATEMENT

We need new approaches to address the heavy burden of food allergies. Based on the Delphi process of expert consensus and a review of the evidence, GA^{2}LEN's position regarding omalizumab in IgE-mediated food allergy is as follows.

6.1 | Target population

We encourage clinicians to consider whether omalizumab is right for selected patients with IgE-mediated food allergy. It can cover several food allergies at once and seems equally effective for adults and children. As omalizumab is a non-specific anti-IgE, its efficacy is the likely similar for any ethnic group and for any food allergy that is IgE related.

Due to the cost and administration form, we suggest offering omalizumab as an option for those who may benefit most. This includes those at greatest risk of life-threatening anaphylaxis with food allergy to multiple foods, who have failed oral immunotherapy (e.g., due to adverse events) irrespective of their reaction threshold or low reaction threshold, who experience repeated accidental reactions to undeclared allergenic ingredients despite good dietary compliance, and food allergic individuals receiving omalizumab due to other co-morbidities (e.g., asthma) (Figure 1C). The use may expand widely once the drug receives regulatory approval for the treatment of food allergy, in which case the direct costs to the patient may decrease considerably.

We advise caution if considering administering omalizumab to pregnant women. However, this should be balanced against the risk of anaphylaxis in pregnancy and thus risk and benefit need to be discussed with the patient.

6.2 | Treatment regime and evaluation of success

Omalizumab is efficacious in clinical trials but unlikely to be cost-effective as monotherapy in most patients. Monotherapy may require long-term treatment (6 months to several years), whereas omalizumab can be used for short-term treatment (12–18 weeks) to support oral immunotherapy. Specific immunotherapy with food allergens appears effective but is often associated with systemic adverse effects. Omalizumab can reduce this, making immunotherapy more tolerable and safer for a greater number of people. However, for patients with multiple food allergies where immunotherapy may not be practical if there is allergy to a large number of foods, long-term monotherapy may well be the most reasonable approach.

Currently, the dose of omalizumab for treating food allergy is determined by body weight and total IgE levels.[10] It should be administered subcutaneously once every 2 or 4 weeks. The fraction of allergen-specific/total IgE may be useful to predict patients at greater risk of food dosing reactions after reintroduction.[12] The duration of the treatment cannot be predicted at the time of initiation, but it has been suggested that patients should be reevaluated at regular time intervals of no more than 3 months. Controlled food challenges may be warranted for further decision-making.

6.3 | Optimizing safety

Omalizumab has a good safety profile. Admission to the hospital is not required for administration. As this is a biological medicine, it

should initially only be administered by a healthcare professional trained to recognize anaphylaxis and in an environment with medications and equipment to respond to a systemic reaction. Anaphylaxis is rare in people who receive omalizumab and is most common after the first few doses. Therefore, people who receive omalizumab should be observed for systemic reactions for 2 h after administration for at least the first three injections. The drug is then licensed for home use if these first doses are well tolerated.

Patients with food allergy who receive omalizumab should still receive the prescription for standard emergency medicine for their underlying food allergy based on the recommendations, such as an adrenaline autoinjector (AAI). They should be trained in how to use the AAI and where to seek help in an emergency.

Based on the available data, the ANACARE experts are of the opinion that patient selection and initiation of omalizumab treatment should be carried out by recognized clinical specialists (Figure 1D).

7 | OTHER CURRENTLY APPROVED BIOLOGICS FOR FOOD ALLERGY RELATED DISEASES

Dupilumab, a monoclonal antibody that blocks interleukin 4 and interleukin 13, has been approved for eosinophilic esophagitis (EoE), a chronic disease characterized by symptoms of esophageal dysfunction and eosinophil-predominant inflammation which frequently associated with IgE sensitization to food allergens. However, research has shown that EoE pathogenesis is distinct from IgE-mediated food allergy and EoE inflammation itself appears to be largely IgE independent. Dupilumab is indicated for the treatment by subcutaneous injection of adult and pediatric EoE patients aged 12 years and older, weighing at least 40 kg, 300 mg weekly. Dupilumab has been evaluated in a three-part phase 3 double blind placebo controlled clinical trial, which revealed that subcutaneous dupilumab administered weekly improved histologic outcomes and alleviated symptoms of the EoE.[58] The ANACARE experts are of the opinion that Dupilumab, as a monotherapy, is of benefit to patients with EoE (Figure 1E).

8 | CONCLUSION

Omalizumab has been used in individual cases of people with food allergy for some time and is now licensed in the United States to treat selected patients with one or more IgE-mediated food allergies. Currently, the highest level of evidence on the safety and efficacy of omalizumab in treating IgE-mediated food allergies is available from the OUtMATCH study. Other clinical trials are ongoing but have yet to present their findings or to conclude. As more data become available, we anticipate that omalizumab will be licensed in other countries and more confidently used off-label. However, there is now sufficient evidence to recommend omalizumab as monotherapy for use in selected patients with IgE-mediated food allergy, where there is a need to reduce the risk of food-induced allergic reactions due to patient-specific factors. This may include patients with repeated unexplained severe anaphylaxis reactions to exposure to food allergens or those in whom a short treatment course might be indicated to reduce risk while receiving omalizumab treatment (e.g., due to travel, occupations with special risk, being in a remote location without medical support). More research needs to be undertaken to assess optimal treatment duration, longer-term outcomes and cost-effectiveness prior to being able to recommend a wider indication for use. We await outcomes from ongoing clinical trials to inform future recommendations for omalizumab in combination with oral immunotherapy or as a bridge to real food introduction, which may be more cost-effective measures to induce longer-term tolerance.

We encourage considering omalizumab as an option in individual patients with food allergy in collaboration with specialized centers such as the centers of reference of the GA^{2}LEN ANACARE network. We encourage considering inducing specific tolerance or at least increasing the threshold of reaction and pre-treatment with omalizumab can support immunotherapy, but we acknowledge that we do not currently have knowledge about the duration of treatment required and careful supervision on an individual basis is needed. We recommend pursuing further research and future randomized placebo-controlled trials to identify clinically useful biomarkers of response, which might also inform treatment duration, evaluate the impact of dosing and treatment duration on longer term outcomes, and identify patient characteristics associated with higher levels of clinical effectiveness (Figure 1F).

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CONFLICT OF INTEREST STATEMENT

Torsten Zuberbier reports honoraria for lectures from Amgen, AstraZeneca, AbbVie, ALK -Abelló, Almirall, Astellas, Bayer Health Care, Bencard, Berlin Chemie, FAES Farma, HAL Allergie GmbH, Henkel, Kryolan, Leti, L'Oreal, Meda, Menarini, Merck Sharp and Dohme, Novartis, Nuocor, Pfizer, Sanofi, Stallergenes, Takeda, Teva, UCB, and Uriach; Fees for industry consulting were received from Abivax, Almirall, ,Bluprint, Celldex, Celltrion, Novartis, and Sanofi; in addition he declares non-paid organizational affiliations: Committee member, "Allergic Rhinitis and its Impact on Asthma" (ARIA), Member of the Board, German Society for Allergy and Clinical Immunology (DGAKI), Head, European Center for Allergy Research Foundation (ECARF), President, Global Allergy and Asthma Excellence Network (GA^{2}LEN), and Member, Committee on Allergy Diagnosis and Molecular Allergology, World Allergy Organisation (WAO). Antonella Muraro reports speaker's fees from Viatris, DVB Technologies, Aimmune, Novartis, and Nestle Health Sciences, and is a non-paid committee member of "GA2LEN Executive Committee" and "GA2LEN ANACare Steering Committee." Ulugbek Nurmatov declares no conflict of interest. Stefania Arasi reports contracts from Bambino Gesu' Children Research Hospital, speaker's fees from Ulrich and DBV, participation on the advisory board for Novartis and AIMMUNE, and is a non-paid committee member of EAACI. Katarina Stevanovic declares no conflicts of interest. Aikaterini Anagnostou reports consulting fees from Novartis, Genentech, ALK; speaker's fees from EPG Health, MJH, Adelphi, Aimmune Therapeutics, Genentech, FARE, Medscape, Innovation horizons; travel fee support from Novartis, Medscape, multiple allergy societies, and participation on advisory boards for Ready set food, Novartis, Genentech, and Bryn. Roberta Bonaguro declares no conflicts of interest. Sharon Chinthrajah reports grants from Consortium for Food Allergy Research (CoFAR), National Institute of Allergy and Infectious Disease (NIAID), Food Allergy Research and Education (FARE); is an advisory board member for Alladapt Immunotherapeutics, Novartis, Allergenis, Intrommune Therapeutics, Phylaxis, Genentech, and Blueprint Therapeutics; is a stockholder of Intrommune Therapeutics. Gideon Lack reports grants from the National Institute of Allergy and Infectious Diseases (NIAID, NIH) and National Peanut Boards (NPB); consulting fees from Novartis, DBV Technologies, Reckitt Mead Johnson, and ALK Abello; speaker's fees from DBV Technologies, Aimmune, and EPG Health; and is a shareholder of DBV Technologies and Mighty MissionMe. Alessandro Fiocchi reports grants from Novartis, Ferrero, Sanofi, Stallergenes, Danone, and Aimmune; consulting fees from Abbott and Ferrero; speaker's fees from Sanofi; and non-paid committee member of World Allergy Organization (WAO) and American Academy of Allergy Asthma and Immunology (AAAAI). Thuy-My Le reports speaker's fees from Thermofisher and Abbvie. Paul Turner reports grants from the Medical Research Council, Food Standards Agency, JM Charitable Foundation, National Institute for Health and Care Research (NIHR)–Imperial Biomedical Research Center, outside the submitted work, and personal fees from the UK Food Standards Agency, DBV Technologies, Aimmune Therapeutics, Allergenis, and ILSI Europe outside the submitted work. Montserrat Alvaro Lozano declares no conflict of interest. Elizabeth Angier reports support for travel expenses and honoraria from Gp Lecture; is a non-paid member of Primary Care group members BSACI, Anapyhylaxis UK, and Allergy UK. Simona Barni reports speaker's fees from Nutricia and Sanofi. Phillippe Bégin reports payments to institutions for clinical trials from Novartis, DBV Technologies, and Sanofi; consulting fees from ALK, Novartis, DBV Technologies, and Pfizer; and speaker's fees from ALK and Novartis. Barbara Balmer-Webber reports consulting fees from ALK, Novartis, Sanofi, and Allergopharma; speaker's fees from Thermo Fisher, Novartis, Sanofi, and Menarini. Victoria Cardona declares no conflicts of interest. Carsten Bindslev-Jensen reports grant from Novartis and consulting fees from ALK Abello and Novartis. Antonella Cianferoni declares no conflicts of interest. Nicolette de Jong declares no conflicts of interest. Debra de Silva declares no conflicts of interest. Antoine Deschildre reports consulting fees from Novartis, ALK, GSK, Sanofi, Regeneron, Aimmune Therapeutics, Nestlé Health Science, Stallergènes-Greer, Viatris, Celltryon; speaker's fees from Novartis, ALK, GSK, Sanofi, Aimmune Therapeutics, DBV Technologies, Nestlé Health Science, Viatris; travel costs support from ALK, Sanofi, Stallergenes Greer, Novartis, Astra-Zeneca, Aimmune Therapeutics, Celltryon; participation on a data safety monitoring board for the BOOM study. Audry Dunn Galvin reports consulting fees from Novartis; speaker's fees from Novartis and DBV, support for travel costs from Novartis

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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